Technische Universität München

Re-Enacting Stress in the Lab.

On Environmental Epigenetics, Social Adversity and the Molecularisation of Mental Health

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1 Introduction

1.1 A crisis and a presumed response to it

Psychiatry is in a state of crisis. It is a crisis that extends into the most diverse areas of psychiatry, ranging from research on into the causes of mental health conditions to their treatment. It is a crisis very much related to the fundamental question of what constitutes mental health. Does it have to do with the social relationships we encounter from birth to adolescence, above all those with our parents and siblings? Is it related to our successes in life, our material wealth? Or is our emotional and social well-being linked to certain biochemical factors, or the architecture of our brain? These are all questions that accompany a dichotomy that is increasingly questioned by the natural sciences: is it *nature* that determines our mental health or is it *nurture*? The crisis in which psychiatry currently finds itself crystallises in precisely these ambiguities: without answer(s) to such questions, the treatment of mental disorders will remain relatively unsuccessful.

The crisis at hand can be translated into numbers: mental disorders are described to be among the most common causes of chronic morbidity worldwide (Lopez & Murray, 1998) and according to the World Health Organization (WHO, 2013), "persons with major depression and schizophrenia have a 40% to 60% greater chance of dying prematurely than the general population, owing to physical health problems that are often left unattended" (p. 7). Additionally, suicide is the second most common cause of death amongst the young population worldwide (WHO, 2013). Margaret Chan, director general of the World Health Organization, views the high prevalence of mental disorders and their detrimental consequences with concern. In her foreword to the WHO's (2013) *Mental Health Action Plan 2013-2020*, she acknowledges "mental well-being [as] a fundamental component of the WHO's definition of health" (p. 5). Without being better able to understand and treat mental health conditions, we have little chance of reducing these numbers. At the same time, Chan diagnoses an unfortunate trend: despite these alarming figures, mental health issues still are not getting the attention they need, resulting in "neglect of mental health services and care, and abuses of human rights and discrimination against people with mental disorders and psychosocial disabilities" (WHO, 2013). Referring to the WHO's (2013) *Mental Health Action Plan*, clinical psychologist Daniel Vigo and colleagues frankly state that policy and science have underestimated the burden of mental illness (p. 171).

This burden is felt not least by psychiatrists, as they currently experience a treatment plight: they complain that the current therapeutic measures do not reach enough people and do not have the anticipated curative effects. But where does this helplessness, the most obvious symptom of the crisis, come from? Why are many severe mental disorders currently considered un-treatable, despite the fact that there is a range of pharmacological and psychotherapeutic interventions? Many researchers in the

field of mental health attribute these challenges to a knowledge gap in the aetiology of mental health conditions: the reasons behind one person developing a disease whereas others do not are still not fully understood. This gap in knowledge prompts some molecular biologists to "propose that it is now the time for a 'War on Mental Illness' to be officially and rapidly launched" (Licinio & Wong, 2014, p. 1) – a war with the goal of improving the "translation of science into health care, resulting in more efficacious treatments than what we have available today" (Licinio & Wong, 2014, p. 1). That is to say, psychiatry currently suffers from a sort of conceptual affliction comparable to the nature/nurture divide: the link between research and treatment is lacking – the two do not fit together well. To conceive of the two as separate, rather than as two sides of the same coin, is to miss the point.

Against the background of this crisis, a novel life science research approach enters the stage, with the promise to establish a bridge between research and treatment. Environmental epigenetics shows a different way of framing both nature and nurture, and research and treatment: not as opposites, but as *interrelated*. It is a scientific knowledge formation that increasingly informs various biomedical research fields, such as toxicology, gerontology and psychiatry. The central environmental epigenetic hypothesis is: the way we live our lives influences the development of our organism on a molecular biological level. So-called environmental "exposures", which in fact are almost all aspects of our lives (nutrition, toxins, physical activity, etc.), are translated into molecular structures via epigenetic mechanisms (see chapter 1.3) and thereby influence our health and illness.

By proposing that the social relationships we form, the food we eat or the material environments that surround us can change our "inward laboratory" (Huxley, 1869, as cited in Landecker, 2011), environmental epigenetics is an approach that takes into account both biological aspects and social experience as crucial forces for human development. In other words, environmental epigenetics research assumes that it is *neither* nature *nor* nurture alone that determines our mental health. Instead, it conceptualises human life and illness as *biosocial* phenomena in which our molecular body structures and socio-material experiences merge (Meloni et al., 2016). The assumption that we are connected to our life-worlds in manifold ways is an intuition that has been upheld by many people and disciplines, psychology amongst them. There are already several more or less pronounced ideas about how our socio-material environment and social relationships influence our health, vitality and satisfaction. However, environmental epigenetics provides a mechanism to transform these intuitions into a science and to transform this science into practice by gradually deconstructing the nature/nurture dichotomy.

In the field of mental health, approaches from environmental epigenetics are used to study our mental development and to address the question of what constitutes our mental health and ill health. In this context, researchers predominantly focus on psychological stressors and conceptualise adverse human experiences such as trauma or maltreatment as exposures that leave "epigenetic traces" (Doherty et al., 2019) on our molecular structures. Neuroscientists, for instance, currently postulate that negative

events in early life, such as childhood abuse, increase the likelihood of mental illness in later life by altering our development as an organism on a molecular level (Yehuda et al., 2016). Regarding this link between childhood and adolescence, environmental epigenetic knowledge is considered to support a profound understanding of how individual developmental trajectories are "programmed" through the social contexts into which we are born (Murgatroyd et al., 2010). In this context, we can observe how approaches from environmental epigenetics currently reframe mental health research by re-conceptualising the causes for mental health conditions: our pasts, presents and futures are specifically connected through a series of "molecular events".

Moreover, environmental epigenetics guides us to rethink not only the relationship between nature and nurture but also the link between research and treatment. In that context, both scientific and public hopes are high that knowledge of the epigenetic "scars" that remain in our bodies after stressful experiences will further develop valuable insights into the mechanisms and treatment of complex mental disorders, such as depression (Peña & Nestler, 2018; Raabe & Spengler, 2013) – the most common mental disorder. Future visions of applying epigenetic knowledge range from the use of drugs to correct epigenetic "defects", to the prescription of physical exercise to exert beneficial effects by epigenetic processes, to the prevention of mental illness by identifying "abnormal" epigenetic changes (Peedicayil, 2014). The promissory rhetoric around environmental epigenetics therefore encourages some life scientists to regard this approach as "one of the spearheads" (Peedicayil, 2014, p. 960) in the proclaimed "war against mental illness" (Peedicayil, 2014, p. 960). Knowledge derived from environmental epigenetics is perceived as highly accurate because it provides research with the *molecular* mechanisms of our socio-material experiences – a knowledge that is regarded as better for linking research and treatment.

As we can see, the new environmental epigenetic paradigm changes biomedical research and, possibly, future practice as well. By seemingly giving as much space to the social as to the biological, it undermines the longstanding idea of biological destiny. This conceptual change nourished my scientific curiosity and this doctoral thesis. This curiosity finds its foundations in an earlier research project in which I investigated asylum policy issues within psychiatric practices (Samaras, 2019). During the work on this project I was already becoming aware of the relevance of questions such as how the rather elusive phenomenon of mental health is (or is not) grasped in different settings. During my fieldwork in a psychiatric outpatient's clinic for refugees, the Persian interpreter Iraj Mirza, referring to life after escape told me: "When all is lost, memory is the only thing you have left." This quotation powerfully illustrates that individuals who consult clinicians or psychologists about their mental health status are placing something deeply personal and valuable in the hands of institutions. Sometimes it is even the only treasure they have left. And sometimes it is also connected to their access to fundamental rights as they are enshrined in basic law: the patients' memories of their experiences are the basis

for obtaining a residence permit. Only those who have been medically diagnosed as traumatised may stay in the country they have fled to.[1] Given this context, the sentence quoted above also powerfully illustrates that environmental epigenetics potentially adds a new basis to this right, as it regards traumatic experience as having a molecular impact. Environmental epigenetics therefore has the potential to make trauma visible by transforming it from individualised memory into a set of measurable structures.

This curiosity about treatment and its implications led me to look at the production of this epigenetic knowledge – led me, so to speak, to the other side of the coin: in my doctoral thesis, I investigate psychiatric research practices that apply an environmental epigenetic perspective. My aim is to understand how research on mental health is informed by environmental epigenetics and how it is at the same time realigned along this novel epigenetic knowledge. This can be seen, for example, when it is used to introduce novel paradigms that guide research on mental health; how do these novel paradigms change how we scientifically *know* mental health? Based on twelve months of ethnographic observation and thirteen semi-structured interviews in a psychiatric institute that conducts environmental epigenetic research on mental health, my thesis asks the following: *how is environmental epigenetic knowledge both mobilised and produced in different research projects within a psychiatric research institute*? In this context, I argue that environmental epigenetic knowledge is a knowledge-in-the-making: on the one hand, it holds the potential to change the way we *know* and *do* mental health; the way psychiatric researchers conceptualise phenomena such as bodies, environments, or therapy. On the other hand, environmental epigenetic research practices themselves are open to adapt to the contexts in which they are applied, also influencing the scientists' very research practices.

In my thesis, I am critically concerned with environmental epigenetics as a novel way of *knowing* mental disorders. It is a knowledge that many hope will overcome old determinisms and stigmatisations, will raise public awareness towards the fact that the symptoms of mental health conditions – such as fatigue, weight gain, or social withdrawal – are not caused by a lack of willpower but by complex neurological and molecular processes in the body. There is a hope that it will reveal that people who suffer from mental health conditions are not imagining their illness and have not invented their mental state, but that there is a biology behind it that is located in the brain, that there is a biological change in the brain that is "real". However, new insights from environmental epigenetics also reveal new questions and blockages: what social, political and ethical consequences must we expect if we identify emotions and memories with biological labels? How will our society change if we perceive socio-material experiences as "molecular events"? Because knowledge is always related to

[1] For example, in Germany the diagnosis of post-traumatic stress disorder for refugees from certain regions, such as Bosnia-Herzegovina and Kosovo, is no longer a mere basis for suspending expulsion, but has become the main criterion for obtaining a residence permit (Birck, 2002).

power dynamics (Foucault, 1980; see also chapters 2.2. & 2.5.1), we have to hope that our society will not develop into one that finds novel vantage points for discrimination and stigmatisation based on biological difference and thus continues the eugenic heritage. I therefore hope that my dissertation will contribute to a profound social science analysis of new research paradigms introduced in the life sciences. In the first place, my analysis studies scientists' epigenetic research practices and addresses the question of how they access mental health in the laboratory using epigenetic research approaches. Besides the potentials of new environmental epigenetic knowledge for mental health care, my analysis also critically discusses the societal and scientific relevance of this knowledge, if it should become effective in practice: my work sheds light on the possible consequences of an eventual deployment of environmental epigenetics as a novel weapon in the "war on mental illness".

1.2 Outline of the thesis

Following the introduction to my research interest, in **chapter 1.3, *Setting the scene: how epigenetics got an environmental component***, I elaborate on my research topic by showing how environmental epigenetics has developed as a specific thought style in the life sciences and in psychiatric research specifically.

In **chapter 2, *From Genetic Determinism Towards a Theory of Relations***, I develop the conceptual and theoretical framework of my research. In the first part of this chapter, I discuss the general role between the life sciences, biotechnology, and society, and elaborate on theoretical contexts of Science and Technology Studies (STS) and neighbouring fields relevant to this relationship. I then focus on how approaches from environmental epigenetics entered the scientific arena and how STS scholarship responds to and engages with this novel life science perspective. The STS responses delineated in this section range from more enthusiastic reactions to environmental epigenetics that see it as providing a novel and promising reflexivity for conceptualising human life on one side of the spectrum, to rather cautious voices that observe reanimations of old, and the rise of new, determinisms on the other.

In the second part of chapter 2, I present STS approaches to psychiatry, which represents the specific field of biomedical research and intervention that is central to my thesis. I outline how environmental epigenetics as a specific knowledge culture increasingly informs psychiatric research and how STS scholarship has so far discussed the merits as well as rather detrimental consequences this development brings to the fore. At the end of this chapter, I discuss my research questions in detail and show how my thesis connects to earlier work from STS and neighbouring fields.

In **chapter 3, *Research Methods and Material,*** I contextualise my research approach towards emerging environmental epigenetic perspectives within psychiatric research. In so doing, I embed my research design within a constructionist and Grounded Theory approach towards social methodology

and theory, and provide insights into the research institute where I conducted my ethnography. I elaborate, in this section, on the proceedings of my fieldwork and empirical data collection and discuss the strengths and limitations of my research approach. I conclude this chapter with a reflective discussion on my own role as an observer within the research institute – a discussion I deem important in terms of accountability for my own research practice.

Chapter 4, ***Re-Enacting Stress in the Lab: Epigenetic Approaches Within Psychiatric Research,*** represents the first of my empirical chapters. It is structured around three different research arrangements that I observed in my field site: research with cell model organisms (Ch. 4.2), research with animal models (Ch. 4.3) and research with human tissue (Ch. 4.4). Based on these research arrangements, I show how the researchers' decisions for specific substances, experimental set-ups or research designs allow for both similar and different ways of enacting or articulating environmental epigenetics. In every subchapter, by highlighting specific researchers, their research projects and foci, I analyse in detail the different research practices emerging from their respective research interests and selection of experimental arrangements. I argue that scientists re-enact social categories (such as childhood abuse or maternal care) differently in these research arrangements. Hence, they produce different versions of environmental epigenetics. Furthermore, I will show how these versions also reveal a very nuanced promissory rhetoric about how mental health conditions can be better understood and treated.

While in chapter 4 I am predominantly concerned with the researchers' attempts and practices to conduct environmental epigenetics research, in my second empirical **chapter 5**, ***Environmental Complexity Across Different Research Arrangements,*** I deal with "environment" in two ways. First, I focus on the meaning of environment as a term and concept for environmental epigenetic research practices. I explore and summarise how researchers discursively conceptualise environment, what aspects of our human life-worlds they define and negotiate as crucial to the environment they simulate and how they relate potential epigenetic effects upon it. That is to say, in chapter 5 I am attentive to the elements that researchers operationalise in the laboratory's experiments by following specific research protocols where the general design and individual steps of experiments are described.

Second, I discuss the challenges of conducting environmental epigenetic research, which is by definition a research approach that clearly emphasises environmental impact on our molecular processes and bodies. In so doing, I explore environment as a phenomenon of scientific knowledge production that is not intended – in contrast to the systematic re-enactments of environmental factors discussed in the first part of the chapter. I will show how these unintended environments, such as a phenomenon outside the laboratory, may interfere with laboratory practices. More concretely, I take the example of the construction site in front of the research institute that emerged as an important additional field site during my fieldwork. The noise and vibration from the construction site had considerable effects on the scientists' research practices (specifically regarding experiments with mice). Thereby, the con-

struction site created a productive conceptual space for me to reflect on the very conditions in which environmental epigenetic research practices can be carried out and the challenges it may face due to elements that might be out of researchers' control: on the one hand, epigenetic research focuses on environmental factors as part of the epistemic object. On the other hand, the scientists' research practice itself is not immune to the influence of the environment that their laboratory may be exposed to.

It is based on these observations that I introduce the main concept of my work: *unintended environments*. I render it a conceptual possibility to take into account, to collect, and to negotiate environmental aspects that are not regularly made part of standard research practices such as measurements and testing protocols. Such environmental aspects nevertheless frame research experiments and thereby may have an impact on the way environmental epigenetic experiments are conducted and interpreted. Thus, I propose *unintended environments* as a concept that is helpful in reflecting on how researchers attempt to control their experiments by reducing environmental factors and yet, at the same time, are always confronted with environmental factors that disrupt their experiments in an unforeseen way. I conclude this chapter by discussing the different ways researchers attempt to regain control over their research in order to re-stabilise their environmental epigenetic accounts.

In the **discussion chapter 6** of this thesis, ***How Scientists Produce Bounded Imaginations***, I bring together and discuss the central threads of the preceding chapters by arguing that we can observe a divergence between scientists' imaginations of their research practices and their actual feasibility. I show that this divergence is mainly based on biology's notion of environment as a combination of predefined, fixed and topographic factors to be included in their research designs, while many other environmental elements remain unattended. By means of revisiting and extending my concept of *unintended environments*, I propose ways of responding to these challenges. I suggest that my empirical findings contribute vantage points from which to discuss, through an STS approach, the current conditions and challenges of scientific research practices that deploy environmental epigenetic approaches. Based on this discussion, I conclude this chapter by submitting possibilities as to how the laboratory as a space with its own infrastructures might be related to the world within which it is embedded, to the *environment* of which it is a part.

In my concluding chapter **7, *Environmental Epigenetics as a Specific Mode of Scientific Knowledge Production***, I open a dialogue between the key results of this thesis and the discourses on scientific responsibility and accountability of feminist STS literature, which draws on the idea that the scientific gaze is always based on deliberate decisions of what to include and exclude. Based on my discussion on *unintended environments*, I suggest that environmental epigenetics is a field that shows us that learning to live with indeterminacies instead of insisting on scientific certainty is important to the possibility of telling better technoscientific stories.

1.3 Setting the scene: how epigenetics got an environmental component

1.3.1 From a collection of biological curiosities to a dissected research field: basic epigenetic ideas and mechanisms

Until the early 1940's, the life sciences were faced with a mystery: "How can a single fertilized egg give rise to a complex organism with cells of varied phenotypes?" (Felsenfeld, 2014, p. 2) What was known to molecular biology at the time was that all of the cells of plants and mammalians, including humans, originate from one fertilised egg cell; they hence contain the same identical information. Nonetheless, these cells differentiate into more than two hundred different cell types with very diverse characteristics and tasks: human organisms for instance consist of heart muscle cells, which in their entirety are responsible for the contraction of the heart; of liver cells, which utilise, store, convert or break down substances we take in through our nutrition; or of blood cells which transport oxygen from the lungs to the various organs and tissues in the body (Slack, 2012).

Before the 1940's, some biologists, such as Barbara McClintock, already had the vague idea that there might exist some regulative mechanisms that ensure that: "identical genetic material can be maintained in different 'on' versus 'off' states in the same nucleus" (Allis & Jenuwein, 2016, p. 487). However, it was only with the introduction of epigenetics as a theory that these ideas developed "from a collection of curious biological phenomena to a functionally dissected research field" (Allis & Jenuwein, 2016, p. 487). The term "epigenetics" provided biologists with a concept and a language to describe the regulatory mechanisms for how identical genetic information contributes to the development of different cells and entire organisms. As I will show below, this regulatory information is stored by various mechanisms, such as DNA methylation, histone modification or modifications at the RNA level. In order for an organ to remain stable and reliably fulfil its tasks, these epigenetic changes are transferred from one cell generation to the next. Therefore, only heart muscle cells can develop in the heart muscle. These phenomena are described to take place "above" the genome (McEwen & Bulloch, 2019). This assumption is also inherent in the term's etymology: epigenetics is a word combination of the ancient Greek ἐπί ("epi") for "besides", "beyond", or "over", and genetics (Wu & Morris, 2001).

In general, we can observe a number of differently nuanced definitions developed to understand epigenetics and although the field has settled on the importance of epigenetics for human development as such, its power to explain specific phenomena (such as the inheritance of certain molecular or behavioural traits in humans) is highly contested. Despite such theoretical perturbations and uncertainties, British developmental biologist Conrad Waddington is referred to without exception as the

"pioneer" or "founding father" of the term "epigenetics".[2] In 1942, he coined the term to describe those mechanisms that lead to changes in the phenotype without altering the genotype. He introduced the "epigenotype" as a biological system in which "concatenations of processes [are] linked together in a network, so that a disturbance at an early stage may gradually cause more and more far-reaching abnormalities in many different organs and tissues" (Waddington, 1942, as cited in Deichmann, 2016, p. 249). To illustrate this network of possible phenotypic pathways, Waddington introduced an "epigenetic landscape" that is still widely cited today.

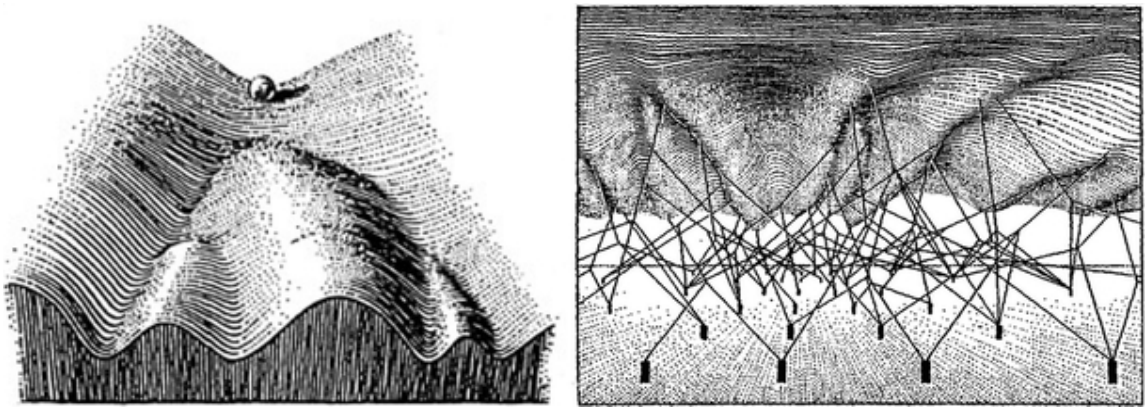

FIGURE 1. (left) The epigenetic landscape in its original drawing by Waddington (1940). It shows the possible developmental trajectories of a cell depending on its tissue environment. (right) A supplemental drawing (1957) that explains how this environment is itself build on complex genetic interactions (Bard, 2007, p. 409)

The epigenetic landscape is a visual metaphor for the development of a fertilised zygote into a mature organism, represented in the illustration by a ball. As proposed by Waddington's drawing, this developmental trajectory is influenced by the activity or inactivity of particular genes, determining the paths on which the ball moves through the epigenetic landscape. The underlying genes can be compared to stilts that structure the "landscape" by building branching ridges and valleys of different shape (Deichmann, 2016, p. 250). Waddington's landscape thereby provides molecular biology with a visual explanation of how cell differentiation proceeds from the embryonic phase to the adult organism in regulated pathways along genetically determined programs.

[2] In this context, it is of note that although Waddington is widely cited as one key representative of the early works on epigenetic processes, other scientists have made significant contributions to epigenetic research as well. Geneticist Herman Joseph Muller, for instance, observed that a specific type of Drosophila mutation leads to a different phenotype (Felsenfeld, 2014). Geneticist and botanist Barbara McClintock conducted seminal research in maize on variegation and so-called transposable elements, which describe DNA sequences of specific length that can change their location within the genome altering the cell's genetic identity (Fedoroff, 2012). Her work significantly contributed to a concept that today is known as "jumping genes", which "provid[e] early hints of non-Mendelian inheritance" (Allis & Jenuwein, 2016, p. 487) – that is, inheritance of specific marks that cannot be explained by the transfer of genetic information from two individuals to the next generation. Current epigenetic theories and scientific data can hence be regarded as continuous extrapolations of life science work on epigenetics that has been carried out since the early part of the twentieth century (Fleck, 1979; Felsenfeld, 2014).

In the following section, I will briefly delineate DNA methylation, histone modification and epigenetic regulation at the RNA level as three epigenetic mechanisms contributing to shape the epigenetic landscape. Today, molecular biology regards them as important, potentially heritable mechanisms that underlie cell differentiation by describing "mitotically and/or meiotically heritable changes in gene function that cannot be explained by changes in DNA sequence" (Riggs et al., 1996; Riggs & Porter, 1996, as cited in Felsenfeld, 2014, p. 2)

DNA methylation

DNA methylation is a mechanism of cellular differentiation and therefore widely referred to as being "of paramount importance for mammalian embryonic development" (Greenberg & Bourc'his, 2019, p. 590). In general, it is described as a molecular process in which a methyl group (-CH3) is covalently added to a base, which mostly is cytosine (C). In mammals, DNA methylation of cytosine can occur in any context of the genome (Jin et al., 2011; Lim & Maher, 2010). From a historical perspective, the discovery of DNA methylation was co-emergent with the identification of DNA as the genetic material in the middle of the 1940's (McCarty & Avery, 1946, as cited in Moore et al., 2013).

The first research that hinted to the relevance of DNA methylation for human development was provided by the chemists John Stanley Griffith and Henry Ralph Mahler in 1969. They proposed that DNA methylation and demethylation could be important biological processes for long term memory in the brain (Griffith & Mahler, 1969). Over the next decades, accumulating research by different biologists corroborated the assumption that DNA methylation can have fundamental effects on gene expression. It was also during this time that the metaphor of switching genes "on" and "off" during development was formed to refer to the demethylation or methylation of DNA. It was upon this foundation that certain biologists suggested a molecular model that explained how DNA methylation contributes to the activation and deactivation of genes and thereby influences gene expression (Holliday & Pugh, 1975; Riggs, 1975).

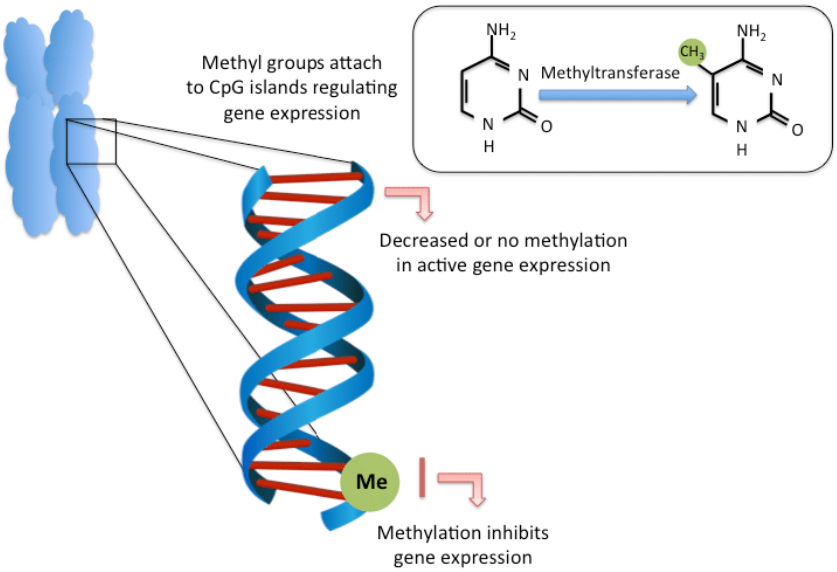

FIGURE 2. The methylation of cytosine nucleotides. Methylation occurs mainly on the 5th carbon of the cytosine base, forming 5-methylcytosine (Nevin & Carroll, 2015)

None of these early papers on DNA methylation and gene expression used the term "epigenetics" to conceptualise the relationship they described, presumably because the way it was defined and its research contextualised remained rather unclear, as Holliday (2006) speculates. Today, the important role of DNA methylation within the epigenome is undisputed and recognised as a common epigenetic signalling tool that cells use to block genes in the "off" position (Philips, 2008). High methylation leads to a repression and thereby prevents the reading of the DNA. As a result, the effected genes are not transcribed into protein.

As already stated above, DNA methylation is currently the most prominent and best understood epigenetic mechanism. Scientists describe DNA methylation as essential for cell differentiation, normal development, and ageing, so it can therefore be perceived as a "normal" process in organisms. Due to its critical significance in cell differentiation and gene expression, aberrant DNA methylation is, however, also associated with abnormalities and physical as well as mental diseases (Nagy & Turecki, 2012). Through such observations, scientists have developed the idea that DNA methylation patterns might provide valuable scientific information for understanding disease aetiologies. In that context, DNA methylation is framed as a quite easily managed research object and is hence one of the principle mechanisms investigated: "The vast majority of human research has been directed at DNA methylation as it is a more easily accessible epigenetic mark than histone modifications, allows for highly quantitative measurements, and can represent overall epigenetic status at a given site" (Cedar & Bergman, 2009, as cited in Park & Kobor, 2015, p. 590). DNA methylation is accessible in particular because the corresponding technologies necessary to study it have been developed: the introduction of the Illumina DNA methylation array, which is a screening tool for analysing genetic variation, is

widely reported to be a cornerstone in molecular biology that facilitated research on methylation patterns across the whole genome.

Histone modification

Alongside DNA methylation, histone modifications are described to "represent the classical epigenetic mechanisms" (Alhamwe et al., 2018, p. 1). Some papers use the more specific denomination of "histone post-translational modifications" (Greer & Shi, 2012) to subsume different covalent modifications of histones, such as acetylation, methylation, phosphorylation or ubiquitination (for a discussion of the basic effects of each form of modification see Alhamwe et al., 2018).

Histones are proteins that exist in the nucleus of eukaryotes. As they are part of the chromatin, the material which chromosomes are made up of, they are regarded as having a significant effect on the packaging of DNA: the DNA is tightly wrapped around the histone core. Due to this molecular architecture, modifications of histones are proposed to possibly affect the transcription of some genes. These modifications serve as regulators between histones and DNA, and are thereby considered to affect chromatin structure. Only in the last two decades has the role of histone modifications been described as an epigenetic "dynamic mark in health, disease and inheritance" (Greer & Shi, 2012, p. 343).

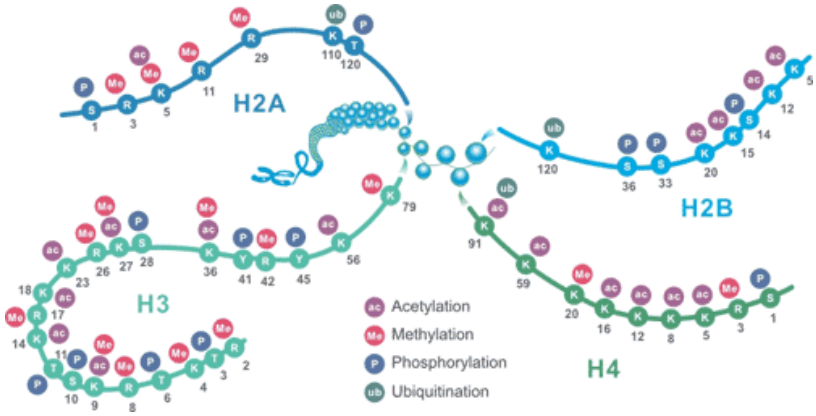

FIGURE 3. Schematic representation of some types of histone modifications (retrieved from https://www.cusabio.com/c-20829.html on 19.8.20)

Similar to DNA methylation, histone modifications are assumed to be able to influence the availability of the DNA nucleotide sequence "to the transcriptional machinery" (Alhamwe et al., 2018, pp. 1-2) without affecting the DNA sequence itself. Depending on the type of modification and on other biochemical characteristics, histone modifications can have repressive or permissive effects on gene transcriptional activity. Histone modifications are thereby reported to organise the genome into euchromatin, which are regions associated with the highest genetic activity, and into heterochromatin, areas in which hereditary information remains largely inactive. The scientific community seems to agree on the need for an "appropriate balance of stability and dynamics in histone PTMs [to be] …

necessary for accurate gene expression" (Greer & Shi, 2012, p. 343). This dynamic control in gene expression programs is meant to contribute to the maintenance of cell identity or to enable organisms to respond to stimuli. Much like DNA methylation, aberrant patterns in histone modifications are associated with potentially pathological health outcomes (Greer & Shi, 2012). This means that the regulatory functions of DNA methylation and certain types of histone modifications share characteristics. Indeed, DNA and histone methylation have been reported to be "highly interrelated [systems that] … rely mechanistically on each other for normal chromatin function *in vivo*" (Rose & Klose, 2014, p. 1362).

Epigenetic regulation at the RNA level

In general, RNA plays a central role in protein synthesis. As it is a nucleic acid, it exists structurally as a chain of many nucleotides (a so-called polynucleotide). As opposed to the double-stranded DNA molecules, RNA molecules are usually single-stranded. Both are polynucleotides in which the nucleobases (adenine, guanine, cytosine, uracil and thymine, in DNA) are linked to sugars (ribose for RNA; deoxyribose for DNA). The single-stranded quality of RNA, however, increases the number of possibilities for three-dimensional structures of RNA and allows it to build chemical reactions that are not possible for DNA. An essential function of RNA in the cell is the translation of genetic information from DNA into proteins. In the form of mRNA, for example, it is involved as an information carrier.[3]

Although post-transcriptional modifications of the RNA have been known to occur, their epigenetic effects have long been neglected (Qureshi & Mehler, 2018; Delpu et al., 2016). Recent research and preliminary studies in molecular biology, however, hint at their role as control systems that modulate genomic structure in human tissue, such as the nervous system. Today, they are thereby described as dynamically regulating global processes in the human body and possibly participating in the regulation of diverse physiological processes. Because of their ascribed importance in regulating the fates of cells and embryonic development, these changes are highlighted as "another layer of epigenetic regulations at the RNA level, where mRNA is subjected to chemical modifications that affect protein expression" (Yue et al., 2015 p. 1343). In this context, studies indicate for instance that lower expression patterns in the brain might lead to a higher risk of developing stress-related disorders (Engel et al., 2018). However, a profound biological mechanistic understanding comparable to that around DNA methylation and histone modifications does not yet exist (Qureshi & Mehler, 2018).

[3] More specifically, there are three different types of RNA with specific functions within the conversion of DNA into proteins: the messenger RNA (mRNA), the transfer RNA (tRNA) and ribosomal RNA (rRNA) (Clancy, 2008).

1.3.2 A farewell to genetic destiny? Environmental epigenetics and the emergence of a novel mode of thinking

Since the early 2000's, a new perspective has been added to the hitherto existing notions of how epigenetic processes can be understood: while in the early conceptualisations of epigenetics the "beyond" or "on top of" connoted by "epi" was predominantly related to the genomic location surrounding a gene, the scope for interpretation of what aspects might affect epigenetic processes is now much more broad. Today, a great deal of research has been conducted in order to prove an *environment's* power to affect epigenetic processes: environmental aspects such as toxins, nutrition, physical exercise or the experience of stress are described as influencing epigenetic profiles in specific cells, ultimately affecting gene expression in these cells. In other words, early versions of epigenetics were focused on the environments of cells, which were necessarily internal to the organism. Many current versions of epigenetics, however, focus on environments external to the organism as well (though not exclusively, as epigenetic changes caused by external environments may also affect epigenetic changes caused by the genomic location surrounding a gene). At present, genes and environments are understood to be interacting with one another. This further developed conceptualisation of epigenetics gave rise to novel terminologies to describe gene-environment interactions. Today, scientists commonly speak of "environmental", "social" or "behavioural" epigenetics to demarcate their research from Waddington's concept of epigenetics, which strongly builds on epigenesis – a term that describes the process by which organisms develop through a sequence of molecular steps.[4]

By proposing that our genes and environments interact, environmental epigenetics leads to the formation of a novel mode of thinking within the life sciences: molecular structures are rendered as specifically open to different contexts. The most important aspect of this novel thought style (Fleck, 1979) is that it is seen as offering a counter-concept to genetic determinism, a life science perspective that persisted as the leading theory for many years. The twentieth century was dominated by research approaches that targeted the question of how the molecular makeup that we receive at conception influences or even determines our health and disease throughout life. Therefore, much life science scholarship has focused for decades on research approaches seeking explanations for common human pathologies, such as cardiovascular or metabolic diseases. Such "gene-for" approaches were thought to identify the *one* gene that in each instance would lead to cancer or depression but were ultimately harshly disappointing, as human pathologies turned out to be far more complex than this perspective would imply. Humans, it became clear, are more than the sum of their genes.

[4] The idea of epigenesis was already articulated by Aristotle and finally coined by the physician and physiologist William Harvey around 1650, "for the conception of development as a gradual process of increasing complexity from initially homogeneous material in the egg" (Deichmann, 2016, p. 249). As Felsenfeld (2014) delineates, until the 1950s the term epigenetics was used in a broader and less narrow manner to denote "all of the developmental events leading from the fertilized zygote to the mature organism – that is, all of the regulated processes that, beginning with the genetic material, shape the final product." (p. 2)

Environmental epigenetics, in contrast to genetic determinism, takes a different perspective on human life. By exploring specific biological pathways, it promises to elucidate how socio-material factors interact with our genome and even are translated into bodily changes on a molecular level, impacting our trajectories of health and disease alike. That is to say, environmental epigenetics widely dismisses the assumption that our body is a molecularly sealed system and instead conceptualises the body as malleable by the environments it inhabits; a body whose boundaries are not closed, but porous; a body in flux that is in close conversation with its environments. The environmental epigenetic body, therefore, is "biosocial". By investigating the gene-environment interactions of human bodies, environmental epigenetics is hence positioned as a field which could help to develop a better understanding of how living conditions and environmental influences regulate human development, possibly leading to better therapies.

Today, environmental epigenetics is a research perspective that informs many different biological and biomedical research fields, such as nutritional sciences, developmental sciences, and psychiatric research. The increasing knowledge of epigenetic mechanisms leads to novel research questions, which are investigated in novel research arrangements. With an environmental epigenetic perspective, scientists now build their experiments around social categories, among them the experience of stress, parental care, or dietary habits.

In this context, it is important to mention that epigenetic modifications are currently described to be potentially inheritable. Several studies indicate that epigenetic changes may not remain restricted to the individual who makes the experience, but could possibly affect the generation proceeding them. As I will show below, these novel assumptions from environmental epigenetics extend current theories of heredity. While biologists described heredity until recently as a form of genetic inheritance through recombining parts of the genome of two individuals (parents), known as Mendelian inheritance, environmental epigenetics indicates that epigenetic reactions to environmental experiences may also be passed on via two pathways.

First, some studies from environmental epigenetics suggest that gestation is a period in which the exposed individual's (the mother's) experiences may also affect the foetus, altering its epigenome and thereby developmental trajectories. This process is termed "intergenerational epigenetic inheritance". The concept of intergenerational epigenetic inheritance is embedded in the research field of the Developmental Origins of Health and Disease (DOHaD). This biomedical approach emphasises the role of prenatal and perinatal exposure to environmental factors, such as undernutrition during these periods as a determining component in the development of human diseases in adulthood. In this context, two studies from environmental epigenetics are considered to deliver molecular proof both of the existence of such hereditary pathways and of the ways nutrition can affect our bodies molecularly.

The first study was conducted in 2003 by molecular geneticists Robert Waterland and Randy Jirtle in a rodent experiment. They worked with so called "viable yellow agouti mice" to show how a dam's nutrition can affect her offspring's phenotype concerning fur colour and other physical characteristics. The viable yellow agouti mouse is a mouse line that is genetically modified for the laboratory and is used to study metabolic conditions. The agouti gene is responsible for the distribution of melanin pigments in mammals. While in the wild type mouse the agouti-allele presents a grey phenotype, many allele variants have been identified, for instance the yellow mutation. Though this mutation makes mice viable, it is associated with pathological phenotypes, such as adverse metabolism, obesity, and tumorigenesis – all phenotypes that are transmitted to the offspring. Waterland and Jirtle fed their pregnant viable yellow agouti mice a diet that was supplemented with extra nutrients such as folic acid and vitamin B12 and observed a phenotypic change in the offspring: the new-borns were rather small, of brown colour and healthy. The scientists used the term "pseudoagouti" to describe animals in which agouti gene expression is silenced in the vitamin-dosed mothers' pups. In their paper, Waterland and Jirtle speculate about the translational potential of their mouse study for human development: "These findings suggest that dietary supplementation, long presumed to be purely beneficial, may have unintended deleterious influences on the establishment of epigenetic gene regulation in humans" (Waterland & Jirtle, 2003, p. 5293).

Today, sixteen years later, the study is still referred to as giving molecular proof for the connection between gestational nutrition and later life health outcomes. Also, the agouti mouse model still is a prominent experimental arrangement in a field called "nutriepigenomics", the discipline that links epigenetics and gestational and lactational nutrition to non-communicable diseases. Against this backdrop, the agouti mouse model is regarded as "an epigenetic biosensor for nutritional and environmental alterations on the fetal epigenome" (Dolinoy, 2008, p. 7). Despite its success, Jirtle's and Waterland's study was also received with a certain degree of caution by some representatives of the scientific community: as the model was criticised for being a mutational model organism, some scientists challenge its validity for epigenetic research.

The second study was conducted by DOHaD researcher Bas Heijmans and colleagues. In 2008, they published a study in which they related a historical event to health outcomes in a specific group of people. In this research, known as the "Dutch Hunger Winter study", scientists conceptualised the offspring of those who experienced severe hunger during the winter of 1944 as an epidemiological cohort.[5] By framing these individuals as having been "prenatally exposed to famine" (Heijmans et al., 2008, p. 17046), Heijmans and colleagues studied the epigenetic effects of early malnutrition. They observed a lower birth weight and relatively high vulnerability to specific mental and physical disor-

[5] In the winter of 1944, the western part of the Netherlands suffered from an extreme food shortage, which was connected to the very cold winter and in conjunction with a German food embargo (Heijmans et al., 2008).

ders in the Hunger Winter offspring, that is, those individuals who were exposed to undernutrition in utero. As regulatory explanation, the authors suggested a specific epigenetic mechanism, namely "less DNA methylation of the imprinted *IGF2* gene" (Heijmans et al., 2008, p. 17046), a protein that is described to play an essential role in growth and development before birth. By conceptualising the maternal womb as an epigenetic environment, the scientists operationalise the Hunger Winter as an event "to study effects of undernutrition during gestation in humans" (Roseboom et al., 2001, p. 94).

Furthermore, other studies claim that epigenetic changes could possibly be passed on from generation to generation via the germline through a process known as "transgenerational epigenetic inheritance" (Anway et al., 2005; Hanson & Skinner, 2016). In 2005, developmental biologist Michael Skinner and his colleagues provided a proof of concept experiment in a rodent model experiment. The initial interest of their study came from the knowledge that some treatments – among them chemotherapy – and environmental toxins "pose a threat to the integrity of the genome", leading to "genetic or developmental defects in the offspring … from an exposed gestating mother" (Anway et al., 2005, p. 1466). To study these effects, the researchers exposed pregnant rats to vinclozolin, a chemical that is a known endocrine disruptor, to study sexual differentiation in their embryos. Unexpectedly, Skinner and his colleagues could observe sustained effects not only in the second but still in the third generation of the rats. They base this finding on the reprogramming of the male germline, thereby showing that environmental factors can induce an epigenetic transgenerational phenotype. In their conclusion, the authors thereby state: "The ability of an environmental factor (for example, endocrine disruptor) to reprogram the germ line and to promote a transgenerational disease state has significant implications for evolutionary biology and disease etiology" (Anway et al., 2005, p. 1466).

Despite the fact that Skinner's work is still heralded by many scientists as the first proven evidence of transgenerational epigenetic inheritance, it has not been spared criticism either. In the first place, criticism of the study targets experimental arrangements that are not considered to be representative of the human world. For example, the extremely high concentration of the chemical used in the experiment was criticised for not being a realistic epigenetic exposure in the human world. Epigenetic inheritance in the human context via the germline phenomenon is therefore still scientifically disputed (Heard & Martienssen, 2014).

1.3.3 Environmental epigenetics as a novel research perspective in psychiatry

1.3.3.1 The "maternal programming paper": a spark for the emergence of environmental epigenetic approaches in psychiatry

In psychiatric research, approaches from environmental epigenetics have been integrated mainly through a single study, one that generated excitement, quickly attained prominence, and was by no

means free from critique. With their paper on "Epigenetic programming by maternal behavior" the Canadian-based scientists Moshe Szyf, Michael Meaney and others (2004) are described as having shown evidence for the reprogramming of genes via changes of DNA methylation in response to differences in nurturing behaviour or the upbringing of individuals. In this experiment, the McGill University scientists invested in exploring how certain aspects of a mother rat's behaviour are linked to their offspring's phenotypes. To make their experiment feasible, the researchers subsumed specific forms of caring behaviour in rodents as "maternal care": "licking", "grooming", and "arched-back nursing" were all grouped under maternal care. They then operationalised this paradigm as a mechanistic-molecular phenomenon, namely an epigenetic environment. Their scientific gaze focused on observing how the quantity of caring behaviour – that is, of licking, grooming and arched-back nursing – performed by the rat mother forms the offspring's epigenetic profiles in genetic regions associated with brain development. These epigenetic changes can affect gene expression and as a consequence thereof the number of glucocorticoid receptors in the brain, glucocorticoid being a protein related to the genetic regulation of development, metabolism and immune response (Weaver et al., 2004).

In their study, the McGill group treated "maternal care" as a quantifiable variable by observing which mother rat licked and groomed their pups more or less. Then, the scientists categorised the offspring accordingly into offspring of high- versus offspring of low-licking mothers and investigated their behavioural response to stress. Additionally, the researchers dissected and examined the pups' brains for epigenetic and genetic differences. On that basis, Szyf, Meaney and their colleagues argue that a lower number of glucocorticoid receptors alters stress response and thereby leads to more anxious and aggressive behaviours in the offspring. This change is said to "program" offspring behaviour, as it is believed to remain stable throughout their lives. In sum, the paper centrally postulates that the offspring of "high-LG-ABN mothers" are epigenetically "better prepared" for responding to stressful situations as adult mice, based on differences in DNA methylation patterns (Weaver et al., 2004).

Finally, the programming metaphor gave rise to the early-life paradigm, which draws attention to the significance of early-life experiences that determine the course of development throughout life, not only in psychiatric research but in many other life science research fields as well (Murgatroyd et al., 2010; Hoffmann et al., 2017). In this context, the early-life period comprises prenatal, postnatal and, recently, even pre-conceptual phases in an individual's life that are framed as periods with the highest level of (neuro)plasticity. These developmental phases are conceived of, on the one hand, as "critical" or "sensitive" time periods in which negative environmental factors may lead to pathologies in adulthood. On the other hand, scientists conceptualise these phases as "windows for opportunities for primary prevention of environmentally induced disease either through removal of the adverse exposure(s) or implementation of countermeasures" (Ho et al., 2012, p. 299), with specific nutritional

treatment counting amidst such exposures or countermeasures. This means that early stages of life are understood to be both pathogenic and protective under certain circumstances. In sum, it is a paradigm that has gained so much importance that some scientists relate it to a separate sub-field of research: "*Social epigenetics* is the study of the molecular mechanisms by which early-life experiences influence gene expression and have persistent effects on human physiology and health" (Park & Kobor, 2015, p. 89).

As already mentioned in the beginning of this section, the maternal programming paper generated polarising reactions. On the one hand, it is seen as having propelled epigenetic knowledge and research like no other study: this paper and the other work conducted at McGill University still have a pioneering significance for the field of psychiatric research. The 2004 paper is heralded as *the* proof of concept experiment showing that early experience can have lifelong effects. Although the link between early-life experience and health outcomes in later life was a known phenomenon in psychiatry (Brückl & Binder, 2017), it was only with the epigenetic work of Szyf and Meaney that the field was furnished with a molecular mechanism to understand and mechanistically describe this connection. This enthusiasm is also reflected in figures: with almost 6,000 citations, it is one of the most frequently cited articles in epigenetic research. On the other hand, STS scholars in particular gave voice to a more cautious reception, referring to certain critical aspects of the paper and the way the authors partly interpreted the results of their study to translate it into the human context (see chapter 2.5.3).

1.3.3.2 Can trauma be inherited? Environmental epigenetics, psychiatry, and notions of inheritance

In psychiatry, several different hypotheses regarding how traumatic experiences are passed on from one generation to the next pre-existed the rise of environmental epigenetics. Several disciplines, among them psychology, study the possible pathways this transmission can take. In this context, social and environmental aspects have been predominantly discussed as giving explanation to the effects of traumatic experience being passed on to offspring (Kellermann, 2013). Such social and environmental aspects include parenting style, for example, which most notably plays a role in the so-called "cycle of abuse" – a psychological concept that explains that parents who have experienced domestic violence may also show violent behaviour towards their own children (Walker, 1979). As we will see below, in the same field of research, approaches derived from environmental epigenetics have led some researchers to re-orient their scientific gaze which has given rise to new theories around hereditary components of violent experience or persecution.

Neuroscientist Rachel Yehuda and colleagues (2016) sampled Holocaust survivors as an epidemiological cohort to investigate the epigenetic pathways of severe trauma experiences and their intergenerational effects. They conducted epigenetic analyses of the FKBP5 gene, a gene that is associated with

immunoregulation. As this gene is related to the human stress response, changes in it are described as being involved in various stress-related disorders, such as depression. The authors compared different methylation patterns in this gene in "exposed" and "control subjects": Holocaust survivors and their adult offspring on the one hand and demographically comparable parents and their offspring on the other hand.

With their study, the authors argue that they deliver the "first demonstration of an association of preconception parental trauma with epigenetic alterations that is evident in both exposed parent and offspring, providing potential insight into how severe psychophysiological trauma can have intergenerational effects" (Yehuda et al., 2016, p. 372). According to the authors, these intergenerational effects can make offspring more vulnerable to stress, a result which the authors describe as the most central contribution of their study. They relate this conclusion to their main finding that Holocaust survivors and their offspring have methylation changes on the very same location in the FKBP5 gene. After further research on this phenomenon, they went on to state that they have ruled out the possibility that these epigenetic changes in the offspring are consequences of their own childhood experiences.

Neuroscientist Isabelle Mansuy and colleagues (2010) suggest another pathway of the transmission of traumatic experience. Through research with mice, the researchers have explored how epigenetically fixed environmental adaptations in mammals can also be inherited by future generations, that is, transgenerationally. Therefore, they have isolated mice pups from their mothers for three hours a day for the first two weeks of their lives, implementing a stress paradigm known as "postnatal maternal separation" (Franklin et al., 2010). Thereafter, the researchers observed depression-like symptoms in the animals throughout their lives. This result is not new and is attributed to an epigenetically induced increased susceptibility to stress. However, Mansuy and colleagues also found that the offspring of the affected male mice initially exposed to postnatal maternal separation showed some of the same symptoms as their fathers, even into the third subsequent generation and even though they were reared completely normally.

The assumption that early childhood stress experience can be inherited via epigenetic mechanisms is supported by another finding: Mansuy and colleagues also found some of the typical changes to the DNA methylation pattern in the sperm of the "traumatised" mice. They argue that "these findings are the first to demonstrate that postnatal stress in mice can persistently affect behavior across generations and DNA methylation in the germline" (Franklin et al., 2010, p. 414). Moreover, the Zurich-based research group believes that it is likely that their results can be transferred to humans, as the "behavioral defects induced by MSUS[6] in our model are reminiscent of several neuropsychiatric diseases in human" (Franklin et al., 2010, p. 413). That is to say, translating these epigenetic insights to the

[6] Abbreviation for the stress paradigm of unpredictable maternal separation combined with unpredictable maternal stress.

human context would re-conceptualise trauma as a chemical coating upon an offspring's chromosomes; as a form of "biological memory of what the parents experienced" (Kellermann, 2013, p. 33).

Despite all the clarity that these studies deliver in the experimental set-ups with rodents, the assumption that epigenetically fixed environmental adaptations can also be passed on to future generations in humans remains highly controversial. Similarly, these studies have been partly received with strong reservations by scientists of the same research field. For instance, critique of the study of Yehuda and colleagues first targeted the robustness and plausibility of the applied biology. On the blog of the Center for Epigenomics at the Albert Einstein College of Medicine in the Bronx, New York City, the paper is ranked as the "over-interpreted study of the week". Among other points, epigeneticist John Greally criticises the authors for neglecting confounding molecular processes which, if taken into account, would make the study uninterpretable – a problem that, according to him, would be "pretty typical" for many environmental epigenetics studies today (Greally, 2015).

In this context, it is important to mention that, in psychiatric research, epigenetic studies are always characterised by methodological challenges as well as by some degree of uncertainty. The brain, as an important epistemic object of psychiatric research, cannot be accessed on its molecular level in the living human. Therefore, the field reverts to cell and animal models or uses peripheral human cells, such as blood or saliva as a proxy. However, results from cell and animal model experiments first have to be translated to the human context and, even if mice and humans share 99% of their genes, we find great differences in social and life forms between mice and humans; this is translated, in the researchers' object of study, the environment. In addition, epigenetic changes appear to be highly cell specific: methylation patterns in neurones have regulatory effects beyond methylation patterns in blood or saliva. Therefore, it is important to ask what insights methylation patterns of peripheral cells can deliver for the development of neurological and brain structures. How accurately can brain processes be represented in the blood?

What we can therefore observe is that, despite providing seemingly powerful theories of how our bodies are interacting with our lifestyles, research in environmental epigenetics is also very much characterised by several epistemological challenges that might result in analytical ambivalences. Environmental epigenetics is therefore still a more or less vague object, a knowledge-in-the-making that, with the accumulation of research, may achieve new levels of importance and, furthermore, may change.

2 Conceptual and Theoretical Grounding: From Genetic Determinism Towards a Theory of Relations

We live in a *knowledge society* – a society that is characterised by a "penetration of all its spheres of life by *scientific* [emphasis added] knowledge" (Böhme & Stehr, 1986, p. 8). This "scientization" of society, already proclaimed by sociologists of science Gernot Böhme and Nico Stehr in 1986, is a phenomenon we can still observe today, more than 30 years later. Disciplines such as the Philosophy of Science or Science & Technology Studies address the relationship between science and society and recognise science, technology and society as being in an intertwined relationship (Hackett et al., 2008; Beck et al., 2014). Acknowledging science and society as entangled phenomena opens up a variety of different social science research endeavours that target everyday life phenomena. This scientific perspective generates research sites that range from the architectural design studio to the political institution to – as in this thesis – the biological laboratory, in which elements of our lives such as diseases are investigated (Beck et al., 2014). Such STS scholarship on knowledge infrastructures always takes into account their repercussions for science and/or society.

Given this context, we can observe that since the twentieth century, biology and the life sciences have gained great societal and political dominance in explaining human life. The "truths" produced in these disciplines are often regarded as incontestable (Beck et al., 2014) and contribute to processes of social order in everyday life. In the following section, I give an overview of studies from sociology and STS that describe and investigate this relationship between the life sciences and society with a specific focus on biomedical and genetic research. In this vein, I first (Ch. 2.1) focus on STS's key assumptions of life science and society as intertwined phenomena, providing us with a relationship from which we can learn about science and society. Thereafter, I elaborate on processes of *medicalization* and (novel) forms of biopolitics as central concepts arising from the analysis of biomedical knowledge penetrating our contemporary Western societies (Ch. 2.2.). The following subchapter (Ch. 2.3) outlines a scientific paradigm shift that led to increasingly address the environment in life science research. In subchapter 2.4 I will outline STS responses to environmental epigenetics which represents an emerging thought style within the aforementioned new life science research approach.

Thereafter, I turn to social science research on psychiatric approaches (Ch. 2.5) as a specific way of *researching* and *knowing* both bodies and the mind. Here, I retrace how we came to know mental health predominantly "as brain kind of thing" (Rose, 2019, p. 10), which is a development that turned mental health conditions into a central life science research object (Ch. 2.5.1 – Ch. 2.5.2). Finally (Ch. 2.5.3), I will discuss how epigenetic knowledge is informing research on mental health conditions and what important and constructive research questions arise from this disciplinary development. Towards

the end of this chapter, I will outline my own scientific research questions that guided me through my ethnography and analysis (Ch. 2.5.4).

2.1 Science and society as entangled phenomena

In his seminal book *Genesis and Development of a Scientific Fact* (1979; originally published as *Entstehung und Entwicklung einer Wissenschaftlichen Tatsache* in 1935), the Polish physician and molecular biologist Ludwik Fleck was one of the first to focus on the production of scientific knowledge as a *practice* rather than a logical structure. By highlighting in particular the relationship between science and society, he developed different concepts describing the very conditions of scientific knowledge production. Following Fleck, scientific knowledge is produced within *thought collectives*, instead of by single genius scientists; these thought collectives in turn share a distinct *thought style*. Additionally, he introduced the notion of *proto-ideas*, which precede the formation of scientific facts. He describes these *proto-ideas* as pre-scientific ideas that reveal the coherence and interrelationship of knowledge conceptions that emerge during different epochs. With these concepts, Fleck defines scientific cognition as a historical process and acknowledges the contingency of scientific facts.

One of his arguments is particularly strong in STS research today: the idea that knowledge production is always socially conditioned. As Fleck (1979) writes, "cognition is ... not an individual process of any theoretical 'particular consciousness.' Rather it is the result of a social activity, since the existing stock of knowledge exceeds the range available to any one individual" (p. 38). Acknowledging scientific knowledge production as a thoroughly social process allows us to consider the cultural and historical environments in which science and scientists are embedded as formative for scientific practices themselves. Such notions regarding the relationship between science and society, as one of Fleck's core arguments, are, among other ideas, concepts that social science research on scientific knowledge production has taken up. It even presents the relationship between science and society in a completely new light: the dichotomy of these two spheres has become increasingly permeable.

Many STS scholars have developed similar ideas, especially with respect to our increasingly technologised societies and daily lives. Today, STS emphasises even more radically that science, technology, society, *and* politics are entities influencing each other in manyfold ways. STS scholar Sheila Jasanoff (2004) conceptualises this mutual relationship as processes of "co-production":

> Briefly stated, co-production is shorthand for the proposition that the ways in which we know and represent the world (both nature and society) are inseparable from the ways in which we choose to live in it. Knowledge and its material embodiments are at once products of social work and constitutive of forms of social life; society cannot function without knowledge any more than knowledge can exist without appropriate social supports. Scientific knowledge, in particular, is not a transcendent mirror of reality. It both embeds and is embedded in social practices, identities, norms,

> conventions, discourses, instruments and institutions – in short, in all the building blocks of what we term the *social*. The same can be said even more forcefully of technology. (pp. 2–3)

Understanding science and technology as embedded within society conversely means that social and political conditions *permeate* processes of knowledge production: the ways we produce knowledge are shaped by societal contexts, and in turn shape society. Science and technology production thus appear as a social process that can also be researched as such. Understanding science as open to social science investigation is particularly important today, in our *knowledge societies*, as many current social phenomena and processes are ordered through science and scientific knowledge.

This is especially the case with regards to modern biomedicine and the life sciences. These scientific disciplines have a decisive influence on how we think about the body, disease, health, and the environment. Given this influence, knowledge from the life sciences shapes how we imagine life itself and also frames what we perceive as "healthy", "right", or "normal" life. Against the background of the increasing approaches to explaining our lives and behaviours within a biomedical framework and rationale, philosophers and social scientists have developed crucial concepts about the societal impact of such explanations of human life. I will turn to these concepts as theoretical frameworks of this thesis in the following subchapters.

2.2 From healing to controlling to optimising? *Medicalization* and the expansion of medicine

Diseases known to us today are not *eo ipso* a medical problem. In the first place, they are human phenomena that can be interpreted and negotiated by science and society in different ways. A sociological perspective on depression might for instance foreground its social, structural and/or economic causes and effects instead of regarding it as a form of chemical imbalance in the brain. Of course, decisions about how we can *know* diseases influence the ways we deal with, solve and control these problems. Emerging or newly described phenomena, such as attention deficit hyperactivity disorder (ADHD) in children or post-traumatic stress disorders (PTSD) in veterans are examples of conditions that have been *made* medical. Similar developments can be observed with more "ambiguous" phenomena, such as alcoholism, homosexuality, or acne, which were subject to a long process of negotiation until they were named and partly renamed as medical problems (as compared to, for example, homosexuality, which today is no longer rendered a disorder but is accepted as sexual orientation). Such historically contingent processes of transforming elements of human life into medical events are conceptualised as *medicalization* (Conrad, 1992; Zola, 1972), a process through which problems are rendered as medical and no longer as social or structural problems, therefore giving medicine a significant amount of social control (Zola, 1972).

In general, processes of *medicalization* are supported by an increasing degree of mechanisation of science and society. Since the end of World War II, the role of medicine in society has undergone significant changes. These can be described as social transformations, as they altered not only ways of thinking about and handling human conditions, but also notions through which life as such is understood: medical explanatory power expanded to aspects and phenomena of social life that heretofore were administered by other institutions, such as religion or law (Clarke et al., 2003). Such a shift in defining social phenomena also affects their ontological status. Today, alcoholism and homosexuality are prominent examples that illustrate how human behaviour previously deemed as morally reprehensible was put under the realm of medical jurisdiction, transforming them from "badness [in]to sickness" (Conrad & Schneider, 1980).

Keeping in mind the ongoing technologisation of science and society, sociologist Adele Clarke and colleagues (2003) argue that today, medical jurisdiction has undergone yet another transformation: highly techno-scientific innovations, such as molecular biology, have led to an increasing reorganisation of medicine that the authors describe as *biomedicalization*. They describe this shift as a series of "complex, multisited, multidirectional processes of medicalization that today are being both extended and reconstituted through the emergent social forms and practices of a highly and increasingly technoscientific biomedicine" (Clarke et al., 2003, p. 163). The shift from *medicalization* to *biomedicalization* is an analytical shift from medicine exerting clinical or social control over human conditions to a technoscientific biomedicine which has the power to *transform* bodies and lives and, therefore, *life itself* (Rose, 2007). Following Clarke et al. (2003), this shift was made possible through innovations that harness and transform the "internal nature [of organisms] (i.e. biological processes of human and nonhuman life forms)" (p. 164). Walking with the help of prostheses or the removal of specific genes in non-humans are only two examples that illustrate this expansion of biomedical opportunities since the mid 1980's.

The progression of *biomedicalization* and the related development of biomedical innovations go hand in hand with social implications for individuals and for society as a whole; implications that can be both supportive and harmful. On the one hand, thinking and conceiving of phenomena in medical ways clarifies institutional responsibilities and defines courses of action. On the other hand, it gives medicine a monopoly on social control. This monopoly in turn grants medicine a huge explanatory and regulatory power over life and runs the risk of undermining the authority of alternative approaches towards the phenomenon at stake, among them social or structural explanations. Thus, a state guided by medical knowledge exercises a specific form of power and control over those who are governed by regulating processes of life by for instance defining the boundaries between pathological or deviant behaviour (Canguilhem, 2012; e.g. ongoing negotiations on whether paedophilia should be conceptualised as mental disorder, as a sexual orientation, or as a criminal offence).

With his micropolitical analyses of power and knowledge, the French philosopher Michel Foucault (1980) has made an important contribution to our understanding of how constellations of power, similar to those described above, are reproduced or changed. His well-known and central thesis suggests a change in how political authorities, in alliance with other actors, exercise power over people: he argues that for many centuries, one of the privileges of sovereign power was the right to either allow life or impose death. "This was the juridical form of sovereign power – the right of a ruler to seize things, time, bodies, ultimately the life of subjects" (Rabinow & Rose, 2006, p. 1). Since the eighteenth century, however, the organisation of and concern for life has shifted to the centre of politics. Instead of deciding between life and death, the modern model of power applies mechanisms through which living bodies and beings are subjected to a different political power and control, which Foucault terms *biopolitics*. With this concept he describes a mode of politics whose targets are the life of the population and the biological processes that permeate this group of people. That is to say, *biopolitical* practices seek to regulate and normalise living individuals and populations. Foucault complements his concept of *biopolitics* with the concept of *biopower*, which conveys an understanding of power that primarily not only forbids and restricts, but can also be productive and can be designed to enhance life. *Biopolitics* thus implies an ambivalent form of exercising power, which can be both caring and controlling (Foucault, 1980; Folkers & Rödel, 2015).

The development of such biopolitical practices is inseparably linked to the advancement of the life sciences and clinical medicine: novel biomedical opportunities may reframe normal phenomena of human life as undesirable and render them medically solvable. Thereby, through processes of *medicalization*, medical *biopower* is expanded to areas of *health*, in addition to illness and disease. This expansion of medical jurisdiction beyond the boundaries of healing diseases ultimately leads from control (*medicalization*) to optimisation (*biomedicalization*) of specific phenomena. This development, also termed *enhancement* (Clarke et al., 2003), moves normal behaviour and physical conditions towards disorders in need of therapy (Wehling et al., 2007). This reinterpretation of phenomena can be observed and understood very well with the example of ADHD: previously understood as an, albeit undesirable, expression of behaviour, the concept of ADHD is today used to diagnose and treat a specific behaviour in children.

Rendering social difference as medical problems treatable with biomedical innovations (Goffman, 1963) also gives rise to aspirations to stratify populations into different risk groups. This becomes visible above all through novel strategies for the diagnosis of (hereditary) diseases on the basis of genetic tests which render individuals as particularly susceptible to diseases based on kinship – such as is the case with hereditary breast cancer (Felt & Müller, 2011) or experience, such as trauma that may lead to PTSD. Risk in this context increasingly becomes an "illness category in and of itself" (Fosket, 2004, p. 294). This reinterpretation is particularly supported by a focus on the gene as a core explana-

tory concept of development in the twentieth century. Known as the "century of the gene" (Fox Keller, 2009), this era on the one hand was accompanied by great social and medical hopes and on the other hand has contributed to the emergence of new socio-political implications engendered by novel notions of health, disease and social life.

2.3 From genetic determinism towards a relational view of life

The twentieth century was characterised by a re-orientation of research and everyday thinking: the gene has increasingly become the focus of attention as a means of explaining diseases and human behaviour. As historian of science Evelyn Fox Keller writes: "Genes have had a glorious run in the twentieth century, and they have inspired incomparable and astonishing advances in our understanding of living systems" (Fox Keller, 2009, p. 147). Besides Fox Keller, many social scientists and philosophers have tried to understand and recount the success story of the gene and its societal implications from a contemporary perspective (e.g. Beurton et al., 2000; Kay, 2000; Nelkin & Lindee, 2010).

From a historical point of view, the progression of biology as we know it today is closely tied to the history of how life is envisioned: the invention of novel research techniques to access and describe life phenomena also allowed for the development of novel perspectives from which to interpret these phenomena (Kay, 1992). For instance, novel imaging tools enabled novel ways of interpreting our brain's architecture and the technical progress in microscopy gave researchers access to micromorphological body structures. Historian of science Lily E. Kay states that these technologies even gave rise to a "new" biology that "endow[ed] scientists with unprecedented power over life" (Kay, 1992, p. 3), today known as molecular biology. This biological approach was new in the way that it reoriented the life science gaze towards the function of DNA and RNA from a *molecular* research perspective; a perspective propelled by a "reorganization of ... institutions, procedures, instruments, spaces of operation and forms of capitalization" (Rose, 2007, p. 44). Following British sociologist Nikolas Rose (2007), this molecular gaze as a way of regarding life to a great extent changed the scale on which human phenomena were studied. In the nineteenth century life phenomena were mostly described by approaching the body as "a vital living system, or a system of systems" (Rose, 2007, p. 43). The discovery of the structure of DNA by Francis Crick and James Watson in 1953, however, was one of the most important events that propelled the reorganisation of biology into an information science. From this point on, the following dogma has long been valid: "a gene is a sequence of the DNA nucleotides coding for a sequence of amino acids, transcribed into a unit of messenger RNA, and translated into a protein" (Fox Keller, 2009, p. 14). For a long time, the idea dominated that humans are equipped with a certain set of genes by birth. With this assumption, the gap between nature and nurture finally became insurmountable, at least temporarily.

The genomic discourse of the twentieth century reduced the question of where to locate human abilities and certain diseases to the gene: the molecular vision of life "sees genes as the essence of the person; they are 'what makes us human'" (Nelkin, 2001, p. 557). The scientific prominence of the gene also changed the ways we think about bodies, life, health, disease, people, and people's potentials on a broad social level. In their book *The DNA Mystique*, sociologists of science Dorothy Nelkin and Susan Lindee (2010) argue that the gene has become a *cultural icon*, a symbol which has almost magical forces and has also been heavily discussed in popular culture. This shows the extent to which scientific propositions are always interwoven with social discourses: society has also eagerly awaited the deciphering of the mystery of life with the expectation of finding solutions for improving everyday life (such as a "gene diet" that promises the long-awaited success to those who have struggled for years with various weight loss strategies).

Without losing sight of the important insights that the shift to molecular biology brought to an understanding of the human body, social scientists have also pointed out the potential dangers of a narrowed view of human life. Reducing human abilities and certain diseases to genetic causes may run the risk of stigmatising these people as biological victims, trapped in the genetics with which they were born. In light of the eugenic ideologies of the nineteenth and early twentieth centuries, in which results from human genetics were misused for population politics, sociologists particularly cautioned against a resurgence of biologically based racist ideas that divide individuals into "superior" and "inferior" on genetic grounds. Canadian feminist and epidemiologist Abby Lippman (1992) furthered the concept of *geneticization* to critically describe narratives around differences in humans that prioritise or exclusively rely on genetic accounts.

On the level of scientific research, efforts to decipher the *code of life* culminated in the Human Genome Project (HGP). Launched in 1990 as an international research endeavour with the participation of more than 30 nations, its anticipated goal was to map all human genetic information. Thus, at the beginning of the twenty-first century, "an old dream of mankind seemed to come to mind: the dream of the 'legibility of the world'" (Blumenberg, 1981, as cited in Lemke, 2002, p. 400; author's translation). By sequencing the entire human genome, scientists hoped to be able to correlate human traits or a certain health status, such as depression or cancer, to one single gene. In the HGP, all of the hopes as well as potential repercussions for society as they relate to a genetic view of life are condensed into one space. On the one hand, it was accompanied by the idea of improving the diagnosis and therapy of diseases, as scientists anticipated therapeutic opportunities that could directly regulate diseases via genetic pathways. On the other hand, it has also fuelled ideas of "good" and "bad" genes – an association in which "good" genes can explain certain talents and "bad" genes help to explain social problems (Nelkin, 2001).

However, after the completion of the HGP in 2003, it became clear that this "gene-for-approach" is too simple a theory to explain the complex development of human traits and pathologies: "The genome is not the organism" (Fox Keller, 2009, p.10), and humans are not the sum of their genes. Instead of proposing that common genomic differences are responsible for the development of human traits, biologists started to realise that "there does not seem to be 'enough' to actually account for what is going on" (Stevens & Richardson, 2015, p. 2). The human genome not only contains far less genes than expected (approximately 25.000 rather than the more than 100.000 estimated); furthermore, the results of the project did not validate the assumption that genes alone are the driving force of human development, either.

As a result, the linear dogma of genetic causality (DNA → mRNA → protein) began to fade in its clarity – a development that heralded a new era of biological thought styles: the postgenomic age, which decentralised the gene as a focal agent of human development. Sociologist Thomas Lemke (2002) writes: "In the postgenomic age, the gene is no longer an unmoved mover, but embedded in flexible relationships" (p. 410; author's translation). And Fox Keller (2009) proposes that the postgenomic genome

> looks more like an exquisitely sensitive reaction (or response) mechanism – a device for regulating the production of specific proteins in response to the constantly changing signals it receives from its environment – that it does the pregenomic picture of the genome as a collection of genes initiating causal chains leading to the formation of traits. (p. 25)

This reorganisation of the concept of the gene from purely agentic to also reactive (Fox Keller, 2009) made room for approaches to human development that realigned the biological and the social anew: the strict juxtaposition of nature and nurture was increasingly questioned and alternative, more complex and relational theories towards human development emerged. In these theories, DNA is regarded as one of many different system components and the scientific gaze is moved towards the functional elements, that is to say the regulatory dynamics of the genome.[7] Novel methodological frameworks and technology, such as microarrays, finally helped the new approaches to break through (Rheinberger, 2008).

In recent years, environmental epigenetics has gained scientific and media momentum as one specific approach within this relational research domain. Epigenetic modifications are described as central mechanisms by which environmental influences are biologically mediated on a long-term basis (Blaze et al., 2015). In other words: epigenetic research studies "how environments come into the body and modulate the genome" (Landecker & Panofsky, 2013, p. 439). As this life science research approach reanimates ideas that social environments play a decisive role for human development, health, and disease (see also Ch. 1.3), environmental epigenetics emerged as an interesting object for social

[7] As follow-up project of the HGP, the research consortium ENCODE (Encyclopedia of DNA Elements) was launched in 2003 to explicitly unravel the principles of this "reactive genome" (Fox Keller, 2009, p. 29).

science investigation. In addition, as we will see in the next section, environmental epigenetics builds on central assumptions of genetic research on health and illness but also significantly engenders novel notions on human life and behaviour. Therefore, it reiterates the need for social science inquiry (Landecker & Panofksy, 2013; Meloni & Testa, 2014; Niewöhner, 2011).

2.4 An environmental epigenetic approach to human life and the body: between empowerment and determination

Environmental epigenetics is an emerging instantiation of life science research approaches, one that has become an interesting phenomenon "to think with" (Niewöhner, 2011, p. 285) in the social sciences. As outlined in the introduction to this thesis, environmental epigenetics is one approach within the study of gene-environment interaction that suggests that the way we live our lives, the environments we experience and the social contexts into which we are born, have the potential to influence who we are and whether we lead a healthy life or are susceptible to specific diseases. Many epigenetic mechanisms are well described in model organisms (such as the notion of the intergenerational transmission of epigenetic traits). Studies in the human context in particular, however, are still characterised by conceptual, methodological, as well as analytical indeterminacies and a certain degree of dissonance (Dupré, 2011; Haig, 2004; Pickersgill, 2016). Environmental epigenetics is an "epistemology of the imprecise" (Rheinberger, 2003, as cited in Meloni & Testa, 2014), yet is accompanied by great hopes and expectations for understanding human development and improving health care.

As we will see below, scientists form STS and neighbouring fields observe environmental epigenetic epistemology and its vagueness as a research field, with both enthusiasm and wariness (Pickersgill et al., 2013; Meloni et al., 2016; Kenney & Müller, 2017). They on the one hand discuss environmental epigenetics as an approach having the potential to no longer prioritise the biological over the social, and, on the other hand, see old and novel determinisms co-emerging with its epistemology. Despite the cautious and to some extent critical social science studies published during the last years, it is important to mention that most STS scholars predominantly urge for creative and productive collaboration *with* the life sciences instead of a critical scrutiny from a detached point of view. Concretely, some STS scholars propose that social scientists could or even should contribute to the design, analysis, and interpretation of epigenetic research endeavours (Kenney & Müller, 2017; Meloni & Müller, 2018). In this context, social scientists suggest treating environmental epigenetics as a biosocial phenomenon in and of itself (Landecker & Panofsky, 2013), as a phenomenon that requires collaborative investigation beyond disciplinary boundaries in order to adequately reflect both its opportunities and challenges. Such collaborative research endeavours could present a possible way of conducting responsible and reflective research that takes into account the complexity of our socio-material worlds and of "becoming aware of the troublesome histories of biosocial research ... to not repeat historical

injustices" (Meloni & Müller, 2018, p. 8). With my work, I move within such a scientific framework, one that regards collaborations between the life sciences and social sciences as constructive projects to explore socio-material experiences and their effects on individual and collective lives.

2.4.1 Human life as a "biosocial" concept: how to think about health, disease and the body after the Human Genome Project?

One of the greatest environmental epigenetic promises is the idea that it will allow us to overcome long-winded debates about the dualistic influence of nature and nurture for human life. Social scientists have welcomed life science's acknowledgement of social experiences and contexts for biological processes: they observe "resonance between imaginaries of development within epigenetics and sociological theory" (Pickersgill et al., 2013, p. 438). Social theorist and STS scholar Maurizio Meloni (2016) outlines how environmental epigenetics has become part of a new "social biology", a conceptual framework characteristic for post-gene-centrism as the dominance of the gene increasingly fades. This implies the hope to finally bury the decades of competition between biological and social approaches towards human development, potentially overcoming the biological determinisms of the twentieth century. Actually, an environmental epigenetic view on life ascribes novel power to the social, as it regards social experiences as possibly altering biological processes and thereby our inner infrastructures, even as deep as the cell nucleus (Feil & Fraga, 2012; Skinner, 2015).

Against this background, it is important to note that the idea that socio-material environments can affect our bodies and biologies is no radically novel perspective originating only from and with environmental epigenetics. It can rather be regarded as part of recurrent processes of negotiations between biology and the social, in which the "separation of biology and society has been the exception rather than the rule" (Müller et al., 2017, p. 1679; see also Meloni, 2016 on "soft" and "hard" heredity). Nonetheless, environmental epigenetics gave social scientists understandable reason to be enthusiastic about the new role of social context for something as seemingly hard-wired as methylation or gene expression. In these discussions, environmental epigenetics is for instance perceived as having the potential to be a "biology without [b]iologism" (Meloni, 2014) and Pickersgill and colleagues (2013) write that the "refusal to grant ontological primacy to DNA is attractive to anthropologists and sociologists who have long been critical of various forms of genetic determinism" (p. 435). Environmental epigenetics thus opens up the scientific discussion towards a relational understanding of biology and the social on the one hand, and life science and social theory on the other – in equal measure.

Against the background of this relational approach, STS scholars discuss new ways of conceptualising the human body within an epigenetic perspective: how can the human body be perceived in relation to its surroundings, environments, and ecologies? What does it mean to be human, to experience, to

nurture, or "to inherit?" (Müller, 2020, p. 189). Many scholars from STS, social anthropology, and the humanities are invested in discussing these fundamental questions by suggesting ways that epigenetic propositions affect our lives, the ways we live them, and how we experience history and politics. An environmental epigenetic view of the body as "biosocial" (Lloyd & Müller, 2018; Meloni et al., 2016; Müller & Meloni, 2018) allows for the human body to be discussed as an "embedded body" (Niewöhner, 2011, pp. 289ff.), deeply entangled within its socio-material pasts, presents and future. That is to say, environmental epigenetics is a perspective that renders our body (molecularly) open to the events and social experiences it encounters (Szyf & Pluess, 2015), and re-articulates the body as seemingly in constant exchange with "the social and material environment within which it dwells" (Niewöhner, 2011, p. 289). This porous and permeable body (Meloni & Testa, 2014) is conceived of as plastic, always in flux, and in constant conversation with its environment.

This *biosocial* body gives rise to the idea that human health is equally shaped by biological *and* social components and the interactions between the two. Discourses on health and illness that were hitherto led within the disciplinary boundaries of biology itself, therefore, are opened up to an interdisciplinary view. Discussing biology and the social environment within a common framework allows for the pursuit of social science questions that have so far passed with little acknowledgment within a biological way of thinking, such as issues of social or environmental justice and their relation to health outcomes (Wells, 2010; Penkler & Müller, 2018). Given this context, environmental epigenetics holds the potential of allowing researchers to profoundly understand far reaching repercussions of different living conditions, such as poverty or wealth, or differently distributed access to resources such as food, on health and disease (Müller, 2017).

This promissory rhetoric around environmental epigenetics (Pickersgill et al., 2013) also leverages the idea of improving diagnostic and therapeutic measurements for both somatic and mental disorders. Imaginations of how to enhance health care range from "epigenetic drugs" to existing psychological and environmental interventions (such as psychotherapy), that "may come to find new legitimacy through research in epigenetics" (Pickersgill et al., 2013, p. 435). Life science researchers have also recently explored "environmental enrichment" as a potential form of improving health – a research paradigm that implies the possibility of reversing aberrant epigenetic effects of stress through positive environmental changes (Zhang et al., 2018; see also Chiapperino, 2019).

Against the background of epigenetic therapy, social scientists also warn of the danger that such therapeutic interventions might bring to light racialised or discriminating ideas of who they would benefit the most. Who will get access to these forms of therapy and how? In addition, the idea that both self-chosen and enforced life experiences might leave their epigenetic "traces" on bodies reinforces a conception of specific populations as environmentally and therefore biologically disadvantaged (Kahn, 2012; Mansfield, 2012). Focusing on pharmacological solutions to complex problems

such as mental health conditions or cardiovascular diseases again prioritises the somatic aspects of health and illness while societal and structural aspects might find themselves in danger of being obscured (Pickersgill et al., 2013; see also Dupras & Ravitsky, 2016 on the risk that a "clinical translation" of epigenetic knowledge may be favoured over a "policy translation"). This is a social science observation that has accompanied the processes of *(bio)medicalization* and gene centrism in a similar way.

2.4.2 Molecularisation and the reanimation of determinism

While environmental epigenetics holds the potential for taking into account biological and sociomaterial aspects in a balanced manner, social science scholars also show how epigenetic perspectives could ultimately not help overcome several deterministic implications we are already familiar with from the case of gene-centrism. Meloni (2016), for instance, cautiously states that epigenetic paradigms might "further racist or classist agendas" (p. 223). He ambivalently states, that "we can't say whether epigenetics will full its liberating potential" (p. 223), as the assumption that social experiences are biologically embodied also ultimately means that the social is gradually dissolved in the biological. In the end, even social experiences are (once again) reduced to biological phenomena: "a previous generation's experiences and environments are deemed to be embedded in the biology of a successive one, and habits are turned into biological instincts" (Meloni, 2016, p. 62).

Moreover, an epigenetic perspective on phenomena of human life arguably "hardens" observations or assumptions about these phenomena, transforming them into "facts" or scientific "truths". Meloni writes:

> The contemporary and epigenetic version of the first line of thought is not truly "degenerationist" because it is mostly moved by a compassionate wish to highlight how various historical and psychological traumas are "real" as they leave (epigenetic) marks on the present and future generations. From the Dutch Hunger Winter of 1944 to 9/11, from the effects of bad parenting to smoking, we witness today an increasing number of claims that exposed and unexposed generations may be biologically damaged by certain historical events that occurred in a near past. (Meloni, 2015, p. 120)

In keeping with this logic, epigenetics lends previous statements based on different scientific approaches, such as epidemiology, the material grounds to be ultimately considered "real". Social anthropologists and STS scholars Jörg Niewöhner and Margaret Lock (2018) share this observation: "It also increases the plausibility and legitimacy of claims to the detrimental health effects of social disadvantage and discrimination – claims that are foundational to at least most Western state social welfare and health systems" (p. 686). Kenney and Müller (2017) provide a similar analysis when they state that epigenetic studies grant a specific "molecular credibility" (Kenney & Müller 2017, p. 817) to life scientists' work. This observation contributes to the assumption that phenomena are only "true"

when they are molecularly traceable, which at the same time empowers those who make these phenomena observable.

As outlined earlier (Ch. 1.3), environmental epigenetics translates environmental aspects and behaviours, such as nutrition or parental care, into epistemic research objects by re-enacting them in experimental settings. It is therefore crucial and necessary to trace the ways in which the environment is operationalised in the laboratory as such re-enactments place the body in a specific way in relation to its environment (Darling et al., 2016; Lloyd & Raikhel, 2018a). Most often, as social science scholars show, strategies for re-enacting social phenomena in the laboratory are based on a molecular perspective on life. The fact that environmental epigenetics "provides an attractive way to study the 'non-genetic', while still remaining within a framework of molecular causal explanation" (Lappé & Landecker, 2015, p. 170) leads to a phenomenon that Niewöhner (2011) calls the "molecularisation of biography and milieu" (p. 290). This concept reveals how differences in our life worlds of high social relevance are levelled out for the benefit of re-constructing them in the laboratory by molecular means. With this proposition, Niewöhner draws on the work of historian of science Hannah Landecker (2011), who scrutinises how food has been reconceptualised with regard to its molecular components. In nutritional epigenetics, what we eat has come to be considered an epigenetic environment, a specific exposure in threatened (early) life phases as well as a potential target for health intervention. Molecularisation in this context describes "a highly selective scanning of the sociomaterial environment in order to make snippets of it available for experimental work at the molecular level. The sociomaterial environment and increasingly everyday life itself is framed and ordered in terms of its effect on molecular processes in the body" (Landecker, 2011, as cited in Meloni & Testa, 2014, p. 448). This molecularisation in particular can become problematic when nutrition or other social categories are regarded as products of *individual* lifestyle decisions instead of as complex phenomena that might be distributed unequally in society.

In this context, political scientist Maria Hedlund (2012) reminds us that epigenetic responsibility should not be grounded in individual action but must be a forward-looking, political task. Neglecting nutrition, for instance, as a structural phenomenon with its own policies can produce what Mansfield (2012) has called a form of "epigenetic biopolitics". An epigenetic biopolitics may racialize for instance reproductive women of colour as threatening future generations by making "false" food decisions. In this context, Müller et al. (2017) similarly emphasise that:

> if we hope to translate the findings of epigenetic research on the developmental mechanisms linking nutrition with disease risk into effective policy, it is imperative that we view nutrition not as a simple exposure in isolation, or a function of individual choice, but as a resource that is constrained in complex ways by social and structural factors that distribute resources, and chances of health, unevenly across society. (p. 1679)

Scrutinising the level at which responsibilisation is currently taking shape is, as Meloni and Müller (2018) remind us, our ethical duty and task. The authors argue that current epigenetic research would mostly render the individual responsible for their health and even for the health of their offspring (in the context of the possible inheritance of epigenetic traits; see Ch. 1.3.3), while neglecting that nutrition or other epigenetic "exposures" are complex structural phenomena. This is a tendency the authors observe with concern as it potentially gives rise to racist and deterministic rationalities. In this context, it is reasonable to specifically ask how matters of epigenetic facts are mobilised as matters of social concern and vice versa. Such a pathway can help dissect notions of collective and individual responsibility in health discourses or notions of stratifying populations in "epigenomically distinct subgroups/subpopulations aiming at objectifying in molecular terms disadvantageous conditions and/or unequal social structures" (Meloni & Testa, 2014, p. 443).

Sociologist Miranda Waggoner and evolutionist Tobias Uller (2015) in a similar fashion further the idea that, through the use of a specific language, an "epigenetic determinism" has superseded the old genetic determinism (see also Tolwinksi, 2013). By drawing on life science publications, they show how epigenetic mechanisms themselves are also subjected to genetic control, despite being a consequence of environmental stimuli such as nutrition or temperature. They furthermore show how epigeneticists' use of the "programming metaphor" (Waggoner & Uller, 2015, p. 184), connotes a specific irreversibility and thus determines individual development to (adverse) early-life experiences. They conclude that epigenetics "rests on the product of genetics. While epigenetics is about potentially rethinking genetic control, there remains an active explanatory linking of outcomes and traits back to genes and genotype" (p. 190). Feminist STS scholar Sarah Richardson (2017) has similarly demonstrated how, in environmental epigenetic research on the formation of sex differences in the brain, the discipline does not fulfil its potential of plasticity. In contradiction to feminist scientists' expectations and hopes, epigenetic perspectives are firmly anchored in biology's dualistic understanding of sex, rather than contributing to a more fluid understanding of sex differences. Both studies show how epigenetic promises of a body that is plastic, malleable in relation to its environment, are not implemented in practice but rather reanimate forms of determinisms, through for instance the programming metaphor.

Metaphors, such as the programming metaphor, contribute to the establishment of a scientific field and its public (mis)understandings. A reflexive analysis of how metaphors in biology change or are replaced is therefore a productive way to scrutinise their political power (Stelmach & Nerlich, 2015). The linguistic repertoire of the life sciences has changed with epigenetics over the last decades from metaphors such as "information" or "code" to more mechanistic and dynamic notions of "switching" or "tagging". In this context, the "memory" metaphor is of specific relevance, as it conveys the idea

that genes can "remember" events in life, which yet again localises responsibility for health issues on the individual level. Stelmach & Nerlich (2015) write:

> In the past, some people tried, for example, to blame their obesity on the bad genes they had inherited. With epigenetics, the blame shifts from the bad genes, for which our ancestors cannot directly be blamed, to a bad epigenome, for which they can be blamed, as it may be the outcome of a bad lifestyle or traumatic life. (p. 208)

By illustratively suggesting how our bodies are interacting with our lifestyle, environmental epigenetics is nevertheless a phenomenon that sparked much public discourse on health-related topics. Research results have received a great deal of media attention, where they are represented as oscillating between determinism and empowerment. On the one hand, we can find one-sided headlines such as "Poverty leaves traces in the genetic make-up of children" (Hütten, 2016; author's translation),[8] which support the notion of somatic reductionism and classified inscriptions of difference and deviation. We can, on the other hand, also observe representations of scientific results that emphasise the idea that DNA is not destiny and that we can improve our health by understanding potential epigenetic health advantages (e.g. of certain foods such as in the guidebook *Epigenetics in Life: How Diet May Influence Epigenetics and Our Health*). Among scientists themselves, opinions vary as to whether or not epigenetics as a biological explanatory framework is deterministic (Tolwinski, 2013). As mentioned earlier, epigenetics still is a field in flux, characterised by heterogeneity and contestation.

Social science scholars have shown how many of these deterministic perspectives on human development are closely related to novel notions of temporality co-emerging with an environmental epigenetic approach and the plasticity that it proposes bodies are capable of. The hypothesis that our genome changes with individual development and environmental experiences gives the genome and epigenome itself a "life span". That is to say, different stages of life are bound to different levels of epigenetic openness (Landecker & Panofsky, 2013; Lappé & Landecker, 2015). This notion stands in contrast to the timelessness that was ascribed to DNA, which was rather associated with a certain sturdiness. Sociologists Martine Lappé and Hannah Landecker (2015) show how this re-configuration ascribes a specific significance to particular human life phases, such as early life, while others are rather eclipsed. The early-life paradigm emerged as *the* central referential concept within an epigenetic framework (see Ch. 1.3.3), providing life scientists with a "coherent interpretative frame" (Niewöhner, 2011, p. 288) for their analyses against the background of the field's heterogeneity and methodological uncertainties previously mentioned.

Revisiting temporality as the connection between past, present and future and its health policy effects has also been explored extensively by STS scholar Becky Mansfield (2017). In environmental epigenetic publications, the foetus is a recurrent figure that is discussed as specifically vulnerable. In these so called epigenetic "windows of opportunity" the mother's behaviour and her exposures are perceived

[8] German original: "Armut hinterlässt Spuren im Erbgut von Kindern"

as having an impact on the foetus itself. It is this re-configuring of the maternal womb as the initial epigenetic environment that produces specific "pathways of epigenetic plasticity" (Mansfield, 2017, p. 361). The centre of these new configurations builds the foetus, in which a "folded futurity ... brings multiple generations into the present and in so doing shifts the threshold of fetal vulnerability and intervention to other entities, including germ cells and babies, which require intervention now, in the enduring present" (Mansfield, 2017, p. 357). When the origins for an individual's development is sourced ever deeper in the past, the responsibility for a current health status emerges as a form of a retrospective heritage for an "enduring present: always yet always deferred for a future that itself constantly recedes" (Mansfield, 2017, p. 360; see also Pentecost & Meloni, 2020 on preconception care).

Such novel temporalities and the early-life paradigm in particular are rationales that almost inform all biomedical fields that are adopting epigenetic research approaches. As we will see below, the early-life paradigm is a rationale that is increasingly harnessed for understanding the development of mental disorders. It was, so to speak, the vehicle by which environmental epigenetic approaches were integrated into psychiatric research and ultimately connected mental health conditions to our "inward laboratory" (Huxley, 1869, as cited in Landecker, 2011). The idea to relate mental disorders to biomedical phenomena and molecular structures, however, is an understanding that has developed over the last centuries. Historically, mental health problems have also been understood differently; the next section is intended to briefly delineate how we came to understand mental health in biomedical realms.

2.5 Between madness and malady: how can we know mental health conditions?

"What is psychiatry?" (Pickersgill, 2012) While in this quote sociologist Martyn Pickersgill presents us with a central and straightforward question, the answer(s) to it have changed tremendously over the last centuries. What is clear is that contemporary psychiatry as the medical discipline that engages with the prevention, diagnosis and treatment of mental illness is characterised by "epistemological and ontological un/certainties" (Pickersgill, 2011). The ways science defines and researches mental disorders is still characterised today by a certain ambiguity; this is as opposed to some somatic disorders for which knowledge is for various reasons considered more certain, such as cancer.

Today, psychiatry can be described as a heterogeneous field that is informed by a multitude of different forms of knowledge and explanatory frameworks (Pickersgill, 2012), among them neuroscience, biology, behavioural science or psychoanalysis. Such heterogeneous approaches also produce heterogeneous ways of describing mental health problems – terms range from "mental disorder" to "psychiatric illness" to "mental health pathologies". To date, psychiatric nosology, the branch of medicine concerned with the classification of diseases, is described as still being equally ambiguous. Based on

what we know about mental health and *how* we know it, how can we sort symptoms along appropriate diagnoses? Against the background of this heterogeneity, clinicians can be regarded as "ontological bricoleurs" (Pickersgill, 2014, p. 165), making use of these different stocks of knowledge to create meaning.

Despite these different knowledge frameworks, the scientific community and the majority of our Western population seem to have agreed to define insanity as a primarily medical problem. As most readers will know, this was not always the case but is rather the result of 2,000 years of negotiation processes. In his dissertation on *Madness and civilization* (1988), Foucault delineates the historical development of "madness"[9] by focusing on the question of whether madness is a historical universal or something that is constructed. This is an important genealogy as the ways in which mental health conditions are known have a tremendous impact on our societies and ourselves: Rose reminds us that "psychiatry is intensely political" (Rose, 2019, p. 14). Therefore, in the following paragraphs I will outline how we came to predominantly know mental disorders as brain disorders.

2.5.1 Conceptualising madness as medical problem: a short and incomplete genealogy of insanity

While in Western culture today mental health problems are mostly understood in medical terms as *illness*, this has not always been the dominant explanation. Before madness or insanity were rendered as medical problems, there existed several alternative approaches to how they could be conceptualised: from religious or spiritual punishment for sins inflicted by some supernatural power (e.g. ancient Hebrew culture); to the ancient Greek theory of the four humours, which understands health and behaviour as dependent upon the relative proportion of four bodily fluids, among them phlegm (see also Meloni, 2019 on how the humoralist framework already proposed a porous and fragile body); to the notion, localised in the European Middle Ages, that disease was caused by witchcraft. In the seventieth century, lunatics and other deviants were classified as the "mad" and were finally confined in segregated institutions. The first of this kind was the Hôpital General in Paris, built "to rid the city of idlers and beggars and other socially useless individuals" (Conrad & Schneider, 1980, p. 44).

At that time, however, physicians did not yet have any expertise in the domain of madness. These first "hospitals" did not provide medical treatment but were constructed to shift the debate on madness from the public into separated arenas to exclude the mad from the community (Foucault, 1973). Until the end of the eighteenth century, it was the verdict of a magistrate that enforced admission to a

[9] In what follows I will use this term until we reach the conceptualisation of mental health problems as medical problems. This term (*madness* or *insanity*) is also used in the literature I quoted. Moreover, it is a term that makes clear that mental health problems were not yet subject to the medical regime.

"madhouse" – a procedure that was eventually replaced by medical certificates: "the physician became the gatekeeper of madness, in charge of entry" (Conrad & Schneider, 1980, p. 45).

It was not until the spread of the Enlightenment that madness could be investigated on a scientific basic, though with moderate progress. In the nineteenth century, medical conceptions of mental illness began to rise, with insanity becoming defined as a biological disease of the brain, though a "socially conditioned" one, such as due to a lack of discipline. A curative environment was by implication envisioned as a proper treatment for insanity. This idea gave rise to the asylum-building movement that virtually led to an epidemic of state asylums for institutionalising mad people as form of treatment (Conrad & Schneider, 1980). The asylum predominantly functioned as a political or social supervisory authority and maintained or restored a specific explanation of mental health (see also Miller & Rose, 1986). Still, psychiatrists and medical psychologists did not have any theories or treatment that would have rendered madness a medical problem. As Conrad and Schneider (1980) write: "The 'capturing' of madness by the medical profession was a social and political achievement rather than a scientific one" (p. 71), based on humanitarian ideas. There still was no evidence that madness had biophysiological components. Given this context, treatment was based on moral ideas and interventions instead of on medical strategies.

In the late eighteenth century, the success of medicine in controlling infectious diseases, as a heavily somatic approach, contributed among other things to the renunciation of environmental approaches and the increasing relevance of somatic approaches accompanied by the hope that they will eventually enable us to cure the mad. From this point forward, concepts about insanity heavily anchored mental health in somatic structures: "Physicians, armed with the microscope, looked increasingly to the brain, spinal cord, and nervous system for the cause of madness" (Conrad & Schneider, 1980, p. 52). From then on, the somatic model of mental illness was further developed and came to dominate the scientific discourse.

As an exception to this context, the theories of psychoanalyst Sigmund Freud[10] stood – and still stand – in opposition to the somatisation of madness. Freud interpreted mental symptoms as intelligible distorted consequences of an individual's struggles with internal impulses. Hence, Freud's psychoanalysis led to an important alternative theory of madness, which even today is visible in discourses around the brain/mind dilemma. However, like other phenomena, mental health was, from the 1920's onwards, a social phenomenon subject to the forces of *(bio)medicalization* and biologisation – a

[10] The psychogenic movement, led by Sigmund Freud, still alienates the medical model of illness: today we find both psychological (giving the therapist access to the patient's psyche) as well as psychiatric (interpreting and treating mental illness through somaticism) approaches to treat mental health problems.

development that has given those branches within psychiatry a great deal of power that understand mental disorders as neurological disorders (Conrad & Schneider, 1980).[11]

In general, several components of this evolution of psychiatry have been met with sociological criticism, some of it severe. The institutionalisation of mental disorders, that is to say, the mass placement of the mentally ill in medical facilities, was one development in particular that sociologists did not leave uncommented. In his seminal book *Asylums: Essays on the condition of the social situation of mental patients and other inmates* (1961), sociologist Erving Goffman for instance investigated everyday life in these "total institutions",[12] which he described as self-contained worlds built to regulate and control all aspects of an individual's lifeworld for the time he or she was (made to stay) there. As a central thesis, Goffman states that these total institutions are meant to inverse the "moral career" of the patient. He critically argues that the most important aspect that influences a patient, however, is the institution to which he or she is exposed, and not, as one might assume, the disease itself (Goffman, 1961).[13]

Foucault similarly describes clinics as a form of powerful institution in which the conditions for the emergence of a *medical gaze* have been established. Foucault's concept of the *medical gaze* is heavily related to discourses of somatic or biological reductionism, which denote the medical separation of the patient's body from the patient's person or identity. In addition, such a medical gaze works with classifications, defining the boundaries between malady and madness, establishing perspectives on which behaviour can be regarded as "normal" and which as "pathogenic" (Foucault, 1988; Canguilhem, 2012). In this context, Foucault was especially attentive to questions of power relations. In his theory, power and knowledge are two intertwined concepts. That is to say, the way people are *known* always positions them in specific territories of *power*. And the way mental disorders are understood by society and the government affects the way they can be acted upon and by whom (Foucault, 1980).

These contributions in particular carved out a way of understanding how psychiatric knowledge and action affects everyday life. To classify people *makes up people* and defines a novel *way to be a person*, which changes her social everyday life and behaviours. These changes in everyday life in turn have an effect on scientific, political and economic ideas of society and thus, of course, on the concep-

[11] As social science scholar Adam Hedgecoe (2001) shows, scientists have been attempting to "construct schizophrenia as a genetic disease using various discursive strategies" (p. 875), while at the same time seemingly also allowing non-genetic aetiological explanations. To indicate this ambivalence, he introduces the concept of "enlightened geneticization".

[12] Further examples of a total institution beyond the realm of psychiatry are the prison or the monastery.

[13] Given such criticism, it is important to mention that in the 1970's psychiatry began (especially in Germany) to critically examine its devastating past (e.g. the persecution of people with mental illness by the Nazi regime or brutal methods of treatment). This debate culminated, for example, in the Psychiatry Reform, a restructuring of psychiatric care that is still ongoing today, and the *Psychiatry Enquête* (*Psychiatrie Enquête*), a report written by psychiatric staff on the situation of the psychiatric system in Germany (available at https://www.dgppn.de/_Resources/Persistent/80a99fbacaed5e58ef5c0733bdf8af78f8017e3c/Psychiatrie_Enquete_WEB.pdf).

tualisation of mental illness and its categorisation. This is a complex interplay between the diagnosis and the diagnosed that philosopher of science Ian Hacking (1986) so aptly describes as the *looping effect* (see also Thomas Scheff, 1974 on the labelling of mental illness; see Jenkins et al., 2004 on individual experiences of illness). Novel ways of *knowing* mental health conditions therefore influence or produce novel ways of *doing* psychiatric medicine.

Especially through new biotechnologies, we can observe that, today, mental health is first and foremost conceptualised as related to our brain, at least in Western societies (Rose, 2019, pp. 36ff).[14] Psychiatry has become part of a "techno"- or "bio"-medicine (Burri & Dumit, 2007; Clarke et al., 2003). In his latest book, Rose (2019) impressively summarises this developmental history of mental health along a series of rhetoric questions. He asks of the mental disorder, is it:

> as it was for some in the early twentieth century ... a matter of instincts badly managed, of habits poorly trained? Is it a matter of the dynamic forces in the unconscious as it was – and still is – for psychoanalysis and the many related 'dynamic' psychotherapies? Is it an understandable and perhaps even normal reaction to difficult social circumstances, poverty, racism or traumatic events, as many social scientists have long argued? Is it a matter of dysfunctional patterns of cognition to be corrected by cognitive therapy? Is it an outcome of 'toxic stress' in childhood, to be countered by interventions directed at dysfunctional families? Or is a mental disorder, as is increasingly argued, a brain kind of thing, ultimately understandable in terms of neuronal processes? (p. 10)

At the end of this evolutionary story, many psychiatrists seem to share the conception that mental health conditions are brain disorders (Rose, 2019; see Pickersgill, 2013 on neuroscience as a powerful tool for creating novel knowledge about ourselves and our societies). This scientific consensus explains how the human mind has become *the* epistemic object of contemporary psychiatry (Kehl, 2014).

2.5.2 The human brain as a plastic organ: what, then, should we do with our brain?[15]

As today, mental disorders are largely understood as brain disorders, they are localised in brain circuits and neurological structures. Thus, there are several brain projects under way, such as the EU-funded Human Brain Project, with the anticipated goal of revealing biological knowledge about human mental capacities such as thinking, feeling, or remembering. Through this knowledge, scientists and policy makers hope to gain basic insights into brain structures and functions that can contribute to a more profound understanding of mental disorders. As Joshua Gordon, director of the National Institute of Mental Health, argues: "Psychiatric disorders are disorders of the brain, and to make progress in treating them we really have to understand the brain. ... [If we can] get at questions of how

[14] Similar to Pickersgill (2012), Rose also notes that today "there is no one 'psychiatry' – psychiatry is heterogeneous with many different and sometimes incompatible conceptions of mental disorders, and many different treatment practices" (Rose 2019, p. 5).

[15] Inspired by Caterine Malabou's (2008) book *What Should We Do with Our Brain*, in which she deals with the plasticity of the brain from a philosophical perspective.

neural circuits produce behaviour [this] may soon generate new treatments for psychiatric disorders" (Abbott, 2016).

It was the shift to the notion of the "plastic" brain that ultimately gave rise to the idea of culture, behaviour and sociality as brain-based phenomena (Langlitz, 2011) – a ubiquitous focus on the brain and neuroscience that has been termed by several sociologists as "neuromania" (Macvarish et al., 2014). Up until the 1990's, neuroscientists proceeded on the assumption that the adult human brain is fully developed and as such no longer able to change. It was understood as a chemical machine rather than a biological organ subjected to vital processes like growth, death or adaption like other organs in the human body (Rees, 2016). Considering the brain as a "plastic organ that not only shapes, but is also shaped by its historically contingent socio-cultural environments" (Langlitz, 2011, p. 262) has been a major conceptual event that changed the ways in which neuroscientists can *know* the brain and human diseases.

From a social science perspective, positioning the plastic brain in complex ways as a connection between "soma and society" (Pickersgill, 2009) seems, at first glance, to disempower the somatic and biological reductionism that has been a recursive target of critique since the *medicalization* of many aspects of human life. A second and more thorough look, however, reveals that modern neuroscience merely produces more nuanced forms of reductionism. With their "cerebralization of psychological distress" (p. 8), philosophers of science Fernando Vidal and Francisco Ortega (2017) illustrate this ambivalence between empowerment and determinism. As they argue, the neurodiversity movement, a concept that suggests that neurobiological differences be respected as one human disposition among others, runs into the danger of promoting novel forms of stigmatisation and exclusion. In addition, it renders mental health problems as circumstances which are difficult to change by the person concerned herself. At the same time, such a perspective holds the potential of liberating effects, as it makes conditions that have previously been rather elusive more "real" and thereby may grant access to health care.

The potential to relate indeterminate conditions to bodily constitutions is enabled through neuroscience's success in establishing ways to inscribe mental health problems visually into cerebral structures. Medical imaging technologies, such as positron emission tomography (PET) or functional magnetic resonance imaging (fMRI), are applied with the intention of displaying internal physiological processes and looking at the brain through the skullcap. Such brain images are perhaps "the most visible aspects of neuroscience within wider cultural discourse, and the most ubiquitous icon of neuroscientific power today appears to be the brain scan" (Pickersgill, 2013, p. 326) – an icon that inscribes assumptions about the brain into its architecture (Dumit, 2004).

While it is quite obvious that localising mental disorders in brain structures grants even more power to the life sciences (by making them "real"), this shift in perspective also implies massive challenges for diagnosing mental disorders, as the living human brain is not accessible in its inner neurobiological structures. Apart from a few exceptions, physicians and therapists mainly have to draw on the patients' personal narrations and their own observations to come to a diagnosis. In contrast to many physical disorders, there exists no seemingly objective testing for mental disorders. To diagnose cancer, clinicians can analyse cells by conducting a biopsy. But there is no biopsy for depression.[16] Psychiatry has the prominent *Diagnostic and Statistical Manual of Mental Disorders*, published by the American Psychiatric Association (APA). Yet, this classification system has come under increasing criticism for its blurry disease definitions based on purely phenomenological descriptions that make therapy difficult. Thus, today the field of psychiatry is moving towards novel perspectives to approach mental illness, heralded to introduce entirely novel epistemic and ontological frameworks for mental disorders (Rüppel & Voigt, 2019):[17] psychiatry's demand for biology-based diagnoses is becoming progressively stronger and environmental epigenetics is currently emerging as an important approach within these new frameworks.[18]

2.5.3 Environmental epigenetics as a novel thought style in psychiatry

The turn to environmental epigenetics within psychiatric research can be regarded as another attempt to resolve the diagnostic and therapeutical dilemma firmly established in psychiatry as a field. By including the social environment, conceptualised as "adverse experience" or "stress", epigenetic research is heralded as a holistic view on mental health conditions, delivering the molecular knowledge necessary to explain mental health aetiologies more profoundly.

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[16] Somatoform disorders, meaning mental disorders with physical symptoms that are in the foreground, can to some extent be diagnosed by physical examinations.

[17] As was the case with somatic illnesses, much more was expected from the completion of the Human Genome Project for mental illnesses than was ultimately achieved. Researchers hoped to find meaningful gene specifications for certain diseases, such as the gene for depression, or susceptibility genes (Evans et al., 2001). Nonetheless, or perhaps precisely because of this disenchantment, molecular research on mental health was pushed forward. The driving force of this increasing biologisation and molecularisation of mental health was the inability to adequately diagnose and treat psychiatric diseases, as the success of psychopharmacology has stagnated since the 1980's (Conrad & Schneider, 1980).

[18] The nascent biomarker research also speaks to this endeavour towards biology-based diagnostics. Biomarkers are quantifiable parameters of biological processes regarded as implying prognostic or diagnostic validity. As they can be measured in peripheral tissue, such as blood, scientists and clinicians place great hope in the research of biomarkers for mental disorders. STS scholar Ingrid Metzler conceptualises this trend as the *biomarkerization* of health and disease (Metzler, 2010). This branch of research is primarily driven by the vision of personalised medicine (see Prainsack, 2017), a concept that has gained momentum in recent years and is hoped to deliver therapeutic treatments tailored to the individual patient and her biology. Sociologist Jonas Rüppel (2019), however, outlines an ambivalence that characterises this approach: "the vision of personalized medicine has been sustained and even increasingly institutionalized in psychiatry, even though its materialization in sound research results, new therapeutic opportunities, or medicotechnical artifacts has constantly failed" (p. 598).

Given this hope, adverse experience or stress is conceptualised as epigenetic environment as it is harnessed for molecular laboratory research. By interpreting "the individual biography as a list of retrievable molecular biological entries" (Lux, 2012; author's translation), stress can be regarded as an epistemic umbrella term for a multitude of human experiences, ranging from natural catastrophes to terror to parental neglect. Based on this little-differentiated conceptualisation of stress, psychologist and social science scholar Vanessa Lux fears that in epigenetic studies investigating negative human experiences, the difference between these experiences will be smoothed out and the subjective experience widely ignored (Lux, 2012).

To analytically dissect what aspects of human life are made visible in epigenetic research – what epigenetics understands as "environment" – sociologists Sarah Shostak and Margot Moinester (2015) elaborate on the concept of *regimes of perceptibility*, furthered by historian of science Michelle Murphy in 2006. Drawing on the realm of regimes of perceptibility reveals "how the politics of knowledge production and the process of materialisation involve obscuring awareness of certain things in order to make others more pronounced, known, and thus controllable" (Garrison, 2014). By investigating environmental epigenetic publications and the specific scientific techniques applied in research on diet, toxic chemicals, and stress, Shostak and Moinester on the one hand demonstrate that such research may foster very specific conceptualisations of the environment which in turn can lead to certain dimensions of the environment being more relevant than others. On the other hand, the authors show that the "case of stress ... illustrates how the interplay between social environmental factors and the body's stress response system is significantly more complex than previously thought" (p. 228). This analytical result echoes similar findings of social science scholars who state that the epistemological shift towards complexity is part of research that investigates the interaction between genes and the environment (e.g. Rüppel, 2019 on "complexity talk"; Stevens & Richardson, 2015 on complexity as the hallmark of postgenomic research; or Nelson, 2018 on strategies of containing complexity in genetic animal research).

This ontological complexity is deeply connected to the epistemic uncertainties in producing credibility in environmental epigenetic research. Psychiatric research is a field especially characterised by such uncertainty due to the limited accessibility of brain tissue, the zones in which contemporary science widely localises mental disorders (see above). To make epigenetic knowledge in psychiatry valid, the scientists therefore have to develop strategies to manage uncertainty and credibility in new ways. This is, as social anthropologists Stephanie Lloyd and Eugene Raikhel (2018b) speculate, "somehow distinct in the fast-moving, data-rich research that characterizes environmental epigenetics, in which key concepts and assumptions are rapidly stabilized and destabilized" (p. 756).

In another article (2018a), the authors describe such scientific attempts to stabilise contextual and environmental factors as molecular entities that contribute to an individual's health trajectories by way

of an "emergent style of reasoning". Such an argumentation would produce novel configurations that connect past personal experience with present behaviour, for the case of psychiatric research a "'suicidal brain': a brain that responds to adverse life experiences with an increase in risk of suicidal behavior" (p. 491). This type of concept is significantly accelerated by discourses on adaptation that are inherent to epigenetic research and that assume that bodies and brains molecularly adapt to environmental stimuli. This is described as a regulative mechanism that might lead to maladaptation or mismatch and ultimately to bodies and brains that are regarded as being ill.

As I have shown in chapter 1.3.3, environmental epigenetic research perspectives have been introduced into psychiatric research mainly through Meaney's and Szyf's seminal study on "maternal programming" (Weaver et al., 2004). In this experiment, the McGill University scientists investigated how aspects of a rat mother's behaviour was linked to their offspring's phenotypes. The paper's central postulation is that offspring who receive "more" maternal care are epigenetically "better prepared" to respond to stressful situations as adult mice, based on differences in DNA methylation. It is heralded as *the* proof of concept experiment that shows that early experience can have long lifelong effects. As this paper was received with both excitement and contestation in science and the media, a relatively large amount of social science work has been dedicated to this publication and how stress or trauma is investigated within an environmental epigenetic framework. Social science scholarship also pays particular attention to these epigenetic studies, since they analyse humans living together under the scrutiny of a molecular biological gaze and place the results in a molecular biological order. Thus, aspects such as maternal effects or social position are completely subject to the logic of the molecular biology laboratory. This not only leads, as Niewöhner (2011, 2015) puts it, to an *embedded body* whose inner laboratory adapts to its environment and dissects individual biographies and social milieu into sites of exposure with epigenetic effects; it also allows for questions concerning the material dimensions of social life forms to be addressed: to what extent are human bodies embedded in situational *local* materialities and cultural environments? That is to say, "just how and to what extent is the inner laboratory itself localized or situated?" (Niewöhner, 2015, p. 229). With reference to the concept of *local biologies* furthered by Margaret Lock (1993), Niewöhner recalls that such questions are in continuity with anthropological efforts to understand the multiple links between nature and culture.

In contrast to this rather enthusiastic perspective on how epigenetics potentially opens up a new space of engagement between biology and social experience, other STS scholars have shown how epigenetic research on early-life stress excludes the consideration of the wider social and material environments in which individuals live. In investigating molecular life science strategies of deconstruction and reduction, these studies demonstrate how the role of the mother is re-configured through environmental epigenetic research. Richardson, for instance, conceptualises the newly produced motherly figure as an "epigenetic vector": "an intensified space for the introduction of epigenetic perturbations in devel-

opment" (Richardson, 2015, p. 221). Richardson argues that, through epigenetic studies on early-life stress, the maternal body is rendered a causal explanation for epigenetic lesions in the offspring. At the same, maternal epigenetic programming research stages the maternal bodies as "central targets of epigenetics-based health intervention" (Richardson, 2015, p. 221). That is to say, instead of the long-awaited turn toward holistic explanations of life, Richardson states that epigenetic research on early-life stress reiterates, though in a more nuanced manner, traditional forms of determinism and reductionism that we already observed with gene-centrism.

STS scholars Martha Kenney and Ruth Müller (2017) add to such re-configurations of the maternal by delivering a fine-grained analysis of environmental epigenetic experiments on early-life stress. They demonstrate how the scientists' reductionist research approach inscribes common-sense assumptions about categories such as gender, class, or motherhood into the design, interpretation, and dissemination of rat experiments on early-life stress (in particular Meaney's and Szyf's experiments). Focusing on how rat maternal care is investigated and interpreted in relation to human development, Kenney and Müller identify specific challenges they trace in epigenetic research on maternal effects. They, for instance, articulate the different figurations of motherhood present in these experiments, such as the *mediating mother*. By introducing this concept, the authors illuminate how a mother's behaviour (licking and grooming) comes to resemble the whole environment of an infant, while black-boxing all other experimental parameters, such as food or housing. While reductionism is a common and to some extent necessary laboratory method, the authors caution against the detrimental and determining effects it may have when these rodent experiments are used to make claims about humans, whose child-rearing varies from those of rats (e.g. peer relations, the role of the father; see also Müller et al., 2017). An "adequate empirical evidence" (Kenney & Müller, 2017, p. 819) is the scientific practice Kenney and Müller hence often miss in attempting to translate from rodent experiments to human health. Such social science analyses are important and insightful research endeavours, as they can be regarded as a way not to echo the field's question of *is it genes or the environment?* (Shostak & Moinester, 2015), but to instead turn towards questions of concrete knowledge production and to address the question: "how are genes and/or the environment conceptualized and operationalized in this research?" (p. 230).

I would like to situate my dissertation along the line of social science investigation delineated above. These studies yield important insights into epigenetic strategies of harnessing stress and trauma for laboratory research and its social and political implications. Yet, they are largely focused either to literature analyses or to rat models, which, I believe, impose certain limitations. First, analyses that solely draw on scientific publications may not allow for a deeper understanding of the social, epistemic and structural dynamics of knowledge production processes. Studying concrete research practices, in contrast, allows for a consideration of epigenetics as a situated research practice and not as a

uniform configuration *per se*. Such a social science approach "investigate[s] how epigenetic knowledge is adopted and adapted in distinct, e.g. field-specific, research contexts and [asks] what kinds of situated epistemic, social, and political formations arise in relation" (Müller & Samaras, 2018 referring to Richardson, 2017).

Second, an analytical focus that remains within the epigenetic focus on maternal effects and early-life precludes that the field has moved on to study stress and trauma in other phases of life as well, with the aim of elucidating epigenetic effects of stress in the adult organism. Given this context, I believe it is meaningful to also investigate how environmental epigenetics studies and re-enacts stress in *different* experimental arrangements than the rat model. For example, STS has so far paid little attention to epigenetic research in cell models (see for instance Landecker, 2016) and has been greatly focused on the discussion of the implications of research in rodent models. Since environmental epigenetics is so often described as a heterogeneous field of research (e.g. Dupré 2011; Haig 2004; Pickersgill 2016), I think it is also important that we investigate this heterogeneity in order to truly discuss its potential and challenges and explore its relationship to emerging understandings of biology, health, and disease risk (Lloyd & Müller, 2018).

In my dissertation, I therefore provide a field-specific ethnography of environmental epigenetic research practices in a psychiatric research laboratory. With my analysis, I intend to advance the existing state of the art by offering an in-depth analysis of environmental epigenetics research practices that use different experimental approaches. First, in investigating how stress is re-enacted in cell and rodent models of mental disorders and in research with human tissue, I aim to analyse how environmental epigenetics produces different understandings of human health related to the applied model or experimental approach. Second, in providing a reflexive analysis and discussion of researchers' very practices of re-enacting stress, I acknowledge that scientific objects are not objects *a priori*, but objects that are actively enacted – a scientific stance that social anthropologist Annemarie Mol (1999) conceptualises as *ontological politics*. This perspective, I believe, allows me to provide a field-specific empirical analysis that takes into account the very situatedness of epigenetic research practices within the field of mental health.

2.5.4 Research Questions

The following research questions have guided me through my fieldwork and my analysis, even as they have changed somewhat during the course of my research process. As we know from constructionist and Grounded Theory approaches, our research interest often adapts to what we see and encounter in our field sites. Developing a research question is therefore most often a procedural engagement with our empirical material. It is still helpful and to some extent necessary to have a clear research question in mind *before* entering the research field. This helps not only in making a research interest compre-

hensible to informants, but also in providing a blueprint that guides the researcher through the jungle of first impressions of a field to which he or she is a disciplinary stranger. It was nonetheless equally important to me to be open and attentive to the dynamics of my research field (Flick, 1991; Charmaz, 2006).

In that spirit, my initial research interest focused on trauma as phenomenon and diagnostic criterion. I was interested in how trauma is molecularised and transformed into a "molecular event" through research in environmental epigenetics. However, after having spent several weeks in the field, my scientific view was increasingly also directed towards the way scientific knowledge is produced differently in different research arrangements. As I had the opportunity to observe various research projects, I also had insight into different research arrangements, ranging from basic research with cell organisms to mice models to translational research with human tissue. I therefore became progressively interested in the arrangement-specific methods and experimental set-ups that the scientists applied in order to conduct environmental epigenetic research on mental disorders. I aimed to investigate how biology was *made* in the lab and therefore posed, as a main research question, the following:

- How is knowledge from environmental epigenetics both mobilised and produced differently in research arrangements in a psychiatric research laboratory?

In all of these research arrangements (cells, mice, human tissue), the scientists operationalised "stress" or "adverse experience" as an epistemic object of scientific knowledge production. This practice is based on the connection between the stress response and epigenetic processes. Stress, therefore, was re-enacted in every research arrangement as an epigenetic environment, for instance by stimulating cells with a pharmacological substance. In these practices, stress emerged as a central object in the support of knowledge production in environmental epigenetics. Therefore, I more precisely asked:

- How is stress re-enacted in cell organisms, mouse models and humans? And how are variations of these practices to re-enact stress operationalised as a way of seeing and conceptualising molecular difference?

Since the institute's overarching objective is to produce knowledge on environmental epigenetics to increase a molecular understanding of mental health, I furthermore asked:

- What are the environmental epigenetic accounts of mental health conditions that are fabricated in research on stress? To what extent are these dependent on the apparatus of knowledge production that the scientists choose (with cells, with mice, and with humans)?
- And finally, how do the researchers in question imagine environmental epigenetics might be leveraged to improve mental health? What promising rhetoric accompanies research?

After several weeks of ethnography, yet another phenomenon attracted my attention: the huge construction site in front of the building. I had noticed it from the beginning of my fieldwork, but it was only after a few weeks that I was able to grasp its significance for the work carried out at the institute: it literally affected the scientists' research practices, both discursively and practically. I soon recognised that it was valuable, if not crucial, to not think of the construction site as a phenomenon detached from the laboratory. Instead, I re-considered both within a distinct space, in which they (the lab and the construction site) emerge as phenomena that interact with each other and engender productive tensions. Therefore, I developed a further sub-question, namely:

- What are the socio-material environments in which this research is enacted? How does the very situatedness and embeddedness of the laboratory influence the research practices carried out there? And what can those of us in STS learn from this about contemporary knowledge production?

What becomes evident from my research questions is that I approach scientific knowledge production from an STS perspective that is attentive to the procedural, situational and constructionist nature of research practices. Throughout my work, I therefore conceive of laboratories as sites of knowledge production and as interesting infrastructures contributing to scientific objectivity and not as institutions of scientific truth-finding (Latour & Woolgar, 1979/2013; Knorr Cetina, 1999): the researchers' specific epistemological decisions articulate research phenomena in an equally specific way. Hence, I am particularly interested in describing and analysing the scientists' very methods of how they *do* and *talk* about environmental epigenetics and how they relate this *doing* and *talking* to mental health. My scientific gaze is therefore directed towards knowledge production-in-the-making and ultimately on the effects of an environmental epigenetic *knowing* of mental health.

3 Research Methods and Material

"How to re-present others and their diverse practices in good faith?" (Winthereik & Verran, 2012, p. 38). This question that addresses moral, epistemic, methodological as well as political issues of research was and still is a very important endeavour for me. It led me in the analysis and interpretation of my empirical data. It also played a crucial role, however, in earlier parts of my research project, as it was constantly present during my empirical data collection. Conducting a research project entails taking decisions (conscious or not) regarding methods, duration, and various forms of engaging with the field of research – apart from of course the many coincidences that social scientists encounter. Such decisions have consequences, as social science methods are always performative acts and social scientists always interact with their informants and sites of study: they talk to them, they follow them, they are *present* on site. Therefore, it is important to be particularly reflective about the methods used to collect data.

In this chapter I will describe my methodology and explain the choices I have made throughout my research. I hereby attempt to give a faithful account of the different phases of my project. I am aware that this is a re-narration and re-construction of the methods I have applied and of my research process. Therefore, this chapter has to be understood rather as a retrospective reconstruction and legitimation (Knorr Cetina, 1981; Latour, 1999) than as a realistic representation. Also, my research process was messier and more discontinuous than the narrative that I can reassemble here. Still, explaining my approach is a manner of accounting for the ethnographic story I tell with my thesis (Silverman, 2013).

I will therefore first (Ch. 3.1.1) briefly situate my study in the STS tradition of carrying out ethnography of scientific knowledge production. Here, I will delineate how laboratory studies emerged as distinct a social science approach and briefly discuss my own study in regard to some of the structural challenges of this approach. To understand my choice of field site, its dynamics, and its characteristics, I will explain the psychiatric research institute where I collected most of my data in detail (Ch. 3.1.2). Here, I will pay particular attention to its research objectives, its structural and institutional set-up, and how I approached it and gained access to it. In subchapter 3.1.3, I will embed my research and analysis within a body of STS and social anthropology literature on methodology. Here I show how, by choosing a constructionist research approach and Grounded Theory, I was able to be attentive to the very situatedness of both my informants' research practices and my own. In addition, this inductive approach allowed me to derive my results through an intensive study of my empirical data without encountering it with a pre-formed theory in mind. I then go into detail about my methodology and explain how I collected my empirical data (Ch. 3.2). Finally (Ch. 3.3), I will close the chapter with a reflection on my own role as a researcher within the research institute I have studied and by addressing the moral aspects of my research project. This is important not only to an understanding of the dynam-

ics of my very research site on more general terms, but to a scrutiny directed at the scope of my own analytical accounts.

3.1 Situating my research approach and my field site

3.1.1 Studying the construction of scientific knowledge: laboratory studies

My ethnography is part of a long tradition in STS to produce ethnographies of scientific work. These so-called "laboratory studies", which emerged in the 1970's, are deeply entangled with a constructionist approach to ethnography. Social scientists, such as Michael Lynch, Bruno Latour, Steve Woolgar or Karin Knorr Cetina, started – mostly independently from one another – to analyse the construction of scientific knowledge relating to its local material contingencies and the very research practices that comprise it. These classical laboratory studies emphasise the situatedness of knowledge production and acknowledge the embeddedness of scientific practices within local and cultural contexts. By understanding laboratories not as central sites of a scientific truth-finding but as specific infrastructures that contribute to scientific knowledge production and objectivity, laboratory studies demystified laboratories and scientists. Instead of perceiving laboratories as arcane places where "geniuses" produce scientific knowledge, laboratory studies understand practices of knowledge production as *social* practices, turning them into researchable phenomena. Descriptions and analyses about the efforts, complexities, and challenges of the scientists' everyday working lives build the centrepiece of these studies (Beck et al., 2014).

I am aware of the structural problems that laboratory studies today introduce. How can one single laboratory be analytically relevant when research is in fact a practice that is dispersed amongst different actors, practices, and spaces? How can results from studies focusing on one laboratory provide more generalisable results, when research is increasingly carried out in international consortia? Here I would like to refer to STS scholars Ruzana Liburkina and Jörg Niewöhner (2017), who suggest that our own empirical research designs should adapt to these developments in natural scientific knowledge production. Without discarding the insightful significance of classical laboratory studies for STS, the authors propose that today, laboratory studies should rather follow the research object in the sense of a more multi-sited approach instead of remaining in one single laboratory. While I acknowledge this critical and important objection, I still believe that for my research project and questions, choosing a single laboratory has its empirical and analytical strengths.

First, as I will explain later in more detail, the research institute where I conducted my ethnography was a rich and highly diverse site in which mental health conditions are approached not only by basic but also by pre-clinical and translational research perspectives. Given the size of the institute, many different research projects are conducted there by researchers from different scientific backgrounds,

among them neuroscience, biological psychology and biochemistry. This provided me with vantage points from which I could explore very different forms of knowledge production processes without leaving this laboratory.

Secondly, I regard laboratories not as closed spaces that are isolated from the broader infrastructures of scientific research. Rather, I see them as imbued by different forms of sharing and exchange of knowledge and material, visible for instance in the scientists' many collaborations. Describing in detail the very concrete practices of environmental epigenetic knowledge production simultaneously served as a practice of situated ethnographic record-keeping, and also guided my understanding of how they are embedded in a wider context.

3.1.2 The field site: a psychiatric research institute

What did I regard as a "suitable" field site for answering my research question(s)? Apart from certain pragmatic aspects (such as the working language) that were taken into account, I arranged to conduct my ethnography at a laboratory that conducts environmental epigenetic research on anxiety and mood disorders because I was interested in the way environmental epigenetics is integrated into psychiatric research on affective disorders.[19] After a phase of desk research on environmental epigenetic research approaches within psychiatry, I generated a list of possible field sites. I identified one research institute in Germany in particular as being specifically of interest. It was a large non-university research institution in an urban area, a precious field site because it was organised in three different faculties: basic research, clinical research and a psychiatric clinic and day clinic, in which patients are treated in medicinal and psychotherapeutical settings (approximately 2,000 patients per year).

My supervisor Prof. Ruth Müller and I approached one of the institute's directors in early May in 2016 by means of an e-mail in which we laid out our research interests and asked for a personal meeting in order to get to know each other. We proposed a collaboration to investigate from a social science perspective the novel biomedical concepts and research practices the institute is developing with the aim of making an interdisciplinary contribution to reflections on these new approaches and their social potential. As the director responded with a positive answer, my supervisor and I met with her at the end of May and she invited me to present my research proposal to their group's weekly data club[20] at

[19] As opposed to psychiatric research on neurodegenerative disorders, such as dementia or Chorea Huntington.

[20] The research group has two regular, weekly meetings: the journal club, in which they discuss papers that might be relevant for their research, and the data club, in which members present the progress of their own work or rehearse talks for conferences.

the end of October 2016.[21] Having fulfilled all administrative processes necessary to become a member of the institute, I was received as a guest researcher there from October 26th, 2016 to February 28th, 2018.

Research within the facility engages in conducting basic research on the development of stress-related mental disorders directed, ultimately, at developing novel aetiopathogenesis.[22] Apart from translating these research results into therapeutic and preventive practices, the institute's overarching objective is to supply their patients with scientific research findings as quickly as possible. The scientific work at the institute is clustered into twelve research foci which are organised in twelve research groups, each headed by a research group leader, among them translational research in psychiatry, the neurobiology of stress resilience and biological neuropsychotherapy. This broad research orientation suggests that it is a highly interdisciplinary research institute in which scientists from various disciplines work with equally diverse methods and approaches to mental health, ranging from biological psychologists to neuroscientists to art therapists or social workers. In sum, the institute currently has nearly 300 members on different hierarchical levels (e.g. technical assistants, PhD students, research group leaders, assistant physicians).

According to its website, the institute regards its close connection between basic research, clinical research and patient care as "unique", as one of its crucial strengths in gaining novel insights into how mental disorders develop, and as an important asset for developing novel diagnostics and therapeutics. This specific research orientation, which combines basic research and its clinical translations, was particularly valuable to my research. Having the opportunity to immerse myself into different levels of research (such as basic or clinical research), different research approaches (among them environmental epigenetics), different research arrangements (such as research in mouse models or research with human material), and different fields of activity (such as researching mental disorders or treating them) provided me with multifaceted insights into how scientific knowledge on mental health is constructed.

Beyond conducting research and treating patients, the institute hosts events at which researchers and physicians from the institute and from other research and clinical facilities are invited to give talks on their research output. These events are public and primarily address patients and their relatives, as the talks most often aim to provide scientific insights into the development of, or the dealing and coping with, specific diseases such as anxiety or depression. Through this psychoeducational form of dissem-

[21] Building on Rolf Linder's work on participant observation, others have already written about what can be called the researcher's *novel* fear of the field relating to specific forms of (a)symmetries between the researcher and the researched; an aspect that confronts researchers with novel challenges of assertiveness. This is an approach towards new field sites that might be closer to conditions and structures of the researcher's own scientific community. Therefore, they have to defend their "ethnographic authority" (Warneken, & Wittel, 1997, pp. 1-2; author's translation) not only towards their own scientific community but also towards the members of the field itself.

[22] Scientific explanatory model for the cause, origin, and development of diseases.

inating research results, the institute aims to provide patients with novel knowledge on mental disorders and to discuss clinical challenges, such as diagnosing mental disorders. Furthermore, they offer scientific seminars and a psychiatric lecture series in which invited guests or researchers from the institute speak to an academic audience about different aspects of psychiatric research – on, to cite one example, how to model brain development by using specific cell experiments.

3.1.3 A construction approach and Grounded Theory

A qualitative research process can be regarded as a "series of decisions" (Flick, 1991, p. 148), entailing conscious and, most often, intuitive choices and coincidences. On that note, one of my first decisions was to position myself largely within a Grounded Theory (GT) approach (Charmaz, 2006; Corbin & Strauss, 1990; Strauss & Corbin, 1998). GT is a qualitative approach that provides a coherent framework for the whole research process. It was conceptualised in the 1960's by the two sociologists Barney Glaser and Anselm Strauss which characterised its basic idea that theory should be developed from the empirical material and its analysis. Theory should be *grounded* in such material. With this as a point of departure, they provided a systematic methodological framework for constructing theoretical analyses from empirical data itself and distanced themselves from more theory-loaded approaches that tend to impose theory on empirical material, such as studies in the then prevalent sociological tradition of functionalism.

In the past decades, other scholars have extended GT or given it a slightly different emphasis by connecting it to the broader theoretical and methodological developments of the last decades. They have, to some extent, "reground[ed] grounded theory" (Clarke, 2003, p. 553) in a postmodern perspective. Sociologist Kathy Charmaz (2006) invites us to take a social constructionist approach towards Grounded Theory – an invitation I accepted largely for my own research project. A constructionist approach to Grounded Theory considers phenomena of the research field not as something that can be "discovered", but rather as being constructed by the researcher identifying an issue for investigation and giving it a specific shape. In addition, it not only recognises that the knowledge produced by the researchers will inevitably be a contingent construction depending on their research choices, perspective, and positionality; it also acknowledges that the methods employed need to be revised and reconstructed during the research process. As such, research in a constructionist GT approach is underpinned by a principle of openness. This includes the willingness to adapt different phases and elements of a research project, including the research questions, methodology and pathways of analysis, to what is encountered in the field (Flick, 1991). Hence, by choosing a constructionist approach, I regard social reality as an enactment and as an ongoing production process. In that spirit, my ethnographic descriptions can be understood as active achievements that have been constructed throughout the research process.

While naturalistic approaches to research projects in general favour *what*-questions and regard observations as transparent insights to social fields, the constructionist perspective allowed me to ask *how*-questions about my empirical material. I was still interested in the "what" of my research field, but my focus was clearly centred on how the scientists construct and order social reality within their everyday working lives and as members of a specific scientific community. As an ethnographer in the research institute, I attempted to "look at and listen to the activities" (Holstein & Gubrium, 2008, p. 375), to the strategies they devised and the ways they used various methods to build their scientific claims.

Within a Grounded Theory framework, I used coding as a method for my first analytical accounts and for separating and sorting my empirical data.[23] I started with a phase of open coding in which I attempted to be open to exploring whatever theoretical possibilities I might perceive. After I had coded all of my data once, I had a coding framework that showed me the main conceptual categories of my analysis. In a second phase of more focused coding, I used my most significant codes, such as "conceptualising environment as an epistemic object", to sort through and analyse large amounts of my data. In a Grounded Theory fashion, I started the coding shortly after having collected my first empirical data, as this procedure supported me in constructing the remaining time of my ethnography: *theoretical sampling* determined the further data collections. I therefore acknowledged data collection analysis as simultaneous research processes (Charmaz, 2006).

3.2 Situating the analytical material: research methods

3.2.1 Participant observation

Participant observation formed the core of my ethnography. Despite, or even because of, the variety of research groups and research orientations present at the institute, it was important for me to develop a sense of "belonging" to one specific group. This was the director's research group. This affiliation came about partly by chance and partly by way of a conscious decision. As I had already discussed my research endeavour and interests with the director, it seemed obvious to join her group. Additionally, the group's focus on translational research in psychiatry presented me with a very rich and promising site in which to follow my research questions: I hoped to be able to investigate how psychiatric research within an environmental epigenetic framework is conducted *in situ* on the one hand, and, on the other, how the researchers imagine this knowledge could become applicable. I regarded the membership to this group as a starting point and as a "home base" from which I could explore other parts of the institute. The organisation of an institute into different research units exists, of course, for administrative and not only research-related reasons. All of the group's members collaborated to a different extent with their colleagues. In this spirit, I followed the scientists of my "home base"

[23] The software MAXQDA supported me in these coding steps.

research group through their everyday laboratory life and got to know scientists from other research groups, who I in turn followed through their work as well.

I was specifically interested in the very practices by which the researchers conducted their research, in their experiences, and interpretations, which material they used and why, the ambiguities and decisions they were confronted with, how they discussed their research with colleagues. Therefore, I attended the group's weekly journal and data clubs, and I spent time with PhD students and postdocs at their laboratory benches and at their desks. I made use of coffee and lunch breaks as occasions for more informal conversations, to talk with researchers about their broader research interests or about specific experiments that I had observed. I also took the opportunity of shadowing the institute's most important clinical study to understand how environmental epigenetic perspectives are integrated into research approaches different from using model organisms. Additionally, I attended scientific lectures and seminars to understand how scientists discuss their research with national and international colleagues.

Social anthropologist James Spradley (1980) described different degrees of participation, ranging from nonparticipation to complete participation. In this scheme, my own participant observation could best be summarised as "moderate participation" (Spradley, 1980, p. 60): I did not attempt to do what the members of my field do professionally or to learn their practices ("active participation"). My aim was rather to learn the field's dynamics, the scientists' practices of constructing scientific knowledge on mental health issues, to listen to their accounts and to understand the very situatedness of their knowledge production and scientific routines. Therefore, I had different roles within the field. Sometimes, I was a "loiterer" (Spradley, 1980, p. 60) and observed the field from a rather detached point of view (such as in the scientific seminars). Often, however, I attempted to engage with the scientists by actively asking about the different working steps I observed or by spending lunch time with them. To some degree, I became a more involved member over time as I also had conversations about private issues or about the challenges of today's different academic cultures in general. Only rarely did I support the researchers in their practices, simply because of my lack of an adequate training.[24] With this moderate participation, I maintained some form of balance "between being an insider and an outsider, between participation and observation" (Spradley, 1980, p. 60). This was a sort of compromise, partly due to the dynamics of the field (see Ch. 3.3) and partly due to the scope of my own research project, as I did not have the *time* to learn the scientists' sophisticated practices.

Despite being a guest researcher and thereby a member of the group, this status was often a formal label rather than my actual role. Originally, I had planned to be at the institute on a regular basis two

[24] I assisted one postdoc, for example, by entering measurements from a spectrophoto-experiment into a table; on another occasion I donated blood for a small pilot experiment and I was occasionally allowed to pipet some substance into a specimen.

or three days per week. Unfortunately, this proved difficult as researchers were often exhausted when shadowed for the whole day. On other occasions, researchers excluded me from apparently boring tasks (see Ch. 3.3), or did not respond to my e-mails regularly. Often it was not possible for me to simply go to the institute and spontaneously join the scientists' daily practices, as they spent most of their time in their offices or laboratories, for which I did not have a transponder that would have granted me independent access. Therefore, I used the group's regular meetings to arrange specific days for my observation.

During the time of my research stay, my field diary was my most important tool. As I regard ethnography as a constant process of writing and re-writing, my fieldnotes can be interpreted as involving first "inscriptions of social life and social discourse" (Emerson et al., 2011, p. 8). Discussions about ethnographic writing as a distinct form of representation of research results have a long history in the social sciences. In his article on ethnographic descriptions, sociologist Stefan Hirschauer outlines these methodological discussions and advocates ethnographic writing as a method to verbalise "the 'silent' dimension of the social" (Hirschauer, 2006, p. 413). I share Hirschauer's aim to (re-)empower ethnographic writing as a meaningful technique in the social sciences. Therefore, I do not regard my fieldnotes and ethnographic descriptions as mere means against forgetting what I witnessed in the field. Of course, they are to some extent forms of documentation and language is a specific medium that reaches the "limits of what can be said" (Hirschauer, 2006, p. 436). However, I also approach my handwritten notes in my research diary and my digitalised fieldnotes as methods to put "something into words, that prior to this writing, did not exist in language" (Hirschauer, 2006, p. 414). This is very consistent with a constructionist perspective of the research process, as it emphasises ethnographic descriptions as active achievements that have been constructed throughout the research process.

3.2.2 Qualitative interviews

As I have outlined earlier, I took a constructionist approach towards my ethnography; my aim was to understand how the members of my research field constantly re-enact a specific form of social reality through their everyday practices. What, then, was the role of my interviews? I agree with Holstein and Gubrium (2008) when they argue that

> talk and interaction are the everyday engines driving reality construction. All forms of discourse fuel the process, including discourses that coalesce into regimes and regimens of knowledge and understanding ... . Because constructionists are deeply concerned with what is done with language to construct field realities, they not only watch but also especially *listen* in order to discern how the realities are produced and sustained. Taking reality as an interactional project (Mehan & Wood, 1975), constructionist ethnography becomes the study of what people "do with words." (p. 375)

In opting for such a constructionist approach, I focused on the "doings and sayings" (Schatzki, 1996, p. 89) that researchers applied in their everyday work. Talking to the scientists gave me valuable insights into their sense-making of their own worlds. It was also incredibly valuable, however, for my

own sense-making: it provided me with a space for comprehending the scientists' actions by asking them for an explanatory account of said actions. As a consequence, I conducted an interview with almost all of the scientists I shadowed during my ethnography.

Within the social science discourse on methodology, there is an ongoing discussion of how interviews as specific empirical data have been, should be, or should not be seen. This discussion is led against the background of "natural" versus "contrived" data and the very qualities of each form. Sociologists such as Jaber F. Gubrium and James Holstein (2003) or Susan A. Speer (2002) have dedicated themselves to addressing, problematising, and ordering these methodological debates. They propose to view interviews as an interactionalist endeavour between interviewer and interviewee (similar to Grounded Theory approaches towards interviews, see Charmaz & Belgrave, 2012). In this spirit, I regard knowledge, experience, and memory not as something fixed and stable over time but as constant re-enactments situated within specific conditions and circumstances. Social reality is thus not reported on but constructed within material, cultural, and discursive settings (Speer, 2002). While on first sight it might be tempting to conceptualise interviews as depicting an "objective truth" about an underlying reality, seeing them as the substantial conceptualisation of bodies of knowledge, routines, and worldviews seemed more valuable to me.

On that note, I conducted semi-structured interviews with thirteen members of the research institute and three external researchers that collaborated with scientists from the institute. Each interview ranged from 53 to 106 minutes. All interviewees and I myself signed an informed consent, of which one copy remained with the interview partners. I recorded the interviews with a recording device and they have been transcribed by an external transcriber our group collaborates with, in accordance, of course, with our confidentiality policy (the transcriber has also signed an informed consent).

After having briefed my interviewees about my methodology and the context and general aims of my dissertation project, I started the interview by asking them about their own academic backgrounds and biographies and their pathways into environmental epigenetic research. By this open question, I hoped to engender in my interviewees an impulse to talk, to invite them to recount "their" stories as they would like to. After this first narration, I had a cluster of questions relating to the institute as a specific place of work. In this context, I asked for instance about how a "typical" work day looks or with whom they collaborate. My third area of interview questions related to environmental epigenetics as a specific approach within life science research on mental health. I was specifically interested in the scientists' accounts of how they construct environmental epigenetics as a study object and how they relate it to other approaches to mental health. Why did they regard environmental epigenetics as a valuable approach towards mental illness? Why not? Here, I always asked questions that directly addressed the interviewee's research and its specific conditions and consequences, such as how they think environmental epigenetics can contribute to a different understanding of trauma or diagnoses,

such as depression. In all interviews, I also was interested in how the scientists perceive the public discourse around environmental epigenetics and how they experience the social, political, and ethical dimensions of this specific research approach – the norms and values of their research culture. By asking about their future perspectives and by de-briefing my interviewees about the next steps of my study, I attempted to end the interview on a positive note. After each interview, I revisited my interview guide and for instance reframed questions that seemed unclear to the scientists.

3.2.3 How did *they* put something into written words? Analysis of articles and documents

As a third path of investigation, I was interested in the scientists' written accounts of their research. Therefore, I first analysed documents that were part of the written discourse within the institute, among them study and test protocols and research exposés. Second, I incorporated scientific articles researchers have published or were about to publish into my analysis. Despite the fact that I read publications from various researchers at the institute, I decided to include only those written by researchers I talked to and/or shadowed in the centre of my analysis (in addition to articles published in the larger scientific community). My aim here was to understand publications as elements of scientific knowledge production embedded within the other practices of scientific communities. In the analytical interplay with my observations and interviews, they contributed to identifying the institute as a specific instantiation of environmental epigenetic research, as a place with its own logics and dynamics and yet not sealed off from the larger scientific community and its publishing conventions. Additionally, the institute's publications also gave me insights into who the institute's scientists collaborate with. Mostly the publications served to understand a scientist's sense-making more profoundly or to follow some degree of translational: how do they want their research to be understood? Which aspects of their research do they want to discuss with their broader scientific community? And how do they assess the clinical and social relevance of their research?

Some notes on confidentiality

Throughout my research stay, I tried to be as transparent as possible with my research. Since my informants gave me such a deep insight into their work, I tried to provide them with insights into what I was finding out as well. When, for instance, an informant asked about my analysis, I first explained how a social science analysis is performed by using specific coding software. Then, I described my results as precisely as possible so that they could understand them and as vaguely as necessary so as not to influence the remaining data collection.

In addition, I attempted to handle my data as confidentially as possible. All interview transcripts as well as my fieldnotes are stored in a folder on a server, which is password protected and only I have access to. Moreover, the names of all researchers I have shadowed and/or interviewed are pseudonyms

and where it could endanger the identity of my informants, I have also changed or generalised research-specific terms and have, for example, refrained from naming certain genes of which only a small number of researchers are specialists.

Since the institute is very large and many scientists work there, I of course also met other researchers while accompanying my informants. While it was possible to obtain verbal consent from my direct informants, this was difficult in the case of random encounters. Therefore, I did not include in the analysis those moments when the researchers could not be aware of my role as a social scientist.

3.3 Shades of visibility: reflecting on my own role as a researcher

> A few minutes after half past eight I reach the institute and knock on Jano's door. No reaction, although we had arranged a meeting between half past eight and nine. I watch a woman moving between two rooms and ask her if she knows when Jano will arrive at the institute. "He'll arrive at half past ten," she replies. I am confused. "He wrote an e-mail yesterday asking to postpone the experiment," she continues. I'm a little upset. Why didn't he cc me? … A few hours later I'm sitting with Jano in his office talking about this and that. Then, the woman I met this morning enters the room and discusses the procedure of today's experiment. Jano asks if we have met before. "Yes, yes, yes. She was here this morning," the woman replies. Jano seems a bit confused. Then, he admits that he forgot to put me in cc. He's obviously sorry. "I wasn't even awake when you arrived here," he says laughing, though slightly embarrassed. (fieldnotes, 13.4.17)

An ethnography is a specific time and place of social interactions. It is a form of witnessing daily practices and transforming them into rhetoric accounts. By "being there" (Geertz, 1989, p. 1), we attempt to learn and reveal something about the very research object we study. Different ways of seeing produce different ways of knowing the epistemic object. But what we are "allowed" to see is sometimes beyond our control. An ethnography is always characterised by different shades of what is rendered observable by the members of our research fields. Occasionally I, as an ethnographic self, was invisible, as scientists forgot our appointments and were surprised when I knocked on their office doors – as in the situation described in the field vignette above; sometimes the e-mails I wrote were filtered as spam and did not reach the intended recipient, even though I sent them via my working e-mail-address; sometimes knowledge-in-the-making was treated as invisible by my informants and they excluded me from practices like designing poster presentations; sometimes, my informants were afraid of doing boring things and made these invisible to my observational gaze; *Tomorrow I will only sit at the computer doing statistics, that won't be interesting for you*, was a sentence I heard several times in different versions.

These field experiences can be approached from two perspectives. First, they can be regarded as a problem that is structural to laboratory ethnography. Researchers themselves often separate science from culture. They often only regard technologised, visually observable or measurable practices as practices with scientific value: the handling of a microscope, the injection of substances into mouse brains or conducting measurements with a spectrophotometer (Garforth, 2012). More mundane

practices, among them thinking and writing or just sitting at the desk are often discarded by scientists as additional work instead of being acknowledged as important steps in knowledge transition. Second, these challenges of doing ethnography can also be perceived as a methodological problem: by being there, I was to some extent invasive. It is possible that I even occasionally posed a threat to the scientists' experiments.[25]

It would not be productive, however, to only problematise incidences like the one described above as "contamination" caused by the ethnographer's presence in her research field. Instead, these can also be read as inscriptions of broader field dynamics. Life science practices are becoming increasingly hybrid, virtual, and diffuse (Beaulieu, 2010; Garforth, 2012). The experiences of my ethnographic self also referred to properties of my research subject as such: it was often difficult for me to conceive of environmental epigenetics as a phenomenon. While I was often observing how scientists pipetted, incubated, mixed liquids, weighed substances, or used different machines I asked myself: what is the specific environmental epigenetics of this? Environmental epigenetics seemed to be discursively omnipresent,[26] yet still transient and sometimes difficult to *see*.

Because of the very intertwining of ethnographers within our research fields, it is important for us to be reflexive about our own research and consider the contingency and embeddedness and to take into account potential ethical and political effects. In this spirit, I do not regard myself as a witness who only observed how environmental epigenetics is constructed in material and discursive laboratory practices. I rather see my ethnographic self as a "withness" (Sörensen, 2014), a specific form of participation which acknowledges our own performativity in the fields we study. Then, we can define our situated research endeavours as a relational project that considers the entanglements of the human and non-human actors of a research field *and* the practices of the investigators themselves. This accounts for our own research practices as never being innocent and acknowledges that the social situation would often be different without our presence (Kenney, 2015; Verran, 2001). Once, an interviewee thanked me after the interview with the words: "Thank you for your interest in the area and for helping us all think about this and helping provide guidance for where we should go" (Paul, pos. 57-59).

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[25] On our way to the lab, Nadja and I also pass the mouse houses. There are signs in front of the doors reading, "Please be quiet, experiment is running." Nadja pauses, then says that she has to take a quick look. She opens the door. The lower quarter of the door frame has a thin board – presumably to keep a mouse from running away, I think. Nadja climbs over that guard, steps onto a small mat just behind the door, and pulls on blue plastic protectors over her shoes. "These are the mice that I isolated in different cages yesterday," she explains. I nod and enter the room by climbing over the cover. "Ah!" Nadja exclaims. "You're not allowed in here. So, stay on the mat," she suggests. … Later that day, we again come up talking about the separation of the mouse house in the "blue" (clean) and the "red" (dirty) area. Nadja says that it was already borderline this morning, actually I should not have entered the "blue" area. (fieldnotes, 20.5.17)

[26] For instance, in publication, research project titles or study exposés.

Overview of interview partners and main field informants			
Pseudonym	**Main disciplinary background(s)**	**Position within the institute**	**Date of interview (if applicable)**
Adriana	Psychology, neuroscience	PhD student	10.05.2017 (Ger)[27]
Emma	Neuroscience	Postdoc	03.06.2018 (Eng)
Florentina	Radiochemistry	Leading technical assistant	16.03.2017 (Ger)
Julie	Biomedicine, brain and cognitive sciences	PhD student	--
Jano	Neurobiology	PhD student	--
Joachim	Bioinformatics	Research group leader	13.12.2016 (Ger)
Judith	Medicine, traumatology	Research group leader	27.01.2017 (Ger)
Kai	Molecular biology, molecular genetics, neuroscience	External interviewee (research group leader)	11.07.2019 (Eng)
Lucas	Human genetics	Research group leader	08.02.2017 (Ger)
Lydia	Neuroscientist	External interviewee (research group leader)	23.07.2019 (Eng)
Mirena	Medical technical assistant	Head of biobank	12.03.2018 (Ger)
Nadja	Cognitive neuroscience	Postdoc	02.03.2017 (Ger)
Noam	Biochemistry, neuroscience	Managing director, research group leader	09.04.2018 (Eng)
Paul	Biology, molecular biology	External interviewee (research group leader)	27.08.2019 (Eng)
Rahel	Biological psychology	Postdoc	09.05.2017 (Ger)
Stella	Medicine, neuroscience	Director, research group leader	04.04.2017 (Ger)
Valentin	Biology, neuroscience	PhD student	01.02.2018 (Ger)
Zoe	Neuroscience	Postdoc	31.01.2018 (Eng)

[27] Depending on the native language of the researchers, interviews were conducted either in German (Ger) or in English (Eng). For the written thesis, I translated the German quotations into English. In addition, the interview passages were roughly smoothed and gross linguistic errors were corrected.

4 Re-Enacting Stress in the Lab: Epigenetic Approaches Within Psychiatric Research

This is the first of two empirical chapters. Its aim is to provide an in-depth analysis of how researchers investigate environment-related epigenetic changes and relate these to knowledge on mental health. Throughout this chapter, I will focus on three different research arrangements used in the psychiatric institute: research with cells, research with animal model organisms and research with human tissue. Each of these arrangements forms one subchapter in which I showcase different scientists and the various research practices they make use of, in order to provide an analysis of how environmental epigenetic knowledge is both mobilised and produced differently according to each research arrangement.

As we will see later, in all of these research arrangements, stress is implemented as a technical tool to initiate and study epigenetic processes. Here, I argue that in each specific research design the phenomenon of environmental epigenetics is enacted in an equally specific way. This is not to say that these enactments would not to some extent play a role in all approaches, but rather that one certain meaning of environmental epigenetics is made particularly relevant in each of them – a meaning that is in specific ways related to the research arrangement in question. The research arrangement includes, among other elements, the choice of a specific research object (e.g. a specific cell type) and a specific method of analysis or method for re-enacting and modelling stress or social adversity. The latter two, as I will show in my analysis, only become a valid "stressor" *in relation* to specific other elements of the experiment and scientific presuppositions. Before I will turn to epigenetic research projects using cell models, I would like to briefly outline stress as a concept rendered crucial for conducting research in environmental epigenetics. In addition, I introduce two biochemical agents (the glucocorticoid receptor and dexamethasone) said to be important in an organism's or a cell's stress response and which we will therefore frequently encounter throughout this thesis.

4.1 Stress as a tool for seeing difference

The stressed/unstressed divide

> What is actually the ulterior motive: that one simply wants to activate the system, because I do not see anything at a resting state – I see most differences only when I activate the system and then I realise: ok, there... there are differences between patients with and without childhood trauma. (Rahel, pos. 118)

As the quote from the interview with biological psychologist Rahel makes clear, harnessing stress as a technical tool for epigenetic research is based on a proposed binary in an organism: the organism is either in an activated state, an "on-mode", or in a resting state, an "off-mode". While the body normal-

ly maintains a stable equilibrium, the confrontation with a stressor puts it in the activated state; it "responds" to stress. What Rahel only very briefly described in the interview refers back to a long and complex history of efforts to conceptualise stress as an experience that every organism goes through. While many different researchers and notions have contributed to its genealogy, only some instantiations of how the notion of stress has been and still is discussed play a role in epigenetics and psychiatry.

For the demarcation between two conditions of an organism, physician Walter B. Cannon's responsive stress model is important. In the early 1920's, he developed a model that describes excessive physiological dynamics in emergency situations which enables the organism to react: fight or flight. In the absence of such stressful situations, the body maintains a stable equilibrium, known as "homeostasis" (Cannon, 1929). Three decades later, physician Hans Selye established a second reaction-centred stress concept. With his so-called "general adaptation syndrome", he describes a general reaction pattern of the body to longer lasting stress stimuli. His concept is structured in three phases: The "alarm" response is an acute physical adaptive response in which biochemical substances such as glucocorticoids are released. If the stress continues, the organism transitions into the "resistance" phase in which it attempts to reduce the current stress level by reducing the stress hormones released in the alarm reaction. Its goal is to restore the normal state. However, this phase cannot be sustained for long and will eventually lead to the "exhaustion" phase if the stress continues, with possible physical and mental long-term effects (Selye, 1956).

Selye's stress concept was pioneering for the notion of "allostasis". Proposed by neuroscientists Peter Sterling and Joseph Eyer in 1988, this concept describes a process of re-establishing stability, or homeostasis, in response to a challenge: it represents stability through change. This adaptation involves the activation of neural, neuroendocrine and neuroendocrine-immune mechanisms (Sterling & Eyer, 1988). However, these processes of maintaining homeostasis and adapting to stressful events are described as possibly causing damage to the body, termed as an "allostatic load" (McEwen & Stellar, 1993). The allostatic load "refers to the cumulative cost to the body of allostasis" (McEwen & Wingfield, 2003, p. 2), or the "price of adaptation" (McEwen, 1998, p. 33). Over long periods of time, the allostatic load is said to lead to disease (McEwen, 1998, p. 33).

These instantiations of how the notion of stress has been and still is discussed in the natural sciences is important to an understanding of what and how environmental epigenetics within psychiatric research re-enacts as stress in their research objects, "as well [as] the selection of its *molecular* targets" (Niewöhner, 2011, p. 28). As Niewöhner writes:

> In its most recent neuropsychoendocrinological re-writing, the response to the cumulative impact of all chronic stressors on a given organism has been termed 'allostatic load' and this stress response has been molecularised largely to the brain; more specifically to the glucocorticoid system

> and its signature hormone cortisol secreted in the body's stress axis of hypothalamus, pituitary and adrenal gland (Niewöhner, 2011, p. 281).

In the first place, differentiating between two conditions in an organism or in cells provides researchers with the possibility to *see* and *investigate* biological processes of interest. As in the resting state, the organism is supposed to rest in a condition in which its physiological and molecular processes are running at a baseline-level, Rahel renders this information as not valuable for research at the institute: scientists cannot gain insight from homeostasis, "you cannot learn much from this calm, neutral state" (Rahel, pos. 122). To conduct research on a body, or a cell, in this state would be in vain. This changes dramatically when it comes to the second condition, the activated mode. When an organism is aroused, physiological and biochemical processes take place that can be used for research: "Only the stressful state can provide you with sufficient knowledge" (Rahel, pos. 122).

As conceptualisations of stress make clear, researchers assume that the *entire* organism reacts and responds to stress. A body in tension also helps researchers to perceive difference. Based on this premise, researchers additionally assume that only in the stressed, or "activated", system can fundamental differences between individuals with different health states be observed. Rahel metaphorically compares this research perspective with the "Anna Karenina principle": "All happy families are alike; each unhappy family is unhappy in its own way" (Tolstoy, 1878/2003, p. 1). This opening sentence from Leo Tolstoy's *Anna Karenina* divides families into "happy" and "unhappy". From Rahel's stance as a researcher, applying this differentiation of happy/unhappy to psychiatric research would explain the current approach of studying stress: only in the unhappy, the stressed condition, can differences of human development be studied, based on individual responses to stress. Hence, in order to see molecular difference, research on environmental epigenetics is based on this stressed/unstressed divide and therefore re-enacts stressors in its experimental arrangements.

As we have seen above, the delineation of stressed and unstressed states is not a novel research assumption that emerged exclusively through epigenetic research perspectives. It has a rather long tradition as a research perspective in the life sciences. As the concept of stress is a well-established element of biological research and plays such a significant role for the institute's overall ensemble of epigenetic research on mental health, I regard it as a coherent interpretative frame (Rheinberger, 1997; see also Niewöhner, 2011): as a concept that has long been used to gather biological and physiological data on mental health within life science research, it is currently also applied in the emerging epigenetic research approaches. As a more or less standardised concept within biology it stabilises epigenetic research, as it is regarded as a variable that no longer needs scientific negotiation. It is rendered as scientific "fact". As we will see later, this stress concept is simultaneously used as an epistemic object in and of itself, also used in the production of novel knowledge and research strategies (Rheinberger,

1997). Therefore, it stabilises and accelerates research, while at the same time providing a shared interpretative basis for researchers to conduct environmental epigenetic analyses.

Despite the fact that the concept of stress appears as a fixed standard paradigm for conducting research within biology at large and within the institute specifically, in my analysis I am interested in the distinct ways that stress is re-enacted or harnessed for epigenetic research with cell models, mouse models and human tissue. As we will see, the glucocorticoid receptor and the pharmacological substance dexamethasone emerge as crucial biochemical agents in these re-enactments. In the following section, I briefly introduce their general functions in an organism's and a cell's physiology, which will illustrate their use in epigenetic research on mental health.

The glucocorticoid receptor and dexamethasone: two biochemical agents in epigenetic research on stress

The glucocorticoid receptor (GR) and dexamethasone emerge as central epistemic agents: researchers deploy and use their properties to produce environmental epigenetic knowledge. The GR is a protein that is expressed in almost every cell in the human organism. It is involved in the regulation of genes correlated with development, metabolism, and the immune response. As its designation indicates, the GR binds to glucocorticoids that are produced in the adrenal cortex. For the context of psychiatric research, the GR's binding properties to cortisol – known as the "stress hormone" – are of major importance: by binding to cortisol, the GR inhibits the further release of cortisol and initiates the neuroendocrine stress response. In the absence of an external signal, the GR resides in the cytoplasm of the cell. Only after being activated – that is to say, after binding to, for example, cortisol – does it move into the nucleus, where it interacts with the cell's DNA by triggering gene expression processes. Hence, the GR also functions as a transcription factor and thereby can have effects on an organism's biological constitution.

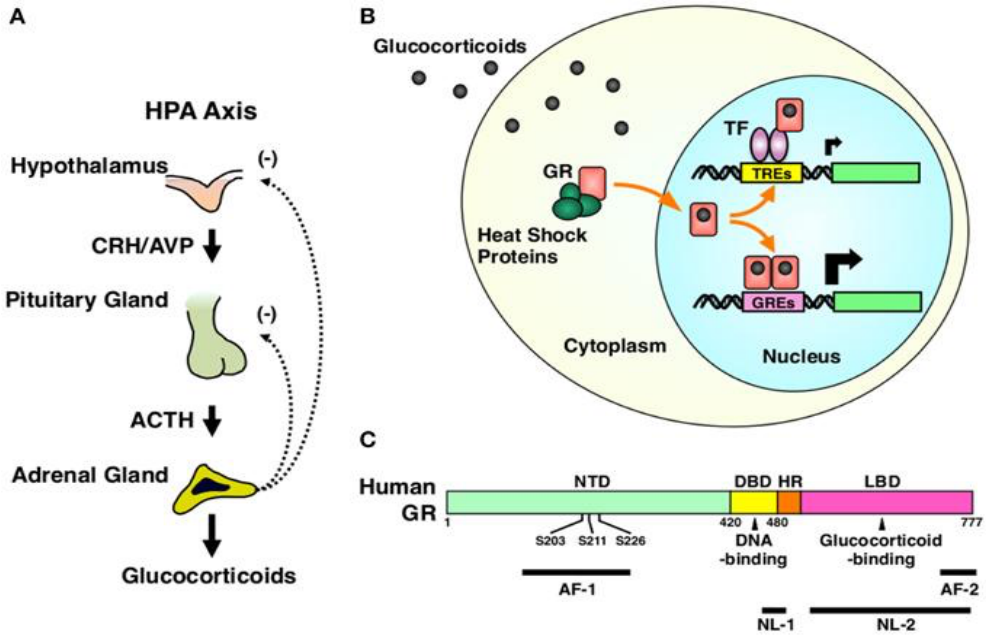

FIGURE 4. HPA axis and the GR (Kino, 2015, p. 4)

The sensitivity of the glucocorticoid-response – the degree of sensitivity the GR has to cortisol, or how likely it is to bind to it – can be increased or decreased by genetic polymorphisms, current diseases, and environmental exposures. In people with depression, a lower GR activity has been observed, which means that during a stressful event, the release of cortisol cannot be restrained by the GR and the neuroendocrine stress response endures: depressed people are described as feeling more "stressed" than people who are not depressed. This observed correlation between a biochemical state and personal emotion led to the interpretation of the GR activity as a proxy for a "normal" or a "pathogenic" stress response. This interpretation attributes a certain diagnostic power to the GR activity (Holsboer, 2000; Lowy et al., 1984).

Besides its significance as a diagnostic tool, the GR is in general an integral part of the central nervous system and also a significant element within an organism's response to stress: when an organism experiences stressful events in the form of a threat or danger, the binding of GR to cortisol leads, amongst other reactions, to a higher heart rate or metabolic changes, which can be measured *in vivo* – the organism "responds" to stress (Ströhle & Holsboer, 2003). Stress in this context is not further defined in the literature and represents any form of threat or danger to the body. Since the GR is categorised as the main stress receptor of the human body, it is an intensively researched factor within the institute as a whole. As the neuroscientist Adriana told me amusedly, "It is the favourite receptor of a lot of people here" (Adriana, pos. 65).

In addition to the GR, dexamethasone emerged as an important biochemical agent across all research arrangements applied to study environmental epigenetics and mental health. Dexamethasone is an artificially produced substance that has a twofold significance in biomedicine. First, it is applied in the

pharmacological treatment of several human symptoms and disorders due to its anti-inflammatory and damping effects on the immune system. Second, dexamethasone is also used as a technical tool in biomedical research. Scientists make use of its property as a synthetic glucocorticoid-agonist: much like to cortisol, it selectively and very powerfully binds to the GR. Researchers make use of this property and deploy dexamethasone to elucidate the GR activity under experimental conditions. By the so-called "dexamethasone-suppression-test", the release of cortisol in patients can be measured. In research that investigates the biomolecular underpinnings of stress and mental disorders, dexamethasone has been used for at least the last fifteen years. As it is understood as "artificial cortisol" (e-mail conversation with Nadja, 23.4.19), it is an established substance for imitating a stress response and is hence widely used in many research contexts.

Also, in the institute, it is the most significant substance for conducting research on the epigenetic effects of stress. As a "stress paradigm" (fieldnotes, 14.2.18), it becomes part of various research designs, most often it is used in cell model experiments. Adriana once stated laughingly, "In fact, we all are doing the same things. Well, these dexamethasone-studies are conducted here in high numbers" (Adriana, pos. 65). The application seems to be quite simple: as dexamethasone is existent in a solid aggregate state at room temperature, it has to be dissolved in ethanol and can then be pipetted into cells in order to spur epigenetic processes on a physiological level (or it can be administered orally to animals or human test subjects). This procedure is a pharmacological intervention: as scientists often explained to me, the cells are "treated" or "stimulated" with dexamethasone. Indeed, dexamethasone is so established and intensively used that researchers have even derived a verb from it: to "dex" cells is a fixed element of the lab-slang at the institute.

After this brief introduction into the basic tools and concepts of epigenetic stress research, in what follows I turn to the researchers' manifold practices of re-enacting and operationalising stress in everyday laboratory work with cells, mice and human tissue. In every case I address the question how they build epigenetic accounts based on the applied research arrangement and methodology.

4.2 Epigenetic research with cell models: enacting a semantic connection between cells and their environments

> And the days how I start and when I start, are also very dependent on what I do. When I'm in the lab itself, then it usually starts earlier, and the day is usually longer, because of incubation periods and stuff... Exactly. And the days on... when I'm just analysing or something, then it's... you don't have to... you're not dependent on schedules that the lab gives you, exactly, or the cells you have in culture. (Valentin, pos. 14)

Today, cells are widely used objects in biomedical research to study different phenomena, ranging from the development of diseases to the effectiveness of drugs to the study of molecular effects of toxins. As the above quotation illustrates, cells also structure the daily laboratory routine: researchers

adapt their practices to the cells they use for their experiments. The cells provide researchers a specific schedule for their laboratory practices. In all cases, these cells are to some extent "cultured": once they have been "sown" in specific nutrients, they can "grow" without the body that they constitute before researchers "harvest" them to perform various analyses. In this chapter, I will turn to the institute's specific research practices that use different forms of cell models for producing knowledge on environmental epigenetics. To better understand these research arrangements, I will first briefly delineate how biology came to know with cell culture. The achievement of standardising human biology is one important development of this story. In the main part of this chapter, I will turn to induced pluripotent cell systems which today constitute the main tool for studying the epigenetic effects of environmental factors in cell culture. Here, I will analyse in detail the research practices of two researchers, Adriana and Emma, and show how they produce epigenetic accounts of mental health conditions by applying specific experimental arrangements.

Knowing with cell cultures: HeLa and the standardisation of human biology

> It is the middle of October. I am shadowing biologist Valentin through his day. In his dissertation-project, he is mostly working with cells to elucidate epigenetic mechanisms that are connected to experiencing different forms of stress. Today, he is conducting an experiment in which he extracts PBMCs[28] from peripheral blood. Due to the circumstances, that the study nurse Julia fails to withdraw blood from Valentin, I offer for her to try on my veins, which finally works. … So, Valentin is later operating with my blood at a working bench in the "cell culture lab", apparently nervous, as "handling blood is always very delicate", he explains. "Especially, because we haven't tested your blood for any pathogens, so the risk of infection and contamination is very high. Just as the phenomenon that numerous cell cultures have been contaminated with HeLa-cells worldwide." (field-notes, 16.10.17)

This was the moment in my fieldwork when I first heard mention of "HeLa-cells", the first human cells from which a permanent cell-line was established. The cells are named after the donor's initials: Henrietta Lacks, a young woman that suffered from severe abdominal symptoms. As she came from a poor black family with restricted access to health care, she consulted a doctor at Johns-Hopkins Hospital in Baltimore in 1951, which at the time was the only hospital nearby where people of colour were treated free of charge. The attending physician not only took cells for the medical surgery, he also kept cells to pursue his intention to establish an immortal cell line robust enough to be used in biomedical research – with success: HeLa-cells is a widely-used cell-line that is applied in various biotechnological lab research contexts, such as in cancer or AIDS research to analyse, to name one example, the functionality of genes and their translation into protein. Its donor, Henrietta Lacks, however, died of cervical cancer a few months after the biopsy.

[28] Peripheral Blood Mononuclear Cell. These mononuclear cells play an important role in the immune system and can be reprogrammed into stem cells from which neuronal cells can be gained for biotechnological research (Delves et al., 2017).

Besides testifying to a huge biomedical achievement, the HeLa story is also a story of ethical misconduct on multiple levels that catalysed political change in the collection and storage of human specimens for biomedical research which in turn resulted in the requirement of informed consent (Beskow, 2016). The young mother Henrietta Lacks was never asked whether she wanted to donate her cells to biomedical research, and her family learnt about the fact that her cells are deployed in innumerable laboratories and biological companies worldwide only twenty years after her death – twenty years during which no family member was financially compensated, despite the fact that HeLa-cells have been widely used in biomedical industries (Keiger, 2010).

As HeLa-cells are very robust and can be easily propagated in culture, it was rather easy to share these cells between many laboratories across the world. In the early 1960's, the suspicion that HeLa cells had contaminated other human cell lines was first confirmed (Lucey et al., 2009). It is to this phenomenon that Valentin refers in the fieldnotes above. Nevertheless, laboratories worldwide have conducted research with HeLa-cells for more than 60 years and the story of Henrietta Lacks reverberates as a narrative of immortality and heroism: Lacks is portrayed as "The Mother of Modern Medicine" (Moorhead, 2010) and the science writer Rebecca Skloot has taken on Lacks' story in her 2010 book *The Immortal Life of Henrietta Lacks*.

The distinctiveness of the HeLa-case is that by reproducing and distributing Lacks' cancer cells, biologists from all over the world are able to work on a standardised – meaning *identical* across the board – model organism for human biology. In her book on biomedical research with cells, sociologist Hannah Landecker (2009) describes the significance of HeLa cells for experimentation in life science research and highlights that the "distribution to and presence in laboratories all over the world of what had been a single specimen from one person was an utterly new mode of existences for human matter" (Landecker, 2009, p. 140). The uniqueness of the HeLa story lies in its symbolic reference to the achievements of modern biotechnology in eternising cells even after the body from which they originate is dead. As Landecker metaphorically concludes, "The woman and the cells are immortal – the woman through the cells' life and the cells through the woman's death" (Landecker, 2009, p. 142).

Today, biotechnological methods for maintaining life in the laboratory and transforming cells into seemingly eternal sources for knowledge production are established laboratory practices. The proliferation, differentiation, harvesting, and finally the freezing of cells are strategies to reproduce and breed cells, store them over a long period of time and then de-freeze them on demand. On numerous occasions during my fieldwork, I observed researchers freezing their cells in different devices with different temperature conditions: some used equipment that looks like a commercial freezer but chills the cells at -80°C, or towers filled with liquid nitrogen that can only be handled with protective clothes. By this so called "cryo-conservation", the cells' vitality can be maintained for an almost unlimited

period of time – a precondition to repeating an experiment with exactly the same cells to verify research results. Much like HeLa, the cells become immortal.

Why is the HeLa case important for telling the story of contemporary cell culture research? From a contemporary point of view, it can be positioned as the origin story of cell culture. First, it embodies the general significance of using cells to understand human biology. The technical preconditions of modern biomedical research made it possible to study human and animal cells *outside* of the body in *in vitro* experimental arrangements. Many cells, particularly sturdy cells like HeLa, can be easily replicated and manipulated in a way not feasible with living beings and their organs. Thus, they can be used as a model to study human conditions, as they provide access to cells that cannot be harnessed in the living organism. Cell culture therefore provides biology with a solution to one of its epistemic problems: the restrictive accessibility of specific cells that are central to scientific inquiry. In the case of mental health research, scientists are confronted with the challenge of not being able to access the human brain regarding its molecular structures, although biomedicine tends to locate mental illness in this organ. This chapter will look at, amongst other topics, how scientists attempt to bridge this gap by using different cell model organisms.

Second, the establishment of HeLa-cells also reveals the need for standardisation in biomedical research. One of the basic principles of biomedical research is its replicability: research results are often only considered to be robust and valid when they have been confirmed by several independent laboratories. As biologist Valentin explains in summarising good scientific practice, "Good science also relies on repetition and reproducibility" (Valentin, pos. 124). The prerequisite for the replicability of experiments is that laboratories work under comparable conditions, using the same cell line for instance, or applying the same methodologies. A potential reproducibility ensures the generalisability of results.

4.2.1 Modelling early life in the laboratory: environmental epigenetics and induced pluripotent stem cells

As mentioned earlier, cell model organisms are used in a wide variety of biomedical research fields. Psychiatric research also benefits from advances in cell culture research. As most readers will know, mental disorders are widely understood today to be *brain* disorders (Rose, 2019). Despite providing scientists with a "locus" within which to study mental health, this notion also gives rise to an epistemological dilemma: locating mental health in the brain transforms neuronal and brain cells into central objects of psychiatric investigation. Yet these cells cannot be accessed in the living human organism. In light of this, biotechnology's achievement of standardising (human and non-human) cells in cell culture becomes the most important development for scientists to be able to conduct research on neuronal structures at all. Biologist Valentin, for instance, told me enthusiastically that research on cell

culture is regarded as the crucial tool for modelling neuronal structures: "We can't always access the human brain. … And that's why you have to help yourself with model organisms. For every organism… for every question there is the perfect or the best model" (Valentin, pos. 66). In sum, using cell culture is one integral element of the epigenetic research apparatus, as "the causal relationship [of symptoms and gene-expression patterns] can of course only be tested in animal or... in cell models" (Stella, pos. 23), by various strategies of manipulation and intervention. Cell models in this sense expand the range and variety of possible research questions.

As we will see later, in addition to these possibilities, research with cell models also brings with it a number of challenges. Often, research output from cell culture has to be fed back to other models of scientific inquiry (such as animal models) or to research with human material, to test and fine-tune hypotheses and reveal causality. Here it becomes obvious that the achievement of growing cells outside of the body presents researchers with the most significant analytical challenge they will encounter with this work: cells in cell culture are always just fragments of whole organisms, they cannot display global bodily processes.

In this subchapter, I will deal in detail with the ways and strategies by which environmental epigenetic research is conducted in using neuronal cell models. Two scientists and their research projects will play a central role: Adriana, a psychologist and neuroscientist who works with a specific form of stem cells and neurones; and Emma, a neuroscientist who works with organoids. Both models are based on induced pluripotent stem cells, yet, as my analysis will show, they enact epigenetics in different ways: the specific characteristics of the particular arrangement of *in vitro* experiments contribute to equally specific environmental epigenetic accounts on mental health.[29] In this context, I am particularly interested in how their guiding assumptions and the epistemic frameworks of the different model organisms affect the scientists' research practices. As we will see below, re-enacting "stress" in cells is the main research practice in studying epigenetic effects. Therefore, in this subchapter I will also discuss what Adriana and Emma understand and define as stress and how they attempt to operationalise it in the laboratory. Before I turn in detail to Adriana's and Emma's research practices to investigate the respective cellular responses to stress, I will briefly introduce induced pluripotent stem cells, which have emerged as important *in vitro* tools for environmental epigenetics within psychiatric research.

[29] The boundaries between these different enactments are not static, but as we will see sensitive to the situations in which they occur. Additionally, we can observe a specific amount of overlap of these enactments and different research practices might also not always be clearly distinguishable. Organoids for instance also consist of neuronal cells and yet have some distinctly different properties than the neuronal model Adriana uses. This means that in every single research arrangement, I could observe distinct ways of how stress and epigenetics is investigated, which I want to highlight here.

Induced pluripotent stem cells: and "ethically justifiable" version of embryonic stem cells

In 2006, after five years of work, the Japanese researcher Shinya Yamanaka succeeded in generating cells that could transform into a variety of different cell types, such as liver cells, heart cells, or muscle cells. He did so by infecting skin cells from mice with a specific virus. This novel type of cells was "pluripotent", as it could be differentiated into any imaginable cell type, just like embryonic cells. Yamanaka's achievement was recounted as "world changing", "ingenious", or even "revolutionary", as with it he had managed to "wind back the developmental clock" (Scudellari, 2016, p. 310). The major hope accompanying the development of so-called "induced pluripotent stem cells" (iPS cells) was to enhance the field of personalised medicine. Researchers imagined that, from that point forward, they would be able to grow any cell that was needed to treat a person's disease from other cells in their body. However, this endeavour turned out to be far too challenging for the successful development of such a therapeutic strategy.

However, the story of iPS cells did not end there. Instead, these cells have since been used in biomedical research to investigate the development of various human diseases. Before iPS cells were ever established as tools for biomedical research, such research had only been possible with embryonic stem cells. As most readers will know, using embryonic stem cells is an approach that involves many ethical considerations and legal hurdles. Since they present research with an ethical dilemma – at what point is a cell body to be regarded as a life worth protecting? – their use is regulated very differently from country to country. The achievement of producing iPS cells can hence be regarded as a biomedical novelty to conduct research on human health without obvious ethical objections.

In the institute, several scientists carry out research by using iPS cells and differentiating them to neuronal cells. It is a rather novel approach to conducting environmental epigenetic research with an origin in a methodical challenge. As delineated earlier in this thesis, the work of the Canadian-based research group around Moshe Szyf and Michael Meaney is widely recounted as the proof of concept experiment that tested how early experiences in life shape later life via epigenetic mechanisms, a connection that was already known but lacked a molecular explanation. Szyf and Meaney's paper is therefore described to have "struck a chord, especially in psychiatry" (Kai, pos. 11), and to have propelled environmental epigenetic knowledge and research like no other study. For research group leader Lucas, the methodological challenge was, however: "how to bring these things from animal experiments to humans" (Lucas, pos. 4). In this context, he regards the possibility of producing human stem cells as providing him with a valuable opportunity to research what he is really interested in as a neuroscientist: human neurones. He and his group have been pursuing this approach for five years and have abandoned research in animal models.

Even if – or precisely because – it is a biotechnological story that began only recently, hopes are high for the further improvement of iPS cells. Lucas, for instance, envisions "

> hat some time it will be possible to generate neurones from patients *in vitro* and that it is also possible to develop and differentiate these into higher cell assemblies with electrophysiological and structural properties, as in the early stages of human brain development. Then, you would have the possibility to carry out research really on patients' neurones… along epigenetic questions". (Lucas, pos. 8)

The quotation illustratively shows that, despite the fact that iPS cells are generated from *human* cells, they remain mere *models* for specific human diseases. Since they are differentiated from peripheral human cells, such as blood cells, they can only *resemble* and not *display* certain neuronal states. Scientists use these models for neuronal development to investigate the molecular mechanisms underlying cellular processes. Despite some literature from molecular biology discussing the challenges and pitfalls of using iPS cells for research on specific diseases (Ohnuki & Takahashi, 2015; Saha & Jaenisch, 2009), the institute seems to fully regard them as a "valid" biotechnological tool to model human neuronal conditions.[30] The increase in knowledge that they provide seems undisputed.

The questions posed to iPS cell systems are similarly compliant. All of the scientists working with iPS cells at the institute pursue practically the same research question, namely: *how do the cells under scrutiny respond to external stress-stimuli*? While it sounds quite simple, this research question is rather a complex endeavour which engenders a series of epistemological questions: what are external stress-stimuli, and how can they be translated into the laboratory context? That is to say, how is stress re-enacted as an element of scientific experimentation? How is the practice of "stressing" cells carried out? And how can a cell's stress response be related to environmental epigenetics? As we will see below, during my fieldwork, I was able to find some answers to these questions while, at the same time, new issues and complexities have emerged, some of which remain unresolved.

4.2.1.1 Building a neuronal model of early development

Adriana is a neuroscientist and PhD student affiliated at the institute. For her project, she is working with a dexamethasone-cell combination to induce a stress response in cells under scrutiny. The human cells that Adriana uses in her research are derived from different cell lines that stem from various sources. For instance, Adriana uses cell lines from a healthy male subject which she has purchased and which have been reprogrammed into iPS cells "in-house" (fieldnotes, 2.3.17) by colleagues following a specific protocol established by a technician. At the beginning of her project, Adriana also operated with a neuronal progenitor-cell line from the cortex of an aborted foetus that the institute imported from the UK. A progenitor cell is a biological cell that has a tendency to differentiate into a specific

[30] However, the procedure of differentiating iPS cells from neuronal cells is a challenging practice that is sensitive to errors. Nevertheless, I could not perceive any internal negotiation within the institute regarding the qualification of iPS cells as a "good" or "bad" model.

cell type, similar to a stem cell and iPS cells. It is, however, already more specific than stem and iPS cells, which means that it has a lower potential for differentiation than them (Seaberg & van der Kooy, 2003), a property that Adriana defines as a limitation for her research approach. The progenitor cells that stem from abortions would already be too mature, as they "are usually relatively old, when they arrive with us. They simply already have properties of older neuronal progenitor cells which differentiate more to astrocytes than to neurones. So, if you are really lucky, there are still a few neurones there" (Adriana, pos. 56).

In this context, it becomes clear that with the development of iPS cells, novel opportunities have been introduced to the field of mental health research. They are described to be "immature", as scientists can influence the developmental stages of iPS cells by using specific culture media, an achievement that makes research in human neurones now feasible. Such cells were, until this development, only accessible as dead material in post-mortem brains. In the interview, Adriana explained the different steps that she takes to generate the cells she needs in order to answer her research question:

> So, I do a directed differentiation, which means I (.)[31] yes, I take the induced pluripotent stem cells and place them in neural induction medium right from the start. First... first in suspension, that means, they are supposed to form such small aggregates and these aggregates are then plated out and then form such neural rosette-like structures. And then, I have to punch out these neural rosettes with a [*amused*] tiny syringe needle and collect them. And in the best case, these then become neural progenitor cells and neurones. (Adriana, pos. 84)

After completing these pre-operational steps, Adriana cultivates her human neuronal cells *in vitro*, in a petri dish, outside of the organism itself. Due to their differentiation status, these "disembodied" cells, detached from any corporeality, serve as a model for an *early* development of neuronal tissue, resembling different parts of the brain, such as the telencephalon (endbrain) or the diencephalon (interbrain). As Adriana emphasised in the interview, her project would even be among the first studies that investigate stress in very early developmental phases using human cells. Therefore, iPS cells give her access to an important epigenetic paradigm: the early-life paradigm.

By using a model for early neuronal development, Adriana aims to model, measure and analyse in fact the impact of the *mother's* stressful experience on the foetus, or, the stress that is translated from the mother to the foetus: her cells model very early "developmental phases, in fact. … It's even prenatal" (Adriana, pos. 52), as she stated in the interview. Here, the synthetic substance dexamethasone stands in for "prenatal stress experiences" and Adriana intends to analyse their epigenetic effects on foetal brain development. When I asked for a more detailed description of what this maternal or prenatal stress might be, Adriana could not provide me with a more fine-grained explanation. "Prenatal stress" is rather black-boxed here:

> In a broad sense, my research could be understood as the influence of early stress on development, on neuronal development. … Well, my model is very reductionist, so it's just – yes – cells, that is,

[31] Indicates a long pause in the interview.

> it's an *in vitro* project and the stressor in that case is the dexamethasone as ligand to the glucocorticoid receptor. … exactly, my hypothesis – I think the hypothesis is very… if at all very broad, so the hypothesis is that stress has an influence at different stages of development. (Adriana, pos. 50)

It becomes very obvious, and Adriana even clearly states, that her approach is a reductionist perspective and only focuses on clusters of neuronal cells and their molecular response to dexamethasone. It is clear from her statement that her experimental design does not allow for taking into account the very different stressors and nuances that are part of an individual's socio-material environment. This limitation contrasts to a certain extent with her attempt to model the development of organismic systems which goes beyond individual cells:

> You just have to start somewhere and I think it is interesting to know in any case what could potentially happen when a *foetus* in utero is exposed to increased levels of cortisol and to what extent this shows at least on the transcriptional level, how this perhaps affects – yes – the *formation of the nervous system* [emphasis added]. (Adriana, pos. 106)

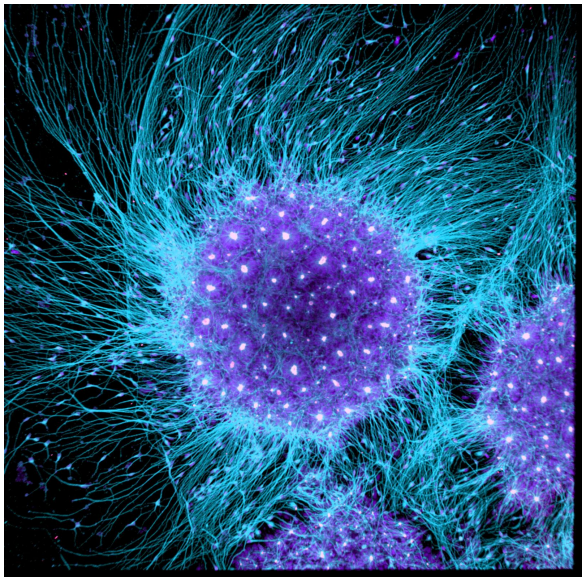

FIGURE 5. Neural rosettes from which progenitor and neuronal cells can be generated, derived from a human stem cell (retrieved from https://www.nikonsmallworld.com/galleries/2016-photomicrography-competition/human-neural-rosette-primordial-brain-cells on 27.8.20)

As indicated above, the interplay of the glucocorticoid receptor and dexamethasone is a significant connection for environmental epigenetic research, in particular within cell models. Adriana also attaches fundamental importance to the GR: it is considered to be "extremely important for development" (Adriana, pos. 46) and is correlated with behaviour and motivation (Lucas). When I asked her in the interview what the GR can tell her about her investigated cells, she replied that it helps her to have "a better basis for understanding … what in fact is happening in the brain during … early development" (Adriana, pos. 46). As a very broad hypothesis, she states that stress can have different effects on gene transcription and on the activation of specific genes depending on the progress of neuronal development. Stress in this context is re-enacted by manipulating the cells with dexamethasone, a pharmacological intervention.

While shadowing Adriana through her everyday laboratory life and during my interview with her, I recognised that *time* has a crucial significance in her project on different scales. First, Adriana hypothesises that the point in time in which stress is experienced might have different effects, especially in such early phases of life as the prenatal phase. Therefore, she has chosen three stages of neuronal development at which she measures and analyses the cells' molecular and epigenetic changes due to stress. By applying dexamethasone to the stem cell population, the neuronal progenitor cells and, finally, the neuronal cell population (the most mature cells) she initiates cells' stress response in accordance with their maturity.

But how does Adriana measure the differences in reaction to stress? Here, the significance of the dexamethasone-GR relation emerges as Adriana's central technical agent. As delineated above, dexamethasone binds to the GR, a bond through which the GR is activated and moves into the nucleus where it initiates the gene-transcription processes. And here lies the decisive point: the translation of genes into protein is dependent on the developmental stage of the cell. In progenitor cells, gene transcription is described to be different from neuronal cells. This difference is the basis for Adriana's hypothesis about the dependence of stress effects on the developmental stage of the cell.

different effects of stress at different stages of development. In each developmental stage, Adriana collects cell material to analyse RNA transcription and DNA methylation as two epigenetic processes that regulate gene transcription differently in each stage.

On the very first day that I accompanied her, I could observe research practices whose purpose was to make these differences visible. Adriana conducted a staining experiment in which molecular structures are colourfully translated into visually perceptible pictures. Staining experiments are an established laboratory method for recording and visualising proteins in cells with the help of immunofluorescence. It is a rather complex and time consuming method: on a specific day of the research protocol, the cells have to be fixed; a primary antibody which specifically binds to the studied protein is then applied to the cells; next, they have to be "washed" several times to remove proteins or other molecular structures that are not at stake in the experiment; the next day, the cells are treated with a second primary antibody that is immunofluorescent in a specific spectrum.

For Adriana, this procedure serves two purposes. First, it is an important technique for determining the identity of her cells, as proteins differ from one developmental stage to the next. For her this ensures that she actually works with the cells she wants to work with, such as progenitor cells. It is furthermore a way to detect how much GR has moved into the nucleus, an important proof for her as she aims to investigate the impact of the GR activation on gene expression in cells of prenatal developmental stages. Below is an excerpt from my fieldwork diary in which I wrote down what I could observe.

> We enter a medium-sized, shaded room in which there is a rather large microscope. This is surrounded by a transparent plastic box, which has square cut-outs covered with flexible plastic (almost like a cat flap), into which one can reach in order to operate the so called "confocal microscope". The microscope is connected to a monitor, on which the experiment's output is visualised. Adriana asks me to sit down on one of the desk chairs with castors and starts with the staining experiment. First, she puts two cardboard boxes on the table where the monitors are installed. One is green, the other blue. She also uses a piece of paper, "I recorded the slides", she explains. On the slides are aggregates that form neuronal rosettes which she has treated with dexamethasone for twelve days. "The GR is supposed to migrate into the nucleus where it should trigger the transcription of genes that depend on it," Adriana explains. These slides are in the green box, in the blue are control cells, "which are hopefully without GR," Adriana says laughingly. First, the microscope has to be adjusted. Then, she picks up liquid with a pipette, passes her hands skilfully through the flexible "plastic flap" of the box surrounding the microscope and drips the specimen stage with a little water. "It always has to be a bit damp," she explains. Then she takes a slide and places it on the stage. "Now I have to look for where I have cells." She sits down and looks through the eyepiece. With her right hand, she operates a kind of joystick, which moves the stage. "I'm staining in 3D, sometimes the cells do not adhere well to the plate." On the screen in front of me, the settings of the laser are displayed. Here, the microscope image is transferred. Then Adriana rolls her chair to the screen, operates the laser, changes settings. She adjusts the laser power, which also changes the image that is transmitted from the microscope to the screen. The blue dots become stronger or weaker, depending on whether Adriana turns the laser power up or down. At some point, she seems to be satisfied, goes back to the microscope, takes out the slide and wipes it with a tissue. (fieldnotes, 2.3.17)

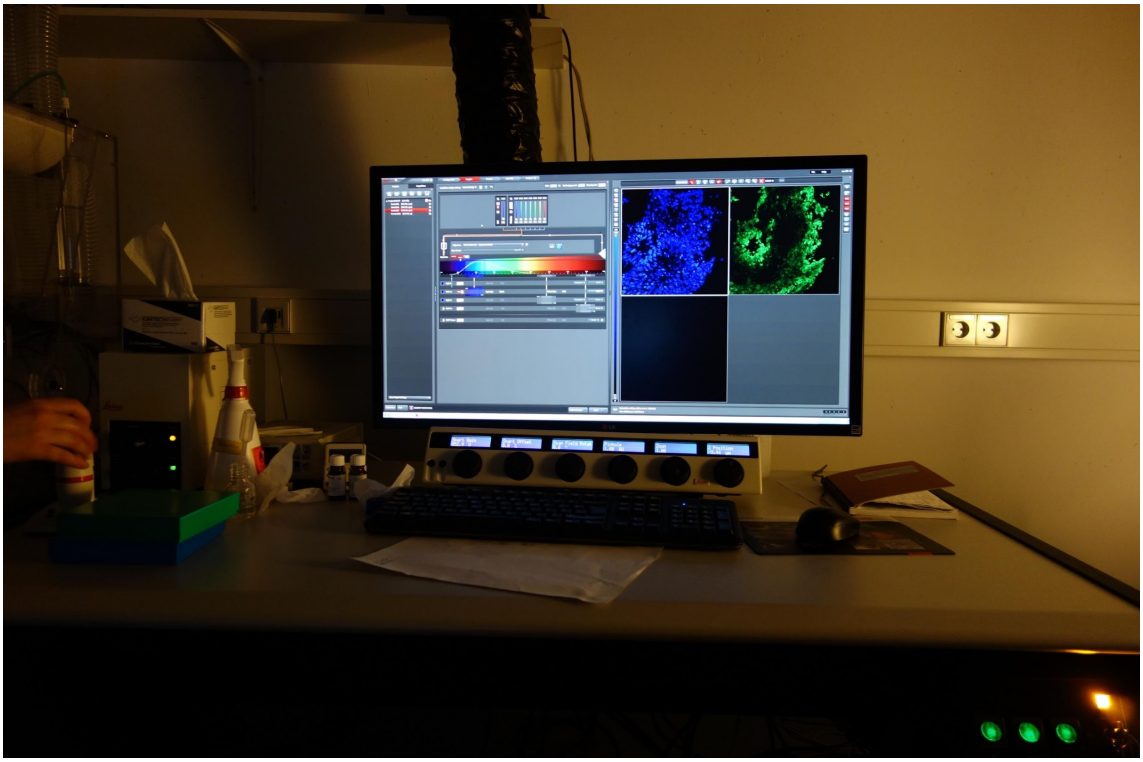

FIGURE 6. Adriana conducting a staining experiment (photograph by the author, March 2017)

Adriana's staining experiment can be interpreted as a scientific practice to visualise (parts of) a cell's stress response. The excerpt from my fieldwork diary vividly illustrates how stress or a stressful experience re-enacted through dexamethasone is translated into the vocabulary and logics of modern

biotechnology. The microscope is used to visualise the final stage of a linear cascade of reactions caused by the stress paradigm dexamethasone: it activated the glucocorticoid receptor which is supposed to migrate into the nucleus where it should trigger the transcription of genes that depend on it. In the end, Adriana hypothesises, different genes might be transcribed in different stages of development. In the stem cell phase, for instance, Adriana found that genes associated with neurogenesis are downregulated, a result that she finds very interesting as she "would not have expected that [increased cortisol levels] would have an influence on that developmental level already" (Adriana, pos. 106). Time therefore plays a role in Adriana's project in the sense that she assumes that the experience of stress may, at different points in time of neuronal development, have equally different regulatory effect. This assumption gives the epigenome and the genome a life span "because temporal experience is being investigated in the body of chromatin, which by definition is the complex of proteins *and* DNA constituting chromosomes" (Lappé & Landecker, 2015, p. 2). The description of Adriana's research that I have provided so far vividly demonstrates that the iPS cell model allows her to translate her assumptions into a feasible experimental arrangement.

Time also plays another significant role in Adriana's research: in addition to the effects of the point in (developmental) time at which cells experience stress, she is also interested in the effects of the *duration* of the stressful experience. Therefore, she conducts an experiment that she calls a "time series experiment". Through this process, as she explained in the interview, she aims to answer the following research question: *What effects does longer lasting stress, in the form of dexamethasone, have on transcription?* Therefore, she has decided for a three, a six, and twelve hour long condition in which she stimulates her cells to dexamethasone for three, six or twelve hours. It is the first study to investigate this question in human neuronal cells so there is not yet a theoretical basis for her to refer to when considering, for instance, which time frames would yield the best results. In choosing these rather arbitrary periods, she "can estimate at least a little bit how the gene transcription changes during this time," while she clearly states that, "If one would take other times, one would simply have different results" (Adriana, pos. 59). In contrast to this arbitrariness, the connection between dexamethasone and stress seems to be rather fixed: a longer exposure of cells to dexamethasone is considered to imitate a longer exposure to "prenatal stress". It therefore appears as something quantifiable, measurable and traceable in epigenetic processes of gene expression.

4.2.1.2 Cerebral organoids: studying mental health in a three-dimensional tissue model

Emma is a postdoc with a scientific background in neuroscience and molecular biology. Since starting her career with the institute, she has been working with cerebral organoids to elucidate how acute and chronic stress impacts the early development of the human brain. For Emma, organoids help her to

"reflect in utero brain development", as she explained in a session of the lab's data club (fieldnotes, 14.2.18). While this is the same claim that Adriana made about her cell model organism, in the following section I will show how Emma's and Adriana's research arrangements still differ in certain of the hypotheses that the different model organisms facilitate. Before I turn to Emma's research practices, I will briefly introduce organoids as novel tool for biological knowledge production.

Organoids are one of the most recent *in vitro* tools used in biomedical research. In 2017, *Nature Methods* chose organoids as "Method of the Year" due to "their fascinating potential as tools to probe human biology and disease" (N.N., 2018). Their etymological background from the ancient Greek "órganon" for organ/tool and "eidos" for figure/form already indicates their relevance for research in cell culture: organoids are artificially grown miniature cell clusters meant to resemble the basic structures of an *in vivo* human organ. In general, "an organoid is now defined as a 3D structure grown from stem cells and consisting of organ-specific cell types that self-organizes through cell sorting and spatially restricted lineage commitment" (Clevers, 2016, p. 1586). Therefore, they are regarded as cellular systems that are supposed to "reflect key structural and functional properties of organs" (Clevers, 2016, p. 1586). No matter whether it is a kidney, retina, or skin organoid – the basis for every organoid is always the induced pluripotent stem cell. As i*n vitro* models, organoids are grown in the petri dish and scientists use cells' self-organising qualities to generate them.

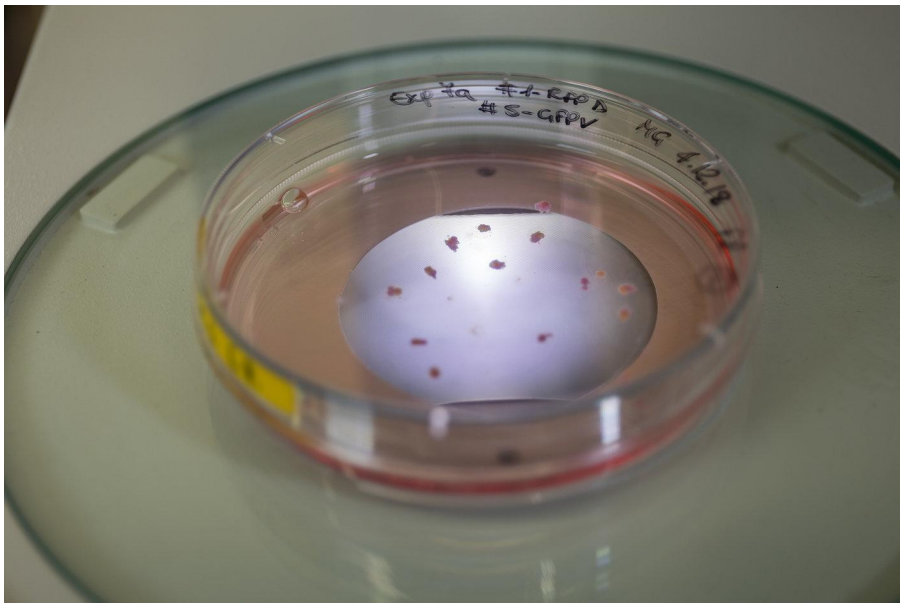

FIGURE 7. Cerebral organoids in a red culture medium (retrieved from https://www.mpg.de/12822832/0312-pskl-115279-organoide-bilden-entwicklungsstoerung-nach on 19.8.20)

Two visions accompany the progress in growing organoids. First, scientists hope to be able to develop alternative therapeutic strategies. In this context, they imagine, for instance, that they will at some point be able to generate a functioning organ that can be transplanted without the danger of an organ

rejection reaction in the receiving patient. Second, organoids are interesting subjects for conducting biomedical research. Scientists use them with the intention of gaining a better understanding of how human organs develop (Eisenstein, 2018). While the former of these two visions is still in the distant future, the second is already part of some biomedical research laboratories, as in the institute where Emma and her colleagues work with cerebral organoids.

I will begin my analysis of Emma's research approach with an excerpt from my interview with her in which she explained in detail how organoids can be generated. This is interesting as it vividly shows modern biotechnology's achievement of being able to build models that approximate human tissue and increasingly authorise scientists in their claim-making.

> Yea. So… so they can be made from any kind of stem cells. … Now we can take skin cells and then return them back to a stem cell state, which is like (.) amazing [*enrapt*] – right? – [*clapping hands*] it's like science fiction stuff. … And these re-programmings happen through epigenetic mechanisms and their… the cell's maturation also happens throughout epigenetic mechanisms, so it was believed that – you know – once this DNA methylation and other epigenetic conformations are put on the DNA, that's it, it's sealed for this path, but now you can kind of remove it, clean it up and then give it another identity. So, that's just the long way to say, now we can get induced pluripotent stem cells, … and we get them from anybody, from you, from me, any of the patients we have. … We then tell them to go down a lineage of brain. And… you use some chemicals that tell them: oh, this is a brain environment, as opposed to limbs for example. … And this can happen *in vitro*. So, cells first of all like to attach to other cells, so one thing we do in the beginning is, we give them a surface they can attach to. It forces them to attach to each other and form this 3D thing and they keep growing, and then at some point we give them… we put them in an extracellular matrix… So, this scaffolding in-between cells, they are just like… if you think of it as a mash… And… yea, now people are working on different tools… different… sort of improving, to say: I want to make a hippocampus [*hitting on the desk*]. So, if I want to make a hippocampus, then I know that the hippocampus needs – I don't know – this transcription factor… But the ones we use right now are kind of general brain, which means… so, you are not going to see them look like a brain, or… they don't form in like this two-lobe thing that the brain has, but they do have the structures of the brain, they are just not in the right order… So, organoids form these ventricles, so far, they don't do the folding. (Emma, pos. 19-22)

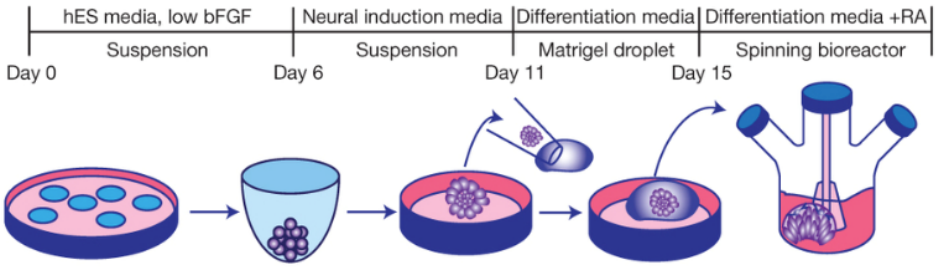

FIGURE 8. Generating a cerebral organoid with the use of specific differentiation media (Lancaster et al., 2013, p. 15)

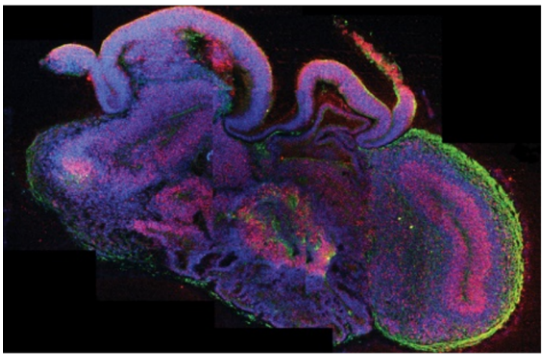

FIGURE 9. Cereberal organoid dereived from iPS cells with neural stem cells labelled red and neurons labelled green (Eisenstein, 2018, p.20)

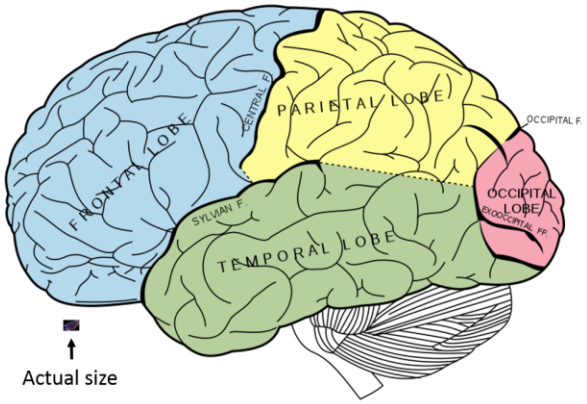

FIGURE 10. Comparison to the basic structure of a human brain (illustration provided by Emma)

Indeed, research with organoids is reminiscent of the storyline of a science-fiction play: the reprogramming of cells; the cultivation of three-dimensional clustering of neuronal cells; the idea of growing different brain areas – all of these modern biotechnological practices are supposed to contribute to building a model for a more profound understanding of mental health. Organoids are the most recent actors in this science-fiction-like scenario in which epigenetics has a twofold significance. First of all, generating organoids is based on epigenetic mechanisms. Scientists use the core characteristic of epigenetics as a signal to the cell to differentiate and reprogram the stem cells into neuronal cells. Second, organoids are at the same time applied as model organisms to *produce* novel environmental epigenetic knowledge about mental health. Hence, epigenetics is both the starting and the target point in Emma's research with organoids.

As Emma has only recently begun to work with organoids, her overarching aim is to establish a model of stress in cerebral organoids that she can use to elucidate the impact of stressful life experiences on gene-regulatory processes in the brain. In this context, organoids are deemed appropriate as a model for the human brain, as a "rudimentary cortex" to model "primitive forms of brain development in 3D" (Lucas, pos. 18). The organoids that Emma applies in her research are supposed to resemble "general brain[s]" (Emma, pos. 22). As mentioned earlier, the basis for generating organoids is formed by iPS cells. Some of them are derived from human blood cells called erythroblasts. Other cell lines are donated by collaborators or purchased from a cell repository in Japan called "RIKEN" which is regarded as a pioneer in the clinical application of iPS cell technology. The cells that Emma and her colleagues obtain from this research institute are derived from skin cells called fibroblasts. As Emma explained to me, "All reprogrammed iPS cells should have equal potential to become any new cell type, no matter the source of cells that they were derived from" (e-mail conversation with Emma, 2.5.18).

As a "tool that [is] close enough to the brain" (Emma, pos. 17), cerebral organoids serve Emma in her effort to retrace brain development in early, prenatal life phases. This is an intriguing notion, as we cannot avoid asking what does *close enough to the brain* in this context mean? What qualities count as *close enough*? And what would disqualify an organoid from being a *proper* model? First of all, for Emma, organoids are a connecting model: they form a bridge between peripheral samples and post-mortem research. Why does Emma consider this bridge important? As she stated in the interview, peripheral blood samples would be widely accessible, however they are too "far from the brain" (Emma, pos. 18) to facilitate claims about epigenetic changes in neuronal tissue. Also with post-mortem material, she recognises a limitation that makes research considerably more difficult: post-mortem brain cells would be very precious research material, but would contain "the whole history of the human being" (Emma, pos. 18). This fact certainly poses an epistemological limitation as researchers could not be sure what they are actually measuring. With the achievement of developing cerebral organoids, the main benefits of both research subjects – the accessibility of peripheral cells and the cell-specificity of post-mortem brains – are incorporated into one model organism, therefore bridging the two approaches.

The second reason that organoids are regarded as *close enough* to the human brain is their genetic similarity to humans. In contrast to other model organisms, such as rodent models, organoids are built from *human* cells, and are hence deemed appropriate for elucidating *human* molecular responses to stress. Beyond this cell-specificity, which is very important in epigenetic research, organoids are models that even contain different brain cells in one and the same system: they are multicellular. This means that, by applying cerebral organoids, researchers assume that they are able to measure how cells *communicate* and, as we will see below, how this communication might affect the brain as a whole organ. The biotechnological achievement of the creation of organoids as a scientific model can be interpreted as an attempt to approximate the human brain as an important epistemic object of psychiatry. These claims about the relationship between the model organism (the organoid) and the organism being modelled (the human brain) can metaphorically be described as being "'stacked' in an epistemic scaffold" (Nelson, 2013, p.8), which is the process of building up a case for a model. STS scholar Nicole Nelson uses the metaphor of an *epistemic scaffold* to examine the dynamics of building claims about what a model is supposed to demonstrate. An *epistemic scaffold* "supports the use of a particular test for producing particular types of knowledge about the human" (Nelson, 2013, p. 5).

Emma applies cerebral organoids in combination with dexamethasone, which represents her "stress paradigm". In general, she pursues three different research approaches to investigate environmental epigenetics and mental health. The first is comparative, using organoids alongside other scientific models. This approach is based on biology's assumption that stress is a reaction that affects the *whole* organismic system – that stress induces a "systemic" response. However, the epigenetic effects of

stressful experiences are described to be highly cell specific. This means that biologists can measure stress reactions in epigenetic changes in the blood, such as in specific DNA methylation patterns. It is, however, still unclear what conclusions can be drawn from these measurements regarding the epigenetic effects of stress in the brain. To get closer to a possible answer to this question, Emma and her colleagues therefore attempt to comparatively analyse the effects of these stress responses "across a number of different biological environments" (Emma, pos. 79). As *biological environment*, Emma denotes different human and non-human tissues in which epigenetic changes due to stress are measured. The idea is to elucidate whether the changes that are related to dexamethasone in organoids can be compared to changes due to stress or dexamethasone in other tissues. As she elaborates:

> So actually, that's a... that's a cool thing that we... we thought about doing as sort of a side project recently to... because we have a lot of these projects, where people – you know – administer dexamethasone either to mice, to cells – was it blood cells, was it brain cells, was it organoids – and then... so we want to take all the data and then try to analyse like what the system's biology responses are and see which ones are parallel across all these different scenarios to then answer that question, like: if we are looking at these change in the blood, can we assume that it's happening in the brain as well? (Emma, pos. 81)

What becomes clear in this research approach as Emma adopts it (even if she has not yet started the project) is that she uses the structural similarities of organoids to human brains, their property of being "close enough to the brain", to perform comparative analyses that target the cell specific epigenetic changes due to stress, which in this case is dexamethasone exposure, across different biological scenarios. The idea behind this comparative approach is to establish causality between the measurable stress response in peripheral tissue and the stress response in neuronal tissue.

In addition to this comparative approach, Emma also applies organoids as a single-approach model for brain development. In this context, she aims to elucidate how stress-related epigenetic changes may affect the differentiation of brain cells, thereby changing the organ as a whole system. Here, Emma takes advantage of the main property of organoids, namely that they combine different brain-like cells in one model. Unlike the neurones employed in Adriana's research, which are the most common but only *one* type of brain cell, organoids are built as models that combine a set of *different* cell types at various developmental stages: neural progenitors, neurones, and glial cells such as astrocytes.

For the analysis, however, this advantage turns out to be rather a methodological challenge: as the cells within an organoid stick together in clumps, they have to be separated as Emma needs them as single cells in order to analyse them. As she told me, it would be "quite a long process to get them to separate without killing them" (Emma, pos. 52). To verify that the cells are alive, she stains the cells by using fluorescent markers. She "only choose[s] the ones that are alive, because if the ones that are dead, what happens is, their whole machinery just shifts and so you don't want to look at that, because that's not going to tell you anything about the biology" (Emma, pos. 53). As Emma told me, researchers have different ways of separating these cells for (epigenetic) analysis. They can, for instance, use single-cell approaches. Here,

Emma and her colleagues look at the whole transcriptome or epigenome of individual cells by using techniques based on microfluidics. According to Emma, this would be "the most unbiased way" (e-mail conversation with Emma, 2.5.19), as it is a rather holistic perspective on the organoid as a whole. When they aim to look at epigenetic processes or RNA methylation patterns in specific cells, Emma and her colleagues use FACS: Fluorescence Activated Cell Sorting. This is a method based on antibodies specific to proteins that are in turn unique to specific cell types, such as neurones. Here, they select only the cells of interest and can then look at epigenetic mechanisms in a group of cells which are more or less all the same (e-mail conversation with Emma, 2.5.19).

Emma regards this as a valuable property of organoids as, much like other researchers, Emma too assumes that epigenetic processes in hippocampal cells may have other effects for organisms than epigenetic processes in cells in the prefrontal cortex. The basic question Emma is pursuing in this context is how different brain cells "are communicating with the others" (Emma, pos. 20). She elaborates that this is a research question she can answers only "with these organoids because they are more... more complex" (Emma, pos. 20).

The main tool to investigate these questions is, similar to in Adriana's approach, to re-enact early-life stress by applying dexamethasone as a trigger that changes RNA methylation and thereby affects the differentiation of brain cells. Emma's main hypothesis in this line of research targets the experience of *chronic* stress. The reason that Emma focuses on chronic experiences of stress is related to the research results of an earlier project of the institute. Using hippocampal progenitor cells and a series of different durations of dexamethasone stimulation, some of her colleagues have shown distinct responses to "chronic stress", as the epigenetic marks had lasting effects. For Emma, chronic stress is also

> more realistic for the human environment because, acute stress would be when your mom was scared – you know – for one evening, but then it's hard to really link that to outcomes, but when your mom was – you know – malnourished or... or maybe abused during her pregnancy, you see the outcomes in the children, so that's really more. (Emma, pos. 87)

With her organoid approach, Emma aims to replicate these finding from the monolayered cellular model her colleagues have used.

> So, what I hope to see or… that's my hypothesis is, that we will find that exposure to stress over a chronic period will change the direction of cells. So, they will not necessarily develop into the same cell types that they would have without the stress, which means that the whole machinery of your brain is impacted. … What I would like to contribute is really an understanding of stress during brain development, what… how – you know – what is that [stress] doing to individuals, what… what the individual becomes? And are there places where we can intervene? (Emma pos. 63)

What Emma hypothesises within her organoid approach is that chronic stressful experiences affect early brain development epigenetically, thereby affecting the *whole machinery* of the brain. It would change *what the individual becomes*. By administering dexamethasone to the organoids, her assumptions about chronic stress are inscribed into her experimental arrangements. Even if Emma also

speculates that they "maybe … find out, that the chronicity of it [the stressful experience] doesn't matter. Maybe it's just a matter of any stress acutely" (Emma, pos. 63), it becomes obvious how the higher degree of "complexity" in organoids facilitates research questions and hypotheses that fundamentally differ from those formulated in research with other cell culture models. Complexity in this context is related to the three-dimensional and multicellular nature in organoids. These properties would enable Emma to shed light on the *cross-dock* between different cell types which is as "we know… very important, and I like in the organoids that you have the different stages of development in the same space and then you can really see how the cross-dock goes" (Emma pos. 93). Therefore, one of Emma's central objectives is to understand the system's interactions and the cell type's specific responses to stress – an approach that, to date, has only been possible in the organoid model.

Emma's third line of research lies in the combination of an organoid model and a cohort study. The cohort study's aim is to elucidate the translation of a mother's stress onto the foetus. In collaboration with international scientists, she therefore analyses cord blood and placenta tissue to investigate the epigenetic changes due to the mother's stressful experiences. In the interview, Emma imagined how this research could be enhanced by an organoid model:

> I think these tools are continuously evolving and they are getting closer to what we are trying to model. So, what's nice is now – you know – if you have particular … epigenetic marks of interest, you can… so, if you identified something, let's say from our… from our placenta study, and then we say: okay, we think it's this methylation pattern that's doing it, let's create that in an organoid. Instead of giving the stress, let's give the mark that we think is the label. Let's see, if we see the same outcome. (Emma, pos. 95)

Even if organoids are still in a very early epistemological phase with many limitations, what Emma is tracing in the above quotation is their potential for a revolutionary shift in the epistemic framework of environmental epigenetic research on mental illness: instead of re-enacting stress by applying dexamethasone, Emma imagines that in the future she will be able to directly enact the *epigenetic mark* that is supposed to be the consequence of the stress exposure. As she explains, this is a similar approach to research already done in animal models, were scientists remove certain genes "we think are important for this and we see, if the behaviour happens" (Emma, pos. 95). Emma, however, sees such research as limited, expressing awareness that "certain things are… human specific. Especially with epigenetics, it's really hard to study that in other species" (Emma, pos. 95). Emma not only speculates about how environmental epigenetic research might be conducted in the future, she to some extent also challenges the validity of using animal models to study human epigenetic processes – one more reason for Emma to accelerate research on organoids as models for human brains.

In a similar way to Adriana's approach, Emma's research is part of the epigenetic research paradigm of early-life stress. Her specific experimental arrangement of combining environmental epigenetics, organoids, and placenta studies in particular contributes to trends within environmental epigenetics towards shifting the temporal origins of mental health conditions more and more into prenatal circum-

stances. In the interview, Emma also drew attention to the significance of the mother's womb, which is experiencing a rather radical change in recently produced environmental epigenetic knowledge: formerly understood as a form of shelter that protects the unborn from the outer environment, the uterus is now being transformed into an apparatus that is no longer thought to shield the foetus from harmful environmental exposures, but rather to *translate* the mother's experiences onto the foetus. Even if pregnancy has been understood as a sensitive period for the mother and the child before the rise of epigenetic knowledge, with epigenetics the connection of a pregnant woman's (stressful) experiences to her child's later health outcome is amplified: they are thought to be manifested in molecular, epigenetic processes which have enduring effects. This notion of the placenta as transmitter of environmental experiences that take place outside the maternal womb also lies at the centre of Emma's research interest:

> it was kind of believed for a long time, that the baby is protected in the uterus and – you know – nothing happens, whatever can happen to the mother, the baby is protected. But it turned out that it's not like that at all. So, if the mother is really stressed and there is like cortisol like – you know – flowing through her blood, it gets to the baby, because it passes through the placenta. And so, that's what we are trying to model in this and see: if we elevate the cortisol levels and simulating stress in the mother, how does that affect the development of this brain-like thing? (Emma, pos. 29)

From a social science perspective, the attempt to show how motherly stress affects the unborn child via epigenetic mechanisms recasts the mother as a "mediating" (Kenney & Müller, 2017) figuration. Drawing on highly cited papers on rat care behaviour (such as Weaver et al., 2004; Champagne & Meaney, 2006), STS scholars Martha Kenney and Ruth Müller have revealed how epigenetic research of this kind is producing a specific causal relation between motherly behaviour and the health outcome of her offspring: these rat experiments assume that the "environment" is reflected in the rats' behaviour, by suggesting that pregnant rats that had experienced stress in the last third of their gestation period will show limited care behaviour towards their own offspring. Such experiments display the mother rat as a victim of the stressful environment she has experienced. Kenney and Müller (2017) argue that, with the translation of such research to the human context, a translation we can already observe,

> mothers are figured … inherently less powerful: … they become pliable mediators of the environment that they themselves are experiencing. Behaviorally vulnerable to environmental experiences, this figure of the mediating mother is programmed by her environment in the same way as she programs her offspring. Her behavior is not her own; it is a mediation of the environment. (p. 33)

What Emma hypothesises in her research suggests a similar direction of how the figure of the mother is re-interpreted by knowledge in environmental epigenetics, despite using a different experimental arrangement than the animal researchers cited above. The *brain-like thing* that Emma mentions above are the organoids she is working with. In this context, it becomes illustratively clear that Emma employs organoids to model the brain of the unborn child. Applying dexamethasone to this in *vitro cell* formation is one attempt to mimic the correlation of how a mother's stressful environment is

transmitted epigenetically to the offspring. By analysing DNA methylation and RNA expression in the organoid, Emma believes that she measures "chang[es] in the biology" (Emma, pos. 29), as she told me in the interview. Here, dexamethasone is regarded as an adequate model for maternal stress, as it is ascribed the ability to release the same physiological and epigenetic processes in the cells as the actual event under scrutiny: the *in vitro* binding of dexamethasone to the GR in the organoid is placed on the same level as the *in vivo* binding of cortisol to the GR in the human brain.

4.2.2 Coda

As I have shown in this subchapter, scientists at the institute apply different cellular models to investigate epigenetic mechanisms initiated through stress. In the concluding section of this subchapter, I will briefly summarise the researchers' practices to operationalise stress within cell culture research and delineate how the different model organism facilitates equally different statements about epigenetics and neuronal development, considered to be the key structures of mental health conditions. In addition, I will embed these cellular research arrangements within the overall research choreographies of the institute.

In both model organisms displayed above, pluripotent stem cells and cerebral organoids, the glucocorticoid receptor and dexamethasone are central biochemical agents. Researchers use the property of dexamethasone as binding to the GR as a basis for modelling stressful experience in their cell organisms. Since the GR also plays the significant role of a stress response *in vivo* – that is to say, in the living organism – applying dexamethasone is a research practice designed to re-enact stress in the laboratory context, making stress a part of a wide range of human experiences amenable in molecular biology.

What we can observe in this context is how epigenetic research within cell culture focuses exclusively on the *cellular* responses to stress, which in itself is no surprise, since the researchers use neuronal cells as epistemic objects. What we can also observe, however, is how the application of these specific cell-dexamethasone combinations as a reductionist approach towards human development is regarded as translating a broad spectrum of social experience into specific measurable epigenetic marks. The scientists' assumptions of what exactly their experimental arrangements are supposed to model remains to some extent rather vague, ranging from "prenatal stress" to "childhood abuse".

Environmental epigenetics within cell culture research thus provides researchers with a molecular connection between cells and their environment. Through the specific cell culture approach, epigenetics is first and foremost enacted as a *semantic* and *practical* connection that enables researchers to translate stress into displayable characters, among them DNA methylation patterns or RNA transcription processes. Stress or environment, in this context, remains fractured as a signal to the cell to

initiate gene transcription processes. Applying dexamethasone as a pharmacological proxy for psychological stress also quantifies something that is in principle unquantifiable: the subjective experience of one's own socio-material environment. The attempt to conceptualise stress as a multifaceted element of the social world in one single pharmacological substance is part of everyday laboratory practices of reducing complex phenomena to parameters that are "researchable". This form of "pragmatic reductionism" (Beck & Niewöhner, 2006) is performed in order to permit some degree of reproducibility and comparability; still it turns dexamethasone into a cypher for a diversity of early adverse life experiences and therefore needs careful and attentive translations when it is used to explain human mental health conditions.

While both cell research approaches delineated above are used to model and investigate early neuronal development, Emma's cerebral organoids enable a more specific approach to the human brain, the object they are supposed to model. Emma regards them as models "closer to the human brain", as they are three-dimensional cell clusters and entail a higher degree of complexity than Adriana's neuronal cells, which are attached in a mono-layered way to a culture medium in the petri dish. Comparing Emma's and Adriana's approaches reveals that as the complexity of the model organism increases, the psychosocial category of "stress" becomes equally more embodied and specific. While Adriana fundamentally investigates how neuronal cell development changes through "prenatal stress", Emma's organoid approaches allow her to speculate about how the embodiment of stressful experiences at a prenatal developmental stage might change what the organism becomes. Since organoids are regarded as a more human-like model due to their specific structural properties, they also allow for more specific statements about human conditions, even if stress as a complex category still remains factorised as a molecular response.

Both cell culture models contribute to the overall choreography of the institute in a specific way. Since they are regarded as tools to study stress responses of human *neuronal* cells *in vitro*, researchers frame them as epistemic supplements to other studies. As we will see in the subchapters that follow, although researchers have access to brain cells in mouse models, these are not human cells. While cohort studies provide scientists with human cells, these are only peripheral cells, and the significance of epigenetic results in these cells for brain processes is still unknown. Serving as an epistemic supplement, cell model organisms are instances to test specific research hypotheses regarding their *molecular* or *epigenetic* underpinnings. For neuroscientist Stella, who as a director is involved in many of the institute's studies, cell models thereby provide the opportunity to test whether observations made in humans are "just associations", or whether there is a "causal connection":

> Okay, we're going into... in humans and we find out through our genetics, gene expression, epigenetics studies things that are associated with certain changes in brain reactivity, psychophysiology, symptoms and maybe we can better characterise these patients. … This means that we first discover the causal relationship in humans and then go into animals and cells in order to test it again or...

> and then to say again maybe to do such a fine-tuning with the hypothesis and then to go back again in humans. (Stella, pos. 23)

As becomes clear from the above quotation, the institute's research approaches with cells are supposed to deliver the mechanistic underpinnings for observations made in humans, a *fine-tuning* towards a molecular understanding of mental health conditions. As Emma concluded in my interview with her, psychiatry "really in a sense [is] behind a lot of fields, like cancer and whatever, we are... because we can't get the right tissue that we are looking for" (Emma, pos. 43). What she emphasised in this context is that mental disorders are "systemic diseases", they affect the whole body. However, through research in cell models she and her collaborators are "trying to really establish now the molecular biology behind it and really to see the epigenetic side of it" (Emma, pos. 33), in order to better understand mental health and "to make it more biologically relevant" (Emma, pos. 4).

4.3 Epigenetic research with mice models: enacting an observable change in the organism

In this second subchapter, I will turn to the institute's specific research arrangements in which scientists resort to mice as model organisms to produce knowledge in environmental epigenetics. In describing in detail their research practices and testing arrangements, I will showcase mainly three scientists and their different approaches to environmental epigenetics and mental health. As in the previous subchapter on cell research, I will describe and analyse the practices that scientists employ to re-enact stress in their mice models – practices that range from pharmacological to behavioural interventions with the aim of producing epigenetic accounts of mental health. Before I introduce the first research scenario, I will briefly delineate how and why mice are regarded as good "tools" for thinking in biomedical research. This is important to understanding how knowledge from environmental epigenetics to a certain extent leads scientists to rethink "classical" research arrangements with mice.

Laboratory mice and scientists: a multi-species encounter

> Where there are humans, there are also mice. (Max-Planck-Gesellschaft [MPG], 2003-2020; author's translation)

This is how the Max Planck society, an important German research organisation, summarises the relationship between humans and mice, stressing that the house mouse has benefitted greatly from humans: "it has followed humans on their migrations, gradually conquering all continents … due to the development of agriculture, livestock and plant breeding, because with this, humans have opened up quite new habitats for the small rodents" (MPG, 2003-2020; author's translation).

In light of today's laboratory culture, this depiction of mice profiting from humans seems rather to have turned around. Since the nineteenth century, scientists have been deploying mice in life science

research with the predominant aim of understanding human pathologies or testing the efficacy of therapeutic drugs. Therefore, scientists analysed the genetic variability in mice to identify the genetic similarities and differences to humans, information necessary to legitimise mice as valid model organisms for human conditions. As researchers found that 95 percent of the genes in the mouse genome are found in a similar form in humans, they have come to conclude that many "of the diseases of mice and humans have the same genetic cause" (MPG, 2003-2020; author's translation). This genetic similarity has brought human diseases like cancer increasingly into the focus of basic research with mice. Hence, today, scientists use the genetic proximity to harness mice as experimental objects for scientific knowledge production. Other characteristics that are also frequently cited to describe mice as adequate laboratory animals are their cheap maintenance, their easy manipulability, their tolerance towards inbreeding (in order to have mice with the same genetic background), or their "predator anxiety", which can be harnessed as a behavioural test in different experimental arrangements. Also, research group leader Noam enthusiastically recognised mice as a valuable laboratory "tool" and especially emphasised the biological manipulations that can be performed on mice:

> It's the closest model to humans. … And I think the mouse is a great tool, it's very important to the stuff we can do in any other model, but it's very important… to improve the tools, the methods we have, not in genetics, because in genetics we are perfect with mice, there are so many techniques [in which] we are great, we can remove genes, we can add genes, we can use viruses. (Noam, pos. 20)

Against the background of the wide application of mice in laboratories, today's relationship between mice and humans has turned from a companionship to a relationship that could be described as an "epistemic partnership" (at least concerning the scientific world). Over the last decades, scientists have developed manifold techniques to harness *mus musculus* – the house mouse – for biotechnological knowledge production: they manipulate mice by removing or adding certain genes, they infect them with specific viruses that induce cancer or they place them in testing arrangements to observe their behaviour under specific circumstances. "We can do everything in mice," is how Noam summarises the advantages of this model organism for biomedical research.

While there exist quite a few different experimental arrangements in which a mouse can be applied as a research object, the mice used are always bred to serve as a tool for biological knowledge production. Laboratory mice are not "wild type" mice, but are raised with the aim of genetic unity. In addition, they live in a reductionist laboratory environment from birth. The current laboratory mouse was bred from the three existing subspecies of the house mouse and hence contains genetic information from all three forms. It is therefore a hybrid organism. Some scientists regard the differences between the wild type and the laboratory mice as so great that they have established a new category for the second: the *mus laboratorius* (MPG, 2003-2020).

The establishment of mice as tools for scientific knowledge production is also obvious in the commercialisation of mice for the laboratory context: they became "a crucial part of the machinery of contemporary biomedicine" (Nelson, 2018, p. 2). As not every research laboratory has the capacities to breed or to generate its own mice models, pharmaceutical and medical corporations provide scientists with specifically modified mice and distribute them via online shops. In these online shops, scientists can choose between hundreds of laboratory "products": from extracellular amplifiers, to petri dishes, to mice. Depending on their research questions, they can order genetically modified animals that are assumed to model human pathological conditions. These models are termed as "diabetic fatty rats", for example, or "ApoE knockout rabbit" and are classified according to categories such as "Oncology", "Immunology", or "Cardiovascular Disease". The option to order "ready-made" mice for scientific laboratory work renders them as universal epistemic elements of scientific knowledge production with clear, pre-set "functions". Hence, the mouse has been commodified into a biotechnological tool serving the scientists' knowledge production by their integration into research projects.

In the laboratory the mouse and the scientist enter into a relationship, a multi-species encounter (Wilkie, 2015). It is a relationship between observer (the scientists) and observed (the mouse) that facilitates the carrying out of scientific research. The mice in this sense become epistemic partners: as mice are living creatures that are even assumed to have their own personalities, that is to show individual behavioural traits (Noam, see Ch. 4.3.3), they play an active role in the experiment and are not merely passive objects of scientific scrutiny. Especially in behaviouristic experimental arrangements, the scientific way of knowing is dependent on the researcher's expectations and affections, which might influence the mouse's behaviour. Researchers and mice become what Despret (2004) calls "sensitive" (p. 114) to each other: in contrast to other research subjects, such as cells, lab animals might respond to a researcher's expectations of an experiment's outcome.

The particular relationship between mice and scientists is also embodied in the fact that mice live in the laboratory and – as they are living organisms – have to be cared for by the researchers and technical assistants. The specific relationship researchers maintain with "their" mice often became visible to me – as was the case, for instance, when I witnessed how cognitive scientist Julie talked to the mice of her current experiments. She addressed them as "cuties", asked them "how are you today?" and purred in a high voice: "Look at those, aren't they cute?" (fieldnotes, 24.4.17). And once while I was making my way through a long corridor at the basement, one door in particular caught my attention as it also hinted to the particular role, mice have in the lab:

> The door is pasted with stickers and small posters. A white mouse is looking at me and communicates: "I love my cage!", which personifies it in a rather strange way. However, there is also a message by the scientists themselves, expressing their careful relationship to their mice: "We take care of our animals, as if our lives depended on it." I stand in front of the door, thinking about this bizarre mode of caring and asking myself who might have applied these posters and with what intention. (fieldnotes, 11.5.17)

This dialectic between caring for animals[32] – feeding them, soothing them or warming them while they are under anaesthesia – and simultaneously conducting stressful experiments with animals – placing them into stressful testing arenas, injecting viruses into their brains or reducing food supply – is a phenomenon of biomedical research the Swedish feminist STS scholar Tora Holmberg (2011) metaphorically calls *mortal love*. "How is it possible to both love and harm?" (p. 147), she asks in her paper on care practices in animal experimentation. For her, the affective dimensions of working with animals, such as emotions of friendship, are "intrinsic elements of the embodied animaling of experimental human-animal relations" (Holmberg, 2011, p. 161). Care practices in the experimental apparatus are therefore subtle practices that enrich a mouse's life and death.

This "paradox of care" (Lappé, 2018) not only denotes the centrality of care practices in scientific knowledge production but also reveals that caring and killing must not be contradictory activities. They are two logics of the same practice. They also give some researchers a certain legitimacy to work with mice. Neuroscientist Nadja maintains a very specific narrative of justification. She told me that she never could kill a rat, as rats would be "very social" living beings and would "recognise" their conspecifics and their owners. "How terrible must it be, when you're killed by somebody you know?", she asked. In this context, an interesting twofold practice of legitimising mice as good research subjects becomes visible: on the one hand, their genetic *similarity* to humans makes them a supposedly appropriate scientific tool to analyse genetic and epigenetic processes. On the other hand, the behavioural *distance* between humans and mice – the ones being "social" and the others being rather "antisocial" – legitimises the manipulation, harming, and killing of mice in the name of biomedical science, at least according to Nadja's logic. In this differentiation, the "perceived similarities … allow one to think with animals, just as it is the perceived differences that allow one to treat them very differently" (Roepstorff, 2001, p. 215).

In the following chapter, I will elaborate on these practices of applying mice in environmental epigenetic research – how they are treated "differently". To this end, I will showcase different experimental set-ups that work with specific mouse models in order to illustrate in each case how environmental epigenetics is enacted in a way that is specific to the chosen mouse model. I will first describe and analyse scientists' work with mouse models in which stress is enacted by intervening pharmacologically in the mouse body. Here, I will show how the experience of stress is turned into a quantifiable phenomenon accessible in the laboratory (similarly to as in cell culture research). I will, in the second place, describe the practices employed by scientists to apply the "chronic social defeat" set-up, an established testing arrangement that predominantly works with two mice and accentuates the behav-

[32] In the institute, animals are not the only subjects that are cared for. Cells also receive a specific form of care, which I also saw performed linguistically: cells had to be "fed" with nutrient solution, they "like" a warm temperature, "don't like" surface tension and have to be handled "gently". All of these practices are applied to reduce the error ratio and to target the best possible comparability.

ioural aspects of interpreting results. Third, some scientists at the institute have established a rather novel approach to studying and modelling mental health conditions: the so-called "social box paradigm". As we will see later, this is a specific testing arena that is believed to mirror some degree of the complexity of the human world and that in this vein challenges classical stress tests in genetic and epigenetic research. Finally, I will showcase researchers' practices that apply epitranscriptomics, a novel research approach that focuses on RNA modifications instead of on DNA modifications as we find them in "classical" approaches. As my analysis will show, this epitranscriptomic approach is ambivalently again a rather reductionist way of investigating human mental health.

As scientific knowledge production is dynamic and complex, all four experimental scenarios cannot be demarcated clearly from each other but are rather characterised by overlapping elements. Also, the portrayed researchers do not work exclusively with the tools and techniques I present in the following analysis but are connected through collaborative projects and research objectives. We will also find similarities with approaches from cell research. Nevertheless, my analysis demonstrates how the decision for certain experimental designs in mice primarily articulates and facilitates equally specific epigenetic accounts.

4.3.1.1 Pharmacological and behavioural experiments: the "classical" approaches to studying mental health conditions

> Nadja: So what... what does the environment do with the genes? – it's the interface, so what... the environment, so to speak, the environment precipitates itself via epigenetics to the genes and changes the phenotype
>
> Me: What then is environment for you?
>
> Nadja: Environment is all kinds of things to me. The environment for me is toxins, whether I smoke or drink [*laughs*], whether I have stress, whether I take medication, my psycho-social environment, whether I have contacts that can absorb it when I am stressed, what I eat, what I can eat, because I can afford it, it's the economic environment in which I grow up, whether I'm abused in some way at home or whether I can go to school and have 13 years of school or 12 years of school and then get paid to study, that's all one... a hotchpotch of things. ... Actually, every... every activity I do – when I read something, I also do something with my epigenetics, because then I learn something and that leaves its mark. Yes, that was very comprehensive now. But in fact, it's really all epigenetics. (Nadja, pos. 121-123)

Nadja is a postdoc researcher at the institute who predominantly works with mice as model organisms. She was trained as a biological technical assistant and has studied neuroscience. As the quotation above shows, she is one of the scientists I have talked to who apply a rather global definition of what can constitute an epigenetic environment. We will see later in this subchapter that, despite her comprehensive description, in her research practices she focuses only on very specific environmental factors.

For several years now, she has been conducting research on environmental epigenetics. This reflects a shift in her research perspective that she describes as having happened "more or less by chance". Her narration of how she came to work with environmental epigenetics is an interesting retrospective story, since it is part of a general "hunch" in the field of molecular biology; at the same time, however, it is also anchored in a specific mouse model which has Nadja left with open questions and therefore prompted her to shift her research perspective to environmental epigenetics. In describing her interest in and fascination with epigenetics, Nadja narratively draws from the often referenced nature/nurture divide: in her work, she would have been surrounded by biologists as well as by psychologists, with the first being mostly proponents of *nature* and the latter being mostly proponents of *nurture* regarding questions that address health and illness:

> There was always this dispute and I never understood it. And I just thought back then, I think there is something in both of them and that has to be somehow connected and that cannot just... it cannot just be the genes and it cannot just be the environment, both are totally wrong and that turns out to be true now. (Nadja, pos. 17)[33]

In Nadja's narrative, environmental epigenetics appears as a mediator between two dichotomous disciplinary positions that seemed to be rather incompatible before, seeing the human organism as flexible and plastic instead of genetically rigid. The metaphor of environmental epigenetics being an "arbiter" that can solve conflicts that take place in scientific and academic discussions on how to understand human development is part of a general conceptualisation we can observe in the life science discourse (Pinel et al., 2018; Stelmach & Nerlich, 2015). Through this metaphor, "epigenetic markers can be understood as enablers of communication between environment and genome, capable of processing and organising signals so as to regulate the interactions between the actors of epigenetic relationships" (Pinel et al., 2018, p. 276).

This shift in perspective – from organisms being genetically rigid to malleable via epigenetic mechanisms – also led to a shift in interpreting results from experiments with mice. As Nadja explained in the interview, conceiving of organisms as plastic turned behavioural differences observed in mice experiments that could not have been explained before into explicable phenomena. This re-conceptualisation was also the central catalyst that prompted Nadja to fully turn to environmental epigenetic research approaches at a time when she was establishing a stress-experiment in neuroscience:

> I actually found... there is one test, the so-called "free choice open field test", which is such a real trait anxiety test for mice … . Because of the fact, that the mouse is housed in the home cage and then after three days the door is opened, it really can decide: do I go to this open field? – and it is not forced into it. And that's really this trait, to decide endogenously: do I go out there or do I not? And that correlated with the subsequent [molecular] response to... stressors. … And with this test, you could actually predict like with a crystal ball in principle two groups: mice that go out and

[33] Of course, it is difficult to know whether her retrospective narrations are due to her individual experiences or if they are just imbued by wider field-specific discourses about how epigenetics became meaningful.

> mice that don't. And the thing is, I did that on... on C57 mice and these are inbred mice, which means that they are genetically almost 100% the same, therefore, in fact it can only be epigenetic. (Nadja, pos. 17)

The above quotation powerfully illustrates how an anxiety-related behaviour in mice (conceptualised as a model for the human trait of *anxiety*) is reduced to one single mechanism: epigenetics. The basis of Nadja's argument is the rodents' *avoidance behaviour*, a behaviour that biologists relate to "trait anxiety" in mice. The so-called "free choice open-field test"[34] that Nadja describes in the above interview excerpt, is derived from the ethological observation that, on the one hand, mice want to stay in a familiar, secure place, but on the other hand tend to explore new environments when they are exposed to them. The test is taking advantage of this assumed inner conflict in mice: mice that avoid exploring are aligned with what is called anxious behaviour in humans; they have "anxious-like phenotypes".[35] As Nadja's narrative reveals, she bases the differentiation between "anxious" and "courageous" traits in mice on *epigenetic* mechanisms. Since the mice have the same genetic background (they are inbred), Nadja has concluded that the behavioural differences can only be explained by epigenetic changes in the mice themselves.

In general, Nadja's research question coincides quite closely with the scientific interests of Adriana and Emma, two researchers who work in human cell models: by conducting research on environmental epigenetics, Nadja also aims to understand mental disorders more profoundly. However, unlike Adriana and Emma, Nadja uses mice as model organisms for human pathologies, which represents a model significantly relevant to the introduction of environmental epigenetic perspectives to psychiatric research (Szyf and Meaney's seminal paper on "maternal programming" has paved the way for epigenetic mouse research in psychiatry). As we will see in this subchapter, mice are model organisms with properties that differ, to a certain extent, from cell models and, hence, facilitate specifically epigenetic accounts on mental health conditions that are different from cell models.

In addition, Nadja places one epigenetic process in the centre of her research: histone modification. The reason that she focuses on this epigenetic process is that histone modifications are described as playing a crucial role in the development of human mental health states. Histones are proteins that exist in the nucleus of eukaryotes. They are part of the chromatin, which is the material chromosomes are composed of and thereby play a major role in the packaging of DNA and in the expression of certain genes. Chemical changes in histones resulting from stressful experiences, for instance, affect the way genes are transcribed and hence are translated into body material. Therefore, histone modifications have been reported to be crucial targets for the interaction with the stress response system and

[34] This animal test is an experimental arrangement to model anxiety in mice. Because of its mediocre standardisation, however, it is also criticised as lacking validity (Walsh & Cummins, 1976).

[35] What the test moreover presupposes is that mice – analogous to humans – have the free will to either avoid the new environment or to overcome their fear and explore the "open field".

are connected to the development of mental disorders, among them depression. This molecular connection is represented in the following illustration cited from one of Nadja's publications:

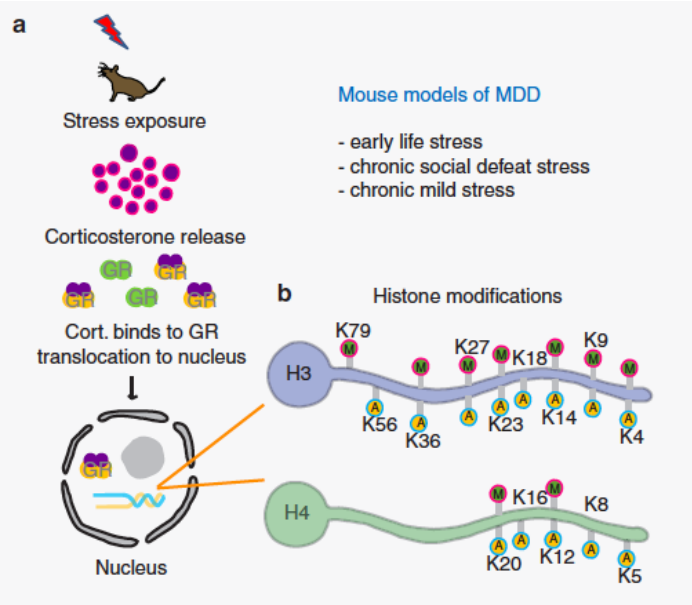

FIGURE 11. Molecular impact of stressors for the development of major depressive disorder (Author X & Nadja, 2017, p. 4)

Nadja attributes the interplay between histone modifications and mental illness (especially depression) to the phenomenon of neuroplasticity, which is the focus of her scientific interest. In the interview, she elaborated on this connection:

> My question is actually to understand neuroplasticity on the molecular level. And that's just changes in gene expression and in order to understand that, one just has to understand such epigenetic markings or marks and I look at acetylation, because it reacts relatively quickly. Of course, I also went through a lot of projects with methylation and the whole thing has something to do with non-coding RNAs too, so I'm looking at different omics sets and... and then putting them on top of each other. (Nadja, pos, 41)

As mentioned earlier, the notion of *plasticity* is a central feature of thought in epigenetic reasoning. It is a concept that co-emerged with the shift from gene-determinism to the notion that the human genome is not stable over the life course but adapts to its environmental surroundings. As the quote from the interview above illustrates, neuroplasticity is connected to epigenetic mechanisms: a better understanding of epigenetic mechanisms is linked to a better understanding of neuroplasticity and thus to a better understanding of the development of mental disorders. In this context, a lack of plasticity for Nadja means a condition that leads to illness: from a neuro-epigenetic view, only *plastic* brains are *healthy* brains:

> Disorders are – well – kind of a getting stuck in a certain state, as the neuroplasticity just doesn't exist. It's no longer present in depression and it's somehow no longer present in schizophrenia. Those people are stuck. … I don't see it as clinician, I see this as a researcher... and from a purely phenomenological perspective, these are changes in the adaptability of the brain. (Nadja, pos. 69)

As we can see in the above interview quote, Nadja relates the development of mental disorders mechanistically to changes in the "adaptability of brains". This is a conceptualisation of mental health conditions, that places the nervous system into the centre of her scientific investigation. In the following sections, I will delineate Nadja's intervention practices in the nervous system of mice as a strategy to study the related epigenetic processes.

Biological interventions in mice

In one of her projects, Nadja intervenes in the mice epigenome by means of biological manipulations. One approach she employs is the knock-out mouse model. In this model, one enzyme that is correlated with histone methylation in neurones is deactivated in the mouse genome: "we have knocked this out in neuronal cells" (Nadja, pos. 45). While the practice of "knocking out" enzymes is narrated by Nadja as rather easy to carry out – "you can use a specific promoter... then this is cut out" (Nadja, pos. 45) – her anticipated results in comparison seem to be very complex:

> So I'll just try to take a look: what actually happens on the behavioural level, on the molecular level, that means gene expression, micro-RNA expression, non-coding RNAs. What happens when you just take that out and how does it affect the... the behaviour? (Nadja, pos. 45)

In this experimental arrangement, we can observe two interesting aspects. First, the mouse model Nadja deploys enables her to pursue a practice that in Emma's organoid approach only exists as an idea, as an imagination of how to carry out environmental epigenetic research in the future: instead of enacting a stressor as proxy for an environmental factor, Nadja directly enacts the cell-type specific modification to study the role histone modifications *in vivo*, in the living organism. Shutting down certain enzymes, a biological intervention into the mouse body, gives her direct access to the mechanism she is studying.

Second, we can see how changes in molecular structures, epigenetic modifications, are placed into a causal relationship with behavioural changes: modifications in histones are known to change gene expression. This molecular change is in turn associated with a change in behaviour, a change that can be *observed* and might only be observed through epigenetic mechanisms, as Nadja's interpretation of the free choice open field test indicates. I will elaborate on this specific style of reasoning (Hacking, 1994) in the next subchapter, in which I will discuss strategies of enacting stress that are described as "social" interventions.

In addition to this biological manipulation based on the removal of molecular information, Nadja carries out interventions by administering pharmacological drugs to their mouse models, "a pharmacological manipulation" (Nadja, pos. 46) as she puts it. Here, she also uses dexamethasone as a stress paradigm: like the researchers from cell research, Nadja administers dexamethasone to mice to simulate experiences of stress and release a stress response in the mouse. As Nadja told me, they have various strategies to intervene into a mouse's organism pharmacologically: dexamethasone can be

applied via intraperitoneal injection into the body cavity, it can be administered through the mouse's drinking water, or it can be dispensed directly into the brain by drilling holes into the skull and injecting the substance dissolved in fluid. In this context, the intended analytical level is the determining factor in deciding which method of pharmacologically "stressing" the mouse will be used. When scientists aim to analyse predominantly central nervous stress effects, they select direct injection into the brain. Oral administration by dilution in drinking water or an injection into the body cavity, on the other hand, enables an analysis of both central nervous as well as systemic effects of stress, as dexamethasone is transported from the peripheral tissue into the brain. This means that these different practices of administering dexamethasone facilitate different access points to the stress response in mice. Such access is made possible above all because Nadja works with a living creature and not "just" with cell clusters. By choosing specific ways of intervening pharmacologically into the mouse body, one substance (dexamethasone) can be harnessed for very diverse targets of analysis.

Furthermore, dexamethasone also allows Nadja to choose between an "acute" and a "chronic" exposure to stress. In injecting dexamethasone, researchers aim to model an experience of acute stress, while by administering it through the animal's drinking water they model chronic stress. This latter approach also allows one to avoid "burdening the mouse with countless additional injections" (e-mail conversation with Nadja, 23.4.19). What we can observe in this pharmacological intervention is a way of enacting stress similar to the cell culture approaches: in adjusting the concentration and duration of the dexamethasone exposure, the stressful experience is translated into a quantifiable paradigm. Short-term applications are connected to molecular profiles that differ from long-term exposures to dexamethasone. In this mouse model, however, the main focus is on dexamethasone as a substance that allows direct molecular access to a living organism; as we will see, this is different in other mouse models. Accordingly, dexamethasone is not so much used as a model for a stressful experience in a human, but is rather framed as a possibility to directly change the molecular mechanism under investigation (histone modification). It is staged as molecular manipulation.

The "chronic social defeat": observing epigenetic change in mice

This chapter has so far focused on biological and pharmacological interventions that induce a molecular stress response in the mouse body. It has dealt with substances that can be administered to a living animal orally or by injection in order to elucidate the molecular basis of the stress response and its epigenetic effects in the mouse brain. Here, stress is directly enacted by the scientists themselves: they apply dexamethasone to the model organism, or they remove molecular information to intervene in epigenetic processes.

However, in psychiatric research, another way of enacting stress in mice is an established procedure which also finds application in environmental epigenetic research: the so-called "chronic social

defeat" model. In this experimental arrangement, researchers aim to elucidate, among other processes, epigenetic changes associated with stressful experiences. As we will see below, chronic social defeat is a scientific apparatus to induce depression-like phenotypes in the laboratory mouse. It is thereby a research practice considered to model depression in basic research with mice.

The very name of this testing arrangement indicates its specificity: it is a "social" stress paradigm and thereby clearly demarcated from other forms of enacting stress, such as pharmacological or nutritional interventions. But what plays the role of the "social" for the scientific community in this experiment? Instead of testing one mouse isolated after the biological or pharmacological interventions described above, in the chronic social defeat set-up two mice are involved in the experimental arrangement. That is to say, while interventions such as dexamethasone exposure are strategies to directly access the molecular stress response, with chronic social defeat, stress is applied as a presumable social variable. The stress response is induced by placing two mice in one cage and harnessing the territorial defence behaviour of mice for research: "the white mouse flogs the black mouse, as it's higher in the hierarchy" (fieldnotes, 28.1.18), as the cognitive scientist Julie who also works with mice expressed rather casually. The scientists are then interested in the epigenetic profiles of the defeated – the "depressed" – mouse. Therefore, in the chronic social defeat model, stress is enacted via *social stimulation*, via *behaviour*: one mouse "stresses" another mouse.[36] In the interview, Nadja elaborated on the procedure of chronic social defeat which Julie has paraphrased as "flogging".

> We use these huge, fat CD-1 mice. This mouse line is muscle-bound, like a pit bull but in mouse form, despite their white colour. … And we select them beforehand, we test them to see if they are really nice biters so to speak, and then it goes relatively fast. … Then we put them in a cage together with another mouse and we wait until we can observe the defeat, that's usually the case after one, two, three bites: fat pit bull mouse comes in, bites the other one in the back and then the defeated mouse turns into a position where it shows its belly to signal, "Don't kill me." And then we put a divider into the middle of the cage and leave the mouse inside the cage, so that the defeated mouse has to smell the other for the next 24 hours and then another pit bull mouse comes in and after 21 days we have a really badly stressed mouse. Yes, and we're also seeing effects on the... the... the histone level, so that... that does a lot. Yes. And the idea is to map now: what are the markers and at which genes and how is the regulation after stress. (Nadja, pos. 52-58)

[36] Within animal research, the discussion around which stress tests are reasonable and thereby should be allowed to be used in biomedical research is a significant issue and legally regulated (in the case of Germany by the *Animal Welfare Laboratory Regulation* (*Tierschutz-Versuchstierverordnung*) that is published by the Federal Ministry of Justice and Consumer Protection). The argument that Julie and her colleagues cite in explaining why the chronic social defeat falls in the category of the permitted experimental arrangements is that here, stress is not directly induced by the scientists themselves but by another mouse. This reflects, in fact, a rather shortened perspective on the expiration of the test: after all, it is the researcher who places the two mice in a shared cage.

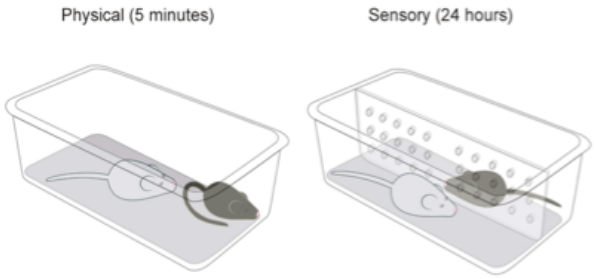

FIGURE 12. Schematic illustration of the chronic social defeat experiment (Engel et al., 2016, p.1883)

Which new perspectives does the chronic social defeat model allow? Which ways of articulating the role environmental epigenetics in context of mental health conditions do we observe? First, the chronic social defeat arrangement accesses a different temporality of organismic development. As I have shown in chapter 4.2.2., cell culture research has a significant focus on very *early life phases*: cell model organisms, like iPS cell systems and organoids, are deployed to model life phases even before birth (by stimulating cells pharmacologically with dexamethasone). Such research is based on the early-life paradigm, a hypothesis that is a common style of reasoning in environmental epigenetic scholarship. The chronic social defeat arrangement, in contrast, allows Nadja to specifically address the effects of stress on and the plasticity of the *adult* organism. Moreover, it is proposed as a powerful tool to investigate the effects of *chronic* stressful exposure, an approach that Nadja describes as allowing them to study molecular aspects of the stress response and treatment strategies in a systematic manner (author X & Nadja, 2017).

Second, the chronic social defeat is a testing arrangement considered to truly model *social* and not *physical* human experiences, it embodies the notion of a "social stressor". In their article on the social defeat experiment as model for depression, biomedical researchers Fiona Hollis and Mohamed Kabbaj (2014) explain that the defeat model has been developed as a progression of animal models of depression-like phenotypes. In the former testing arrangements, researchers induced depression-like phenotypes by exposing their subjects to physical stressors, such as electric foot shocks,[37] loud noises, or cold temperatures. Those would have been criticised as "artificial and not representative of the true nature of stress exposure in humans, which is most commonly *social* [emphasis added] in nature" (Hollis & Kabbaj, 2014, p. 222). Hence, as an alternative model for human depression, the chronic defeat model would focus on "exposure to social stressors" (Hollis & Kabbaj, 2014, p. 222) as, in

[37] In the case of "stressing" mice by this testing arrangement, they are repeatedly subjected to moderate or severe electric shocks over the course of a couple of days, applied to their feet via an electric grid floor. The stress-induced behavioural changes are then observed and assessed by molecular biological methods. This stress-test is (or was) thought to reflect human pathologies such as depression, anxiety, and post-traumatic stress disorder (Bali & Jaggi, 2015).

humans, experiencing chronic forms of stress is associated with a higher vulnerability to mental disorders, such as depression or anxiety (Huhman, 2006).

However, what is thought to be a "natural" (as distinct from an "artificial") stressor in the human world? And which events is the chronic social defeat arrangement supposed to model exactly? What is defined as the "social" in the chronic social defeat set-up? In another paper, neuroscientist Kim Huhman (2006) elaborates on this issue and states that the experience of "losing and … the ensuing social stress that is selectively experienced by subordinate individuals" (p. 640) is reflected in this animal model. As we can derive from her description above, Nadja shares this interpretation: the "normal" mouse is physically subordinate to the "pit bull mouse" and hence can only lose the artificially produced conflict. Here, a difference in hierarchy is the basis of the stressful experience and is at the same assumed to model the experience of a human individual being "bullied" by different events in their life course. After the physical exposure and attack, the "intruder", the weaker mouse, and the "resident", the stronger mouse, are not separated; the former has to tolerate the presence of its attacker for a certain period of time. This is described as a "psychogenic exposure" (Hollis & Kabbaj, 2014, p. 222) that does not physically harm the defeated mouse.

A third remarkable aspect of the chronic social defeat arrangement is the way researchers interpret the results. The interpretation reveals an interesting articulation of environmental epigenetics that refers back to the biological interventions in mice from above: the idea that epigenetic modifications alter *behaviour*. Even if Nadja aims to model a "true" social human experience, in the end she once again focuses on how this experience is molecularly embodied through histone modifications, DNA or RNA methylation. Their basic hypothesis is that "experience can shape brain and behaviour" (Huhman 2006, p. 640). Accordingly, Nadja is interested in the way organisms *behave* after having experienced chronic social stress. In this context, she also studies whether the defeated mice would be more "vulnerable" or more "resilient" to further stress exposures and "how this can be *seen* [emphasis added] in the molecular profile." (Nadja, pos. 46). In this depiction, molecular biology is bestowed with the power to structure behaviour: "Sometimes they [the defeated mice] neglect their grooming and they also change their social behaviour, the stressed mice are not up for social contact anymore. Things, that you somehow can observe in humans [with depression]" (Nadja, pos. 50). Hollis and Kabbaj (2014) similarly report that the induced chronic defeat would lead to various "depressive-like symptoms" (p. 222) in mice, such as anhedonia, social avoidance, locomotor, and metabolic changes – behavioural changes that are referred to on a biomolecular basis: histone modification (Hollis & Kabbaj, 2014, p. 222).

For Nadja, histone modification has a very specific regulatory task. She renders it an epigenetic process mediating between the external environment and the internal genome; a site, where the environment "kicks in" and where exposures materialise in molecular biology. Research from her and

her colleagues suggests, that the interaction of the stress response system with the histone landscape builds one of the *molecular platforms* for the interaction of the environment with the epigenome of an organism. In a publication, they conclude that stressors, therefore, leave "epigenetic scars". Under certain circumstances, these molecular wounds may trigger the molecular and behavioural disease trajectory (author X & Nadja, 2017). The chronic social defeat arrangement is used as a model to study these gene-environment interactions in a presumed very controlled manner, as it facilitates referring the observed behavioural changes in mice back to the "epigenetic scars" through molecular analyses of the mice's brains after the induced stressors. In other words, this mouse model organism propels the hypothesis that adverse experience or stress is embodied in molecular biology, an embodiment that manifests itself phenotypically in the behaviour of the mice. In this vein, epigenetic processes become *observable* with a naked eye.

4.3.2 The "Pheno World" and the "social box paradigm": challenging classical stress tests

It is April, the thirteenth, Holy Thursday, 2017. I am shadowing the neurobiologist Jano. While others colour Easter eggs that day, he ironically has scheduled to dye the fur of the mice he was planning to run the next experiment with: as all of the mice he is using have white fur, colouring them helps Jano to differentiate the mice. After having put my personal belongings into his office, Jano asks me if I would like to see the mice Julie, a colleague of him, painted yesterday. Therefore, we go into the next room. It is dark and it smells of litter and animal. Now, Jano is whispering and shows me a running experiment: I have to stand on tiptoe as the mice are placed in a black box, which stands elevated and is covered with a black cloth. Even the bedding is black. Then, Jano leads me to the small mouse cages that are placed on a shelf at the wall. "These are the ones Julie painted yesterday", he begins and points to a couple of mice with colourful furs: green, red, blue, purple. "They look very good now, yesterday they were totally wet", he explains whispering. He observes one mouse that nervously runs back and forth and asks it: "Why are you so stressed?" (fieldnotes, 13.4.17)

FIGURE 13. Painted mice in the social box arena (photo provided by Jano and Noam)

In fact, this is an important and, at the same time, somewhat obsolete question. It is important in so far as one can object here as to whether mice can indeed be "stressed". And, suppose they can sense something like "stress", it is obsolete, considering that the existence of these mice is based solely on their contribution to epigenetic research by being *stressed*. Scientists talk to their mice to calm them down, but also re-enact stress on their bodies. As we have seen in this subchapter so far, these re-enactments range from pharmacological manipulations to biological interventions into the mouse body to letting two mice fight. The way Nadja is conducting research on the impacts of "social" stress on genetic and epigenetic processes is staged as a clear, systematic story of how stress can be harnessed and studied in the animal model. However, in the research of neurobiologist Jano and his colleagues, these research arrangements with mice seem more complex. As we will see below, based on their criticism of classical animal stress tests, the research group of Noam (who is Jano's supervisor) has established an experimental arrangement that attempts to approach mental health from a more holistic point of view.

The criticism of classical stress tests

While the classical methods of inducing a stress response in mice appear to be highly standardised and systematic strategies for studying stress-related disorders, the way neurobiologist Noam and his group conduct research in neuropsychiatry and environmental epigenetics tells a slightly different story. This stems from their dissatisfaction with current behavioural testing arrangements with mice, such as classical anxiety tests, as presented in the introductory part of this chapter. Before I elaborate on Noam's critique and the strategies mobilised by his team to respond to it, let me briefly repeat how the classic tests are conducted to better understand the criticism of them.

The state of the art of current behavioural tests with mice, such as the open field test, is based on a conflict the animal must solve. Researchers assume that on the one hand, mice are curious creatures and want to explore new environments, a property that Noam describes as "very social" (Noam, pos. 28). This new environment is for instance modelled by placing the mouse in a box, an "open field". Besides this exploring trait, researchers assume that the mice's instincts would teach them to stay in a safe environment as they want to survive: "the mice have a choice: they can explore, can go to the open area and be in the middle. This is the riskiest one, because someone can see him, or it can go on the wall... and, so this is one type of test... the world is using" (Noam, pos. 28). In those tests, researchers not only focus on whether the mouse enters the "risky" area, but also how much time lapses before it enters the open field, its "strategy" to go outside (whether it runs outside impulsively or is more hesitant), or how much time it spends in the new environment.

The research group's criticism is based on three aspects. First, Noam observes a divergence in those tests that he finds problematic: on the one hand, the techniques neurobiologists have to conduct

genetic or epigenetic experiments with mice are, for him, "perfect". What he criticises, however, is the way these results can be interpreted: the methods used to "phenotype" the mice, to interpret the found changes, are rather poor. He elaborated on this disparity between the techniques for conducting and the methods for interpreting mouse experiments as follows:

> When you don't see a difference [in the behavioural test], you don't know if the reason you don't see a difference is due to the fact that there is no difference, or the fact that the test is not sensitive enough. (Noam, pos. 30)

Hence, what Noam basically criticises is that the inherent structure of previous test arrangements with mice does not allow for an adequate possibility to analyse differences. The tests would not be "sensitive" enough to objectively bridge the genotype with the phenotype, which hinders researchers from finding the "molecular signature" (Noam, pos. 30) for different behavioural changes.

Second, the current classical stress models would reduce highly complex phenomena – anxiety and depression – to the tension in a mouse's behaviour between exploring and hiding.[38] This reduced model approach does not account for the complexity inherent in experiencing and responding to stress. As Noam explained in the interview, they would have mice which they "feel" are different based on how they would "respond" or "escape" (Noam, pos. 30) when they are not in the testing area. The classical tests, however, would not allow for this difference to be seen, as they are too simply structured.

A third point of criticism Noam raised was that standard anxiety-assessment tests themselves contained inherently a stressful component: being exposed to a new environment would already be stressful for the mouse, even without having applied additional stressors, a fact that could not be reflected in the later analysis. In this context, he further criticised these classical tests for taking place *outside* of the mouse's usual environments (which is the home cage) and for only representing a 20-minute excerpt from a laboratory mouse's life. These tests would therefore lack the capacity to measure and reflect on the dynamics and complexities of the whole stress response, which might last longer than the testing time defined in the experimental protocol.

The consequence of this criticism: inviting more complexity into the mouse model

Based on its critique of such classical approaches towards animal experimentation, the research group has shifted to a novel paradigm of harnessing mice as objects of scientific scrutiny. For several years now, the research group has been invested in establishing a novel stress testing arena termed the "pheno world, "social box",[39] or "complex behaviour", with the goal of making animal experiments

[38] According to Noam, the classical tests are very "simple" and were developed by the pharmacological industry to mainly screen the efficacy of new drugs (Noam, pos. 28).

[39] As we will see later, the social box is a testing area entailed in the experimental arrangement of the pheno world.

"much more relevant to the human pathology" (Noam, pos. 26). In this sense, the social box paradigm is enacted as a strategy to bridge the gap between the genotype and phenotype – that is to say, between the results and their scientific interpretation. The most salient feature that distinguishes this novel testing arrangement from the classical ones is that the mice are tested *within* their "natural" environments consisting of their "family" and "friends" (Noam, pos. 31), an experimental modification that, it is assumed, allows for the inclusion of "*social*" factors as well.

This inclusion of "social" factors (testing the mice in their "natural" environments together with their fellow species) prompts the group to make equally "social" or anthropomorphic interpretations of the results. For instance, in his PhD thesis, Jano suggests that the tested mice have different "personalities", which are said to give insights into "the biological basis of individual differences". Jano and his colleagues regard these individual differences as important for understanding behaviour and psychopathology. More specifically, they assume that these personalities are based on molecular differences and that they are related with individual behaviour as well as with gene expression patterns in the brain (Jano et al., 2019).

According to Noam, with this hypothesis the group would break with a central caveat in the life sciences: instead of denying animals any individuality, they assume that animals also possess personalities that differentiate one from another. "They are genetically identical", as Noam explains, "but they have… like humans, they have different personalities. So, I don't see why mice should not have different personalities" (Noam, pos. 36).[40] Though, as Noam explains in the interview, to circumvent the terminological discussion ("to make it softer") they would use the term "identity domains" to refer to a "trait-like dimension". These "identity domains" would comprise different behavioural traits and are assumed to be relatively stable over time and throughout changes in environment.

In the following section, I will turn to the social box as a testing arrangement that allows the scientists to formulate such claims. As in the other subchapters, I will also address the question of how "stress" is enacted in this experimental arrangement and what social implications the researchers ascribe to this novel model for stress-related disorders.

The social box paradigm as a complex model to approach mental health conditions

As mentioned earlier, the basic assumption the social box is built upon is researchers' notion of enacting a "social" component, as already indicated by the name. This "social" component is performed by testing the animals in their home cages and not individually, but in groups of four. In addition, the researchers also pay attention to the social behaviour of the animals in regards to how

[40] In ascribing mice personality and individuality, Noam to some extent blurs the border between humans and non-humans. However, by attributing these rather intangible qualities of a living creature to molecular differences, they remain as another term for the biological idea of a measurable "phenotype".

they approach, contact and chase after each other (Jano et al., 2019). The idea behind this practice is to model a certain human sociality, to be attentive to the human way of life as life in family structures. In this sense, the social box paradigm is an attempt to include some degree of complexity instead of applying a radically reductionist approach as in the classical stress tests. As we will see later, however, these enactments of "social" and "complex" parameters are also ultimately reduced to measurable, molecular differences as the group assumes molecular signatures as anchors for the observed behavioural changes.

The social box is an experimental set-up that primarily allows researchers to observe the behaviour of mice. Therefore, the researchers deploy specific technology that tracks the mice's behaviour, for instance by recording the whole experimental phase with a video camera from a bird's eye view. In contrast to for instance the chronic social defeat set-up, the experimental arrangements of the social box is combined with a home cage for every mouse that is deployed in the experiment. When the mice stay in these home cages, different parameters are measured, among them their metabolism or their oxygen consumption – what Jano refers to as "baseline data". In contrast to these measurements, in the social box, which is the centrepiece of this testing arrangement, the mice's voluntary social behaviour is monitored, both on an individual as well as on a group level. Those boxes consist of an arena of 60 x 60 cm and include a covered nest, an open shelter, an S-shaped separation wall, two water bottles, two feeders, and two elevated ramps. Food and water are available *ad libitum*, which means that the mice are provided with an "enriched, semi-naturalistic" (Jano et al., 2019, p. 2023) environment, as they do not have to starve and have plenty of nesting material and toys. The duration of the experiment also differs significantly from other stress experiments: it runs over several days.

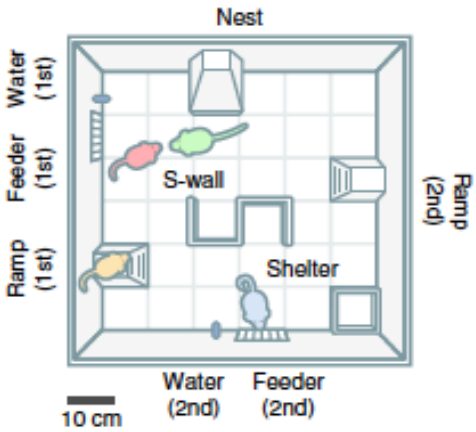

FIGURE 14. Schematic illustration of the social box (Jano et al., 2019, p. 2024)

As mentioned earlier, the social box is a strongly ethological, behaviour-based approach to studying mental health conditions. What do the researchers then define as "behaviour"? According to Jano, behaviour would comprise "everything that can be observed and measured": body weight, the distance travelled, contact with other mice, locomotion, the speed of the movement, metabolism (assessed via

the respirator air). But why are the researchers interested in the behaviour of mice? For Jano and his colleagues it represents a proxy for personality or "identity domains", as "personality cannot be directly measured but it can be inferred from the behavior" (Jano et al., 2019, supplementary material). The fundamental idea of this approach, therefore, is to track the behaviour and translate it into so-called "ethograms". These are detailed catalogues of all different behaviours of a group of animals. Taking the form of a graphic representation, it visualises different aspects of mouse behaviours, such as how much time a mouse has spent in its home cage or how often it approached other mice (see figure 15). Jano creates these ethograms on the basis of the video recordings of the social boxes and by applying a complex "computational framework for capturing and describing the space of individual behavioral expression" (Jano et al., 2019, p. 2023).

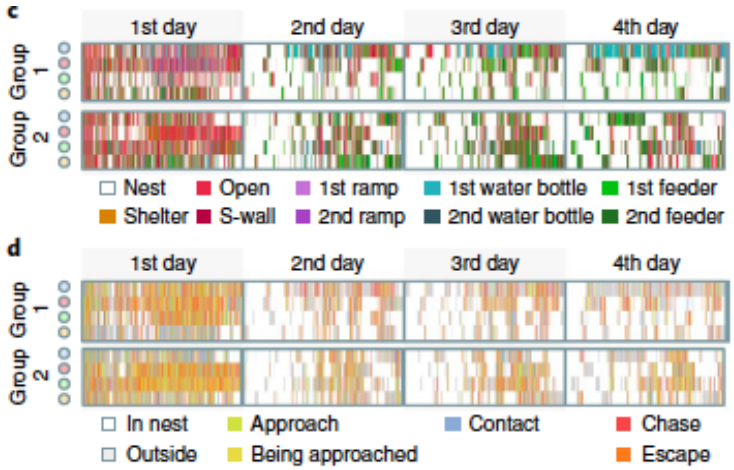

FIGURE 15. Movement ethograms and social ethograms for two groups of mice (Jano et al., 2019, p. 2024)

In addition to these mathematically driven analyses and interpretations, Jano performs sequencing analyses on the RNA level. By analysing RNA methylation patterns of three different brain regions of the tested mice (see figure 16), he attempts to elucidate and describe the molecular underpinnings of behavioural traits. Behaviour is therefore specifically linked to gene expression patterns in the brain.

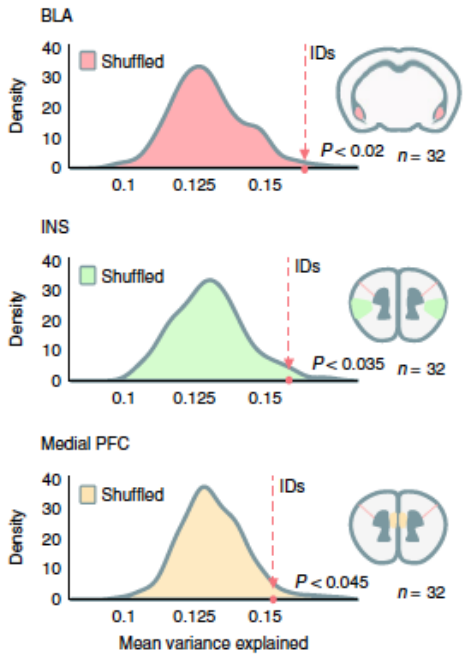

FIGURE 16. RNA-seq results from the basolateral amygdala, insular cortex and medial prefrontal cortex. For the RNA-seq the brains of the sacrificed mice were dissected, and the RNA was isolated (Jano et al., 2019, p. 2027)

As mentioned above, all of these analyses of mouse behaviours aim to assess what the group defines as "personality" or "identity domains". To identify these different domains, the group uses a statistical model (the "Latent Dirichlet allocation"/"LDA") for clustering the observed and measured differences in the tested mice. The statistical analysis results in four "significant IDs" displayed in the figure below.

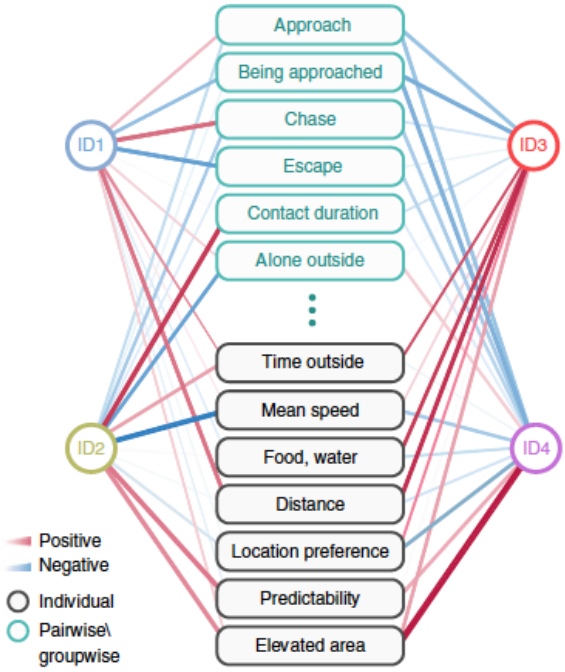

FIGURE 17. The four significant IDs. The width of connecting lines reflects the strength of the correlation. (Jano et al., 2019, p. 2025)

Additionally, the analytical results are the basis for establishing so-called "personality archetypes" depicted in the figure below (figure 18). Such archetypes are supposed to explain the different identity domains of the mice. Jano and his colleagues speculate that they "may correspond to three behavioral strategies that mice exhibit in nature: commensal, non-commensal (ultra-dominant) and subordinate" (Jano et al., 2019, p. 2027). Even if the social box is described as an "enriched, semi-natural environment", Jano and his colleagues cautiously note that the described IDs may not capture the entire extent of individual differences that mice exhibit in more diverse situations. That means, in contrast to the natural habitats of mice, the social box still comprises a modest and simplified environment.

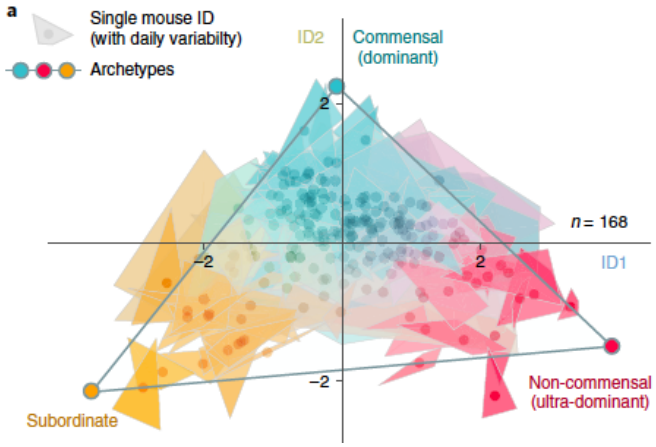

FIGURE 18. Three different "archetypes" (Jano et al., 2019, p. 2027)

What becomes obvious in the description of how researchers apply the social box paradigm is that compared to classical approaches it is a far more complex experimental arrangement to investigate the *biology* of individual difference. Similarly, it also requires a highly sophisticated analysis and interpretation of the data, which is translated into very different statistical models and diagrams. But what do the researchers expect to learn from these analyses about human health? While the systematic categorisation of individual differences in mice is still in its infancy, psychology has already established a widely used taxonomy of human personalities, known as the "Big Five" or "five-factor model" (McCrae & Costa, 2008).[41] While human research in this direction usually relies on questionnaires, Jano and his colleagues attempt to provide essential steps toward exploration of their *biological* underpinnings. Although these data-driven findings are in a very early stage, for Noam they prove that,

> if you have changes in the behaviour, emotion, cognition, it has somehow to reflect in your circuit. Changes which have to reflect eventually in the protein, which make the circuit, in the plasticity, which eventually has to reflect in your transcriptomics. So, it's no miracle here, if something does

[41] According to this theory, the five main dimensions of human personalities comprise "openness (to experience)", "conscientiousness", "extraversion", "agreeableness", and "neuroticism"(McCrae & Costa, 2008). In mice, the researchers could only identify four different personality-forming characteristics and did not create a list of names for the properties as used for humans.

> work differently, something needs to drive this difference. So, I'm sure there are molecular differences that determine this. (Noam, pos. 56)

By linking "identity domains" with a molecular signature, the research group formulates a possible method for assessing how different personalities react equally differently to psychopharmacology. In this vein, specific pharmaceuticals would match more effectively with for instance an "anxiety-type of personality" than with a patient whose behaviour is "a bit more aggressive" (Noam, pos. 44). Referring to the used mouse model, the group "certainly believe[s] that the vast majority of variability in individual differences is not related to genetic differences, but rather to epigenetically mediated effects of the environment" (e-mail conversation with Jano, 23.4.19). Even if this strand of research is a very recent development, the group suggests that these different manifestations of behaviour or personality are grounded in the transcriptome of mice: personality could be captured in messengerRNA, as they hypothesise (Noam, pos. 52).

Re-enacting stress in a complex environment

As I have shown in this subchapter so far, the social box paradigm is a new testing arrangement that distinguishes itself from other mouse experiments. The most salient aspect is that, in this set-up, researchers do not enact stress but instead measure how the social environment leads to molecular differences assumed to be epigenetically mediated. What distinguishes this approach in the institute's research is that the research group collects data from mice that have been "left undisturbed over a period of at least 4 days" (Jano et al., 2019, p. 2023). As a result, the researchers are not only looking at short, sometimes only minute sections of a mouse's life, but also at much longer phases, even if not the complete life of a mouse. Such research is mostly conducted in the social box, which is one distinct arena within the pheno world system.

Apart from measuring these "baseline states" of mice, the pheno world also allows for re-enacting stress within the system itself. As mentioned earlier, the capacity to test mice in an environment that is more or less "natural" or familiar[42] to it is conceived of as a major advantage of this experimental arrangement. In contrast to the "simpler" (Noam, pos. 28) classical testing arrangements, the pheno world is a highly technologised system. For instance, the mice carry an implanted transponder that is programmed in the way that it opens and closes "their" own home cage when they approach it. As the technical assistant Gabriele explained to me, "There should not be five mice in a cage at the same time." In addition, the pheno world is a system that relies on a software which on the one hand makes the handling very demanding (Noam's research group took two years to establish the system) but on the other hand allows the researchers to programme "everything" (fieldnotes, 28.7.17).

[42] At least for lab mice, cages may be assumed to be natural and familiar habitats, as they never experience other worlds.

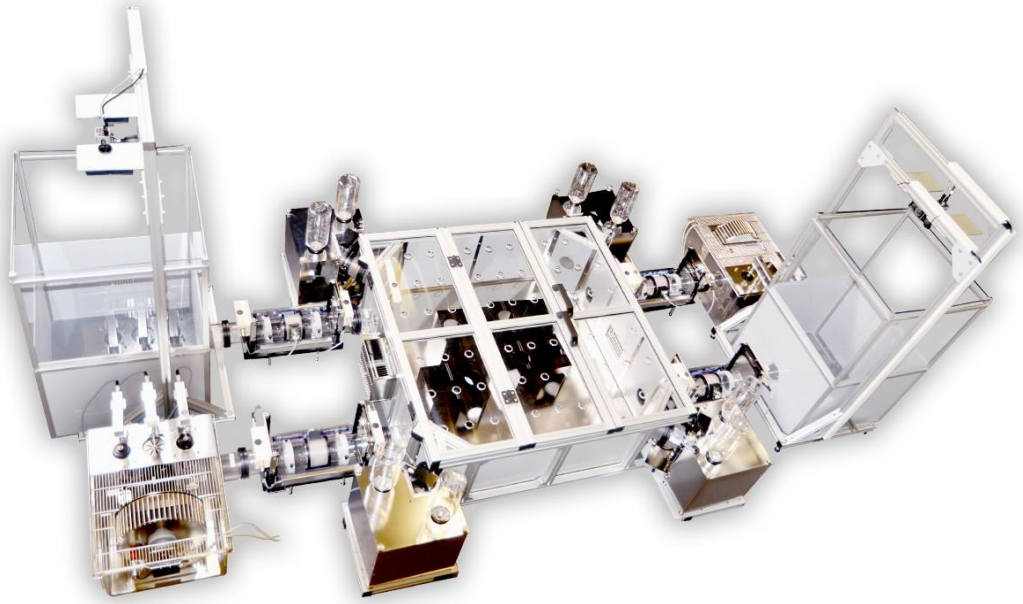

FIGURE 19. Example of a "PhenoWorld" testing arrangement (retrieved from https://www.tse-systems.com/product-details/phenoworld on 27.8.20)

This computer-based testing system also allows for a computer-based enactment of stress: Jano and his colleagues can, for example, program the system so that its feed is offered only at certain times. As the pheno world is a modular system and combinatorial research approach, it also allows for some of the classic test arrangements to be integrated into the system:

> Jano and the technical assistant Gabriele are discussing about "the best intervention", as Jano describes the enactment of stress in mice. Then Nadja enters his office. "Are you doing something at the moment?" she asks. "Yes, but you can help us," Jano answers. He briefly summarises what they are discussing. Together, they weighed the advantages and disadvantages of several ways of enacting stress in the current project. As this is one of the first times they will apply stress within the pheno world, they are not yet able to draw on experience values. Nadja's first suggestion is to place the mice for two to three hours into a "restrainer": a narrow tunnel in which the mouse cannot move back or forth. Jano, however, seems rather sceptical: "How can you explain that you stress the mouse outside this costly system?" he asks his colleague. He therefore proposes the options of "single housing" for a longer period, "foreign male bedding", or "food restriction", which means that food is only available in the home cage. Now it is Nadja who is not really convinced: "This is not a valid stressor. And it's not enough," she replies. In the end, they decide that the stressor has to be applied within the system to be justifiable concerning financial issues: the connecting tunnel between the social box and the home cage will be converted into a restrainer. (fieldnotes, 2.10.17)

What becomes obvious in the above excerpt from my fieldwork diary is that finding a "proper" stressor not only follows a biologically reasonable logic, but also one that is financially reasonable – two logics that are potentially in competition with each other. This means that the researchers may decide for one specific stressor not because they predominantly regard it as "valid", but also because of financial constraints. In addition, while the pheno world and the social box are regarded to model a certain "sociality", the ways of enacting stress are again imagined as physiological manipulations:

food restriction or fixation; stress paradigms that the chronic social defeat was originally intended to replace with a "social" form of stressor.

In sum, the pheno world is a highly complex approach towards studying mental health conditions. First, it is a testing arrangement that enables the researchers to consider and analyse high-dimensional data sets. The methodological framework of the pheno world enables the researchers to conduct research in environmental epigenetics in relation to many other parameters that play a decisive role during a mouse's experience of "stress" or "social environment". Not only are behavioural changes, such as the interaction with other mice, monitored, but a set of additional data such as physiological as well as genetic and epigenetic information is also gathered. Given this complex and diverse experimental set-up, the pheno world can be described as an approach that gives more ecological validity to stress research than the classical approaches.

Second and as a consequence thereof, this holistic research approach is deemed appropriate to adequately display the human stress response, which is regarded as a process that affects the *whole* organism: besides epigenetic processes, brain circuits, cells, and other molecular biological processes are expected to settle a pathway to respond to stress. Even if "stress is not only epigenetics" (Noam, pos. 8), Noam ascribes a special role to epigenetics: for him, it is one of the ways in which the environment and stress "talk" to our genes. Hence, he regards epigenetic research as playing a major role in understanding the "interaction between the environment and genetic predisposition" (Noam, pos. 4), a molecular mechanism granted the ability to control the stress response and behaviour. According to this logic, a dysregulation in controlling the stress response leads to an increased risk of a variety of mental and physical disorders.

In comparison to Nadja's research project, we can observe both similarities and differences in the applied experimental arrangements and the claims facilitated by them. Nadja predominantly deploys the chronic social defeat set-up, one of the more classical stress paradigms, to elucidate the "molecular tags" of behavioural changes. Her research is articulated as a rather clear strategy in which the whole process of stressing and assessing the stress response is imagined as a logical, consistent, and measurable sequence of procedures. In contrast, the way Noam and his research group tackle their research questions is shaped by a specific vagueness and in a way resolves the clarity involved in classical stress tests. This vagueness is predominantly based on the experimental arrangement, which allows for more "complexity", more "messiness": instead of rigidly prescribing the sequence of each individual step, the mice are left undisturbed and "unstressed" for a defined period. The role that the research group assigns to the environment is also rather ambivalent: the research group assumes that the "identity domains" investigated with the social-box paradigm are relatively stable over time and with changing environments. However, at the same time, the researchers suggest that these identity do-

mains are epigenetically mediated effects of the environment. A more open research arrangement thus also allows for different interpretations.

Still, in both research arrangements epigenetics is enacted as an interface or mediator that *molecularly* controls behaviour: behavioural changes or behavioural differences (the "identity domains") are referred back to molecular and epigenetic structures, "captured" (Noam, pos. 52) in the transcriptome and its modifications. In this vein, as with the chronic social defeat set-up, also within the pheno world, epigenetics is transformed into a phenomenon that is legible from behaviour.

4.3.3 Epitranscriptomics: reducing the story again

> It's early 2018. I shadow the cognitive scientist Julie, who is a member of Noam's research group, through her lab day. She has scheduled to slice the brains from mice that have been manipulated with the chronic social defeat arrangement. Shortly after arriving at the institute, she explains to me how she has prepared those brains for today's experiment: she has put the mice on a fixative and accessed the bloodstream of the mouse through the heart. Then, she has "flushed" the mice until there remained no blood in the body. This process is called perfusion and is required prior to colouring the mouse brains. As she is explaining this to me, Julie prepares small plastic jugs, which she labels with different combinations of numbers and letters. She pours the liquid from the tubes in which the mouse brains are located and places the brains on a piece of kitchen paper. She gently pours agarose into each chamber. "Then I throw in the brains" Julie adds casually. … It takes some time until the agarose is hardened. Julie brings out the first brain by cutting the plastic box with a scalpel, sticks the brain with super glue on a plate and places it into the cutting device, which is a small machine in which mouse brains and other animal organs are sliced via vibration and submerged. The cutting process takes quite a long time and Julie discards the slices until she reaches the brain areas she is interested in. While the cutter is doing its job and Julie fishes the "brain disks" out of the water and lays it on a paper towel to dry, I ask her why she needs those brain slices. "Because I want to stain a specific protein, that binds to a specific locus at the RNA. I want to analyse whether RNA modifications influence where this protein is located and how this correlates with stress and stress-related diseases." (fieldnotes, 26.1.18)

The excerpt taken from my fieldnotes above reveals how Julie performs various working steps to prepare mice brains for biomedical research: among other steps, she sacrifices the mice, perfuses the dead mouse bodies, cuts out the brains, and prepares the agarose and the plastic jugs. In preparing the brains, she attempts to approximate her region of interest: the prefrontal cortex. The reason that Julie accesses the prefrontal cortex in mice is because, as she explained to me, it is associated with displaying the effects of chronic stress. More specifically, she is interested in one modification of messenger ribonucleic acid (mRNA), namely the N^6-methyladenosine (m^6A): all of the preparatory steps serve the purpose of making this modification visible in the mouse brain slices.

While the existence of this mRNA modification has long been known, its dynamic regulative character and its significance for global processes in the human body have only been described recently. This newly discovered characteristic gives m^6A a functional importance that goes far beyond its long-assumed role as mediator between DNA and protein. Because of the importance ascribed to it for the regulation of the fate of a cell and embryonic development, it is highlighted as "another layer of

epigenetic regulations at the RNA level, where mRNA is subjected to chemical modifications that affect protein expression" (Yue et al., 2015, p. 1343).

However, with this "novel layer of epigenetic regulation" scientists are also confronted with novel challenges connected to the very properties of RNA. RNA plays a central role in protein synthesis, as its basic function is to translate the genetic information on the DNA into proteins.[43] As Julie explained to me, RNA as a molecule is much more complex and transitory than DNA. Moreover, as research on RNA modifications has only been conducted for a couple of years (since 2012), the methods for studying the processes associated with them are not yet fully established and standardised. The entirety of all RNA modifications is subsumed under the term "epitranscriptome", an analogy of the "epigenome" which signifies the sum of epigenetic modifications on the genome level. According to Julie, her field of research is named "epitranscriptomics", a "fancy" version of epigenetics. In comparison with epigenetics, which describes functionally relevant changes to the genome without altering the nucleotide sequence, epitranscriptomics involves all functionally relevant changes to the transcriptome that take place without altering the ribonucleotide sequence (Angelova et al., 2018).

Despite its recently revealed importance for human development, there are already ideas about how knowledge of RNA modification could improve mental health therapy. In this context, we can also observe a difference to epigenetic therapies connected to DNA modifications. According to Julie, the "good thing about RNA as a target is that no intervention in the DNA is necessary. This is ethically better. This is not gene therapy" (Julie, pos. 7). However, imaginaries about how epitranscriptomic knowledge could improve mental health are still quite limited to a better understanding of the development of mental disorders. Due to the novelty of epitranscriptomics, concrete ideas about how to intervene therapeutically are rather vague.

In her PhD project, Julie is specifically interested in exploring the functional significance of m^6A. Her research questions address the regulatory effects of RNA modifications in neuronal cells: "What effect does stress have on RNA modification?" (fieldnotes, 26.01.18). The reason she studies the implications of stress for an organism is that in humans the experience of chronic stress is associated with disorders: "chronic stress in humans also leads to depression" (fieldnotes, 26.1.18). To answer her questions she investigates the brains of adult mice. This focus on the developing and adolescent body and brain plays out as an enactment that is particular to the mouse model. Like Jano and Nadja, Julie also uses different mouse models in order to elucidate the molecular pathways of how an adult organism copes with stress. However, even if mouse behaviour also plays a role in her research, Julie's focus is not on a phenomenological observation of "stressed" mice; she rather reduces her research to

[43] More specifically, there are three different types of RNA with specific functions within the conversion of DNA into proteins: the messenger RNA (mRNA), the transfer RNA (tRNA), and ribosomal RNA (rRNA) (Clancy, 2008).

the molecular underpinnings and the biological measurability of behaviour or stress – an approach we could also observe in research with cell models.

In all of her publications and in the accounts of her research, Julie highlights the emerging importance of RNA modifications (as m^6A) for the aetiology of human psychiatric pathologies. She hypothesises that "a lower expression of m^6A in the brain leads to more stress, whereas more m^6A has a rescue or buffering effect" (fieldnotes, 26.1.18). By "more stress", in this context she means a deficient ability to cope with stress. This observation would have also been made in post-mortem brains of patients with MDD (major depressive disorder) that have committed suicide. On that front, RNA modifications have been described as essential regulators of gene expression.

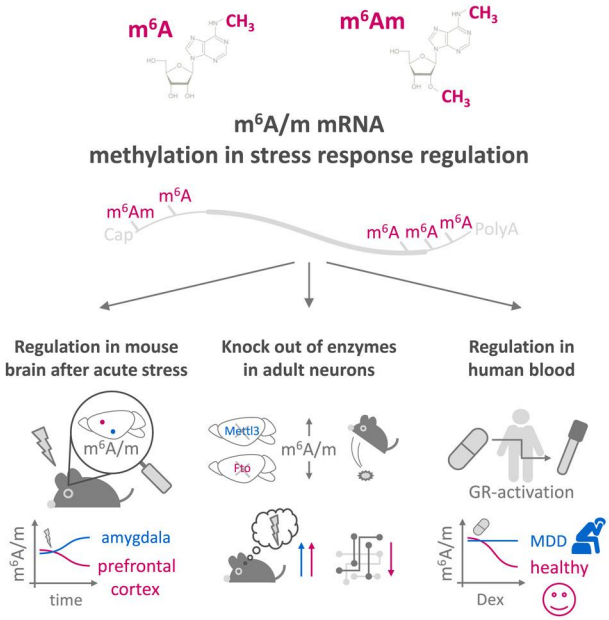

FIGURE 20. Graphical summary of Julie's research (Julie et al., 2018, p. 389)

In order to elucidate the role of RNA modifications for human health and pathological behaviour, Julie combines a series of classical stress tests with methods of sequencing RNA modifications. In this respect, she re-enacts stress in the form of three practices. First, she uses the elevated plus maze, an experimental testing arrangement widely applied in behavioural research. It is used to analyse anxiety-related behaviour in rats and to assess the anti-anxiety effects of drugs. The basic structure of the maze consists of two open and two closed arms. By using video recording, researchers can monitor how much time the tested rodent spends in the open and in the closed areas. Researchers assume that rodents with anxiety-related behaviours spent significantly less time in the open arms. It is considered as a strategy for assessing anxiety in mice (Walf & Frye, 2007).

Second, like Nadja, Julie also works with the chronic social defeat arrangement. While I was shadowing her, she conducted one such experiment:

> "Um, what can we do now? Well, what can *I* do? We can go to my mice as according to the government of our administrative region, I have to check every day whether the animals are doing well." Therefore, we make our way to the animal stable. As I have seen many times before, Julie writes down the time in the protocol that is attached to the door. She points out to me that I am not allowed to cross the threshold. She climbs over the blockade, which is about 30 cm high, positions herself on the small mat in the room directly behind the door and begins to put on the protective clothing. Julie points out to me that we have to be a little quiet now, because in the next room there would also be a mouse experiment running. While she looks at her mice, she roughly explains the experiment to me. "It is about chronic social defeat. In the small cage, there are two mice: one black and one white. … The white mouse flogs the black mouse because it's higher in the hierarchy. Only when the black mouse goes into the defeat posture is the defeat or the bullying finished. Then the two mice are separated by a transparent plastic wall, which contains holes so that the defeated mouse can still smell the other mouse." Julie checks the mice, examining their fur and seeing if they have wounds, for example. If the mice are in pain, they have to be given medication. If the pain is too great, then the animal welfare act requires for the mice to be put to sleep. (fieldnotes, 26.1.18)

What this excerpt taken from my fieldnotes shows is that re-enacting stress in mice is always a balancing act for scientists: on the one hand, the stressor, in other words the defeat, must be strong enough to produce the desired epigenetic effects in the brain. However, if the stressor is too strong (which is determined by pain in the animal), the experiment must be stopped to protect the welfare of the animal. In addition, it is also not always clear what the measured effects result from. Although Julie claims to have found depleted RNA methylation in the "defeated" mice, she does not know whether this is a "random" result or whether it is causally related to stress. "This we are trying to find out, because chronic stress in people also leads to depression," she told me while I was shadowing her.

Second, Julie deploys the restrainer, which is a small tube in which the mice get stuck for a pre-set amount of time, in Julie's case 15 minutes. While in the elevated plus maze, researchers do not enact an explicit stressor, the restrainer is a fixing unit and therefore represents a physical stressor for the mouse.

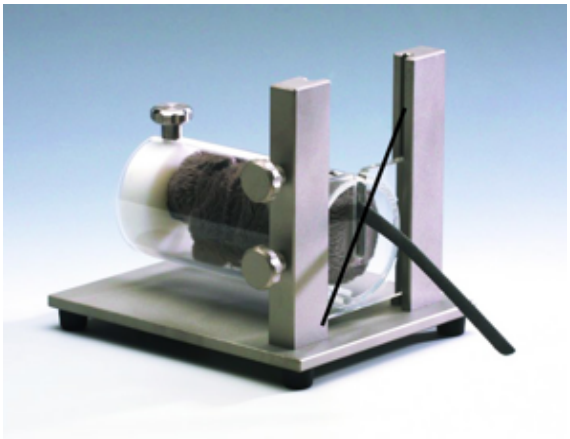

FIGURE 21. Mouse restrainer. Actually used as fixing unit for injections and blood sampling from the tail vein, the restrainer is used in stress research as a stressor (retrieved from https://www.lab-art.de/index.php/mouse-restrainer.html on 27.8.20)

In contrast with the chronic social defeat set-up, the restrainer is a testing arrangement meant to model acute exposures to stress. In order to carry out a more "fine-tuned" analysis of the stress response, Julie uses specific knock-out mice. In these mice, two genes that are associated to play a role within m^6A and to be highly affected by acute stress are deleted. For Julie and their colleagues, this mouse model therefore serves as a "tool" to more specifically investigate the mechanisms of m^6A methylation in adult neurons). In a publication based on this research, Julie and her colleagues state that they were able to demonstrate that deletion of those specific genes "in adult neurons alters the m^6A epitranscriptome, increases fear memory, and changes the transcriptome response to fear and synaptic plasticity" (Julie et al., 2018, p. 389). This result has been previously described by other researchers as well (Molinie et al., 2016).

In addition to analysing the mouse brains, Julie and her colleagues perform a comparative approach in order to evaluate the potential of the mRNA modification as a peripheral proxy. Since the human brain cannot easily be accessed, finding such biomarkers represents a beacon of hope that it might be possible to measure the effects of stress on neuronal tissue. Julie and her colleagues therefore compared global methylation levels in m^6A both in mouse and in human blood. While in the mice, acute stress is re-enacted by placing them in the restrainer, in voluntary healthy individuals and MDD patients the researchers re-enact acute stress by administering to them a 1.5mg dose of dexamethasone.[44] Since both "mice and humans showed global blood demethylation after stress or GC [glucocorticoid] intake, respectively" the researchers conclude that they have "observed that regulation of m^6A/m … in blood may represent a peripheral proxy for part of the brain's m^6A/m responses that seems impaired in patients with a stress-related disorder" (Julie et al., 2018, p. 401). Hence, by combining different material, methylation analysis in human and mouse blood and sequencing analysis in mouse cortex samples, Julie and her colleagues attempted to build a translational approach of their results.

Despite the heterogeneous material and methods Julie applies to study the role of RNA modifications for human development, "stress" as a concept and a term is rather black boxed in the publication. The authors do not elaborate which forms of stress or stressful experiences they aim to model by initiating stress responses through the restrainer or the administration of dexamethasone. These studies therefore focus primarily on the *molecular* response to any form of stressor, rather than on the structure of the stressor and on how different stressors may impact the organism equally differently. Also, the stress response is only measured by its *molecular* manifestations without paying attention to its effects on other, more global processes (such as the metabolism) or the behaviour of the mice.

[44] The administration of dexamethasone is equated with the release of glucocorticoids, hormones that produce an array of effects in responses to stress. Therefore, dexamethasone represents a "glucocorticoid stimulation" (de Quervain et al., 2017).

With regard to the mRNA, the authors emphasise repeatedly throughout their study that "elucidating the underlying molecular processes that regulate the fine-tuned transcriptional response to stress is essential for understanding stress vulnerability and the development of stress-related psychiatric disorders such as depression and anxiety" (Julie at al., 2018, p. 389). The quote powerfully illustrates that the researchers attribute a major regulatory function to very small molecular structures, deeming them appropriate to a more fine-tuned explanation for the development of mental disorders. Human experiences of stress and its health effects are thereby continuously enacted as being decomposed into ever smaller molecular constituents and events. Julie's research approach thus localises crucial parts for explaining mental health conditions to specific sections of and specific molecular loci on the epitrancriptome. At the same time, Julie's experimental arrangement also complexifies possible explanations for mental health conditions. This is done not on a structural or social level (by assuming, for example, that many different socio-material factors play a role), however, but on a purely biological level, by adding an additional molecular process to the aetiology of mental disorders. At the end of their publication, the authors summarise that mRNA modifications "constitute a novel layer of complexity in gene expression regulation following stress exposure, which is pivotal for the adaptation of stress-responsive circuits to acute challenges" (Julie et al., 2018, p. 401).

4.3.4 Coda

In this brief concluding section of the subchapter, I will summarise the researchers' main practices in operationalising stress within mouse model research and delineate how the different experimental arrangements enable different statements about epigenetics and mental health. In addition, I will embed research with mice within the overall research choreographies of the institute.

As I have shown in this subchapter, biology has established a large number of experimental arrangements in which mice are deployed as model organisms to facilitate scientific claims. I have further shown that these claims are most often bounded to the specific experimental arrangement. In these experiments, researchers re-enact stress in mice by applying various strategies. These re-enactments range from physiological manipulations, to pharmacological interventions, to stressors rendered as "psychosocial". The structure of the stressor depends largely on the research question. The same applies to the duration of the stress exposure, which should reflect either acute or chronic stress. In all scenarios, stress is measured by analysing molecular and physiological processes in the mouse-body: DNA-methylation, RNA modification, or histone acetylation; metabolism, oxygen consumption, or endocrinologic changes.

In general, the way environmental epigenetics is enacted and articulated is dependent on the chosen experimental arrangement. Nadja's research tells a rather linear story of how epigenetics and mental health can be analysed. By enacting stress pharmacologically and by the chronic social defeat set-up,

she suggests that stress is visible in the mouse's epigenome. More specifically, it is manifested in histone modifications, which represent one epigenetic mechanism of how the environment can interact with the genome. As a backlash, Nadja assumes that these changes directly affect the social behaviour of mice: as they experience continued stress, they become increasingly "depressed-like".

While Nadja still uses rather classical behavioural tests, Noam and Jano pursue a more complex and multi-faceted approach to the production of knowledge on mental health. Their story of how stress is related to the epigenome and hence to mental disorders is characterised by disruptions and challenges more linear classical research approaches. By using the social box paradigm and the pheno world testing arrangement, they aim to do justice to the assumption that "stress is not only epigenetics" but activates "almost every part of your brain. … it is associated with emotion, cognition and of course memory, locomotion, attention, appetite – everything is responding to stress" (Noam, pos. 78). In contrast to Nadja, Noam and his group use a rather holistic approach in which stress is distributed on many different processes in the body. In the framework of this approach, epigenetic modifications are assumed to be crucial to understanding the interaction between the environment (stress) and genetic predisposition. Still, they are not the only informants. By using the social box framework, the group also attempts to elucidate individual responses to stress. Its research on "identity domains" is the first step towards describing individual differences in responding to stress and medication in a biostatistical language – initially only in mice. Here, an interesting ambiguity emerges: since Noam and his colleagues assume that stress is a phenomenon that affects the whole body, they attempt to inscribe this assumption by making their experimental arrangement more complex and more open, accepting some degree of disorder. In addition, also by using the social box, which is an open arena, and by deploying several mice, the researchers accept more messiness, more "environments". As Jano's close colleague Julie told me, the "open cage is much more contaminated with environmental stuff, they can cough on each other or sit on top of each other. Jano is also much closer to the wild-type mouse" (fieldnotes, 26.1.18). Despite, or presumably because of, this messiness and rather mild form of standardisation, this complexity is ultimately (analytically) levelled out by the group's search for the *molecular* basis for difference. Complexity is thus more or less dissolved into molecular structures.

In contrast to this somewhat open approach, Julie's experimental arrangement radically reduces her focus by "trying to take everything out, because [otherwise] it is not replicable and comparable for us" (fieldnotes, 26.1.18). By narrowing her scientific gaze to the molecular structure of the response to acute stress and by omitting other data such as behavioural observations, her approach can be described as a highly standardised way to study environmentally driven epigenetic changes. In her research arrangement, the experience of stress is radically localised in one epigenetic process, the de/methylation of m^6A.

Within the overall research choreography, we can observe a similar significance of mouse models to models in cell culture: most often, they are used as comparative instruments. They are important elements of translation research. This translation of knowledge can be done in two directions: from human to mouse or from mouse to human. By resorting to a specific mouse model, the researchers attempt to investigate (epigenetic) marks found in human blood in the mouse's brain metabolism. Or they start in the mouse model, by using a model that is supposed to display enhanced anxiety for instance, and translate these findings to the human context. This translational practice is assumed to be crucial, because the researchers also admit to having reservations about the analogy of the two organisms (mouse and human).

Either way, scientists render mice as inevitable apparatuses of knowledge production in psychiatry, as they enable them to look at "where the disease takes place, namely in the brain" (Judith, pos. 54). In being able to access the mouse brain, researchers can "squish it, mash it" (Noam, pos. 24), cut it into slices, stain the molecular structure under the microscope, practices that are very limited with the human brain. In addition, the mouse makes possible claims about the *interaction* of a variety of different physical reactions to stress, from epigenetic to metabolic to behavioural changes. By adding cell culture to these arrangements, the researchers attempt to "molecularly characterise the marks identified in humans and mice at the cell culture level" (Judith, pos. 65).

In addition, throughout this subchapter I have shown how knowledge about environmental epigenetics also changes the way researchers approach and build mouse models; they approach "environment" in a novel way by specifically attempting to take into account what "environment" means to the mice themselves. In considering them to have knowledge about their own environments, they ascribe them a certain "semiotic competence" (Roepstorff, 2001, p. 203): Noam and his colleagues assume that mice intrinsically want to explore new environments but also instinctively want to hide from predators, to live rather with their "family" and "friends" than alone. These assumptions and observations about how mice *think* and *act* are the basis for the "new generation of phenotyping" (Noam, pos. 36). By inscribing these assumptions into experimental arrangements such as the pheno world or the social box, it

> is not a question of using animals as more or less arbitrary resources for the embodiment of 'speculative thought'. Instead, [the researchers attempt to] 'think' along with animals, i.e., they use much more concretely ideas of how animals think about the world to get to know it, and this knowledge has consequences for the way they act in the world. (Roepstorff, 2001, p. 214)

By approaching behavioural experiments from an environmental epigenetics perspective and by increasingly trying to get involved in the "natural" living environments of mice, researchers strive to make these experiments not only "more relevant to human pathology" (Noam, pos. 30), but also more relevant for the mice themselves.

4.4 Epigenetic research with human tissue: enacting the notion of molecularly embodied experience

Epigenetics as the blurring of boundaries: an old idea in new clothes

> Man, as Aristotle remarked, is a *social* animal. This fact introduces him into situations and originates problems and ways of solving them that have no precedent upon the organic biological level. For man is social in another sense than the bee and ant, since his activities are encompassed in an environment that is culturally transmitted, so that what man does and how he acts, is determined not by organic structure and physical heredity alone but by the influence of cultural heredity, embedded in traditions, institutions, customs and the purposes and beliefs they both carry and inspire. Even the neuro-muscular structures of individuals are modified through the influence of the cultural environment upon the activities performed. The acquisition and understanding of language with proficiency in the arts (that are foreign to other animals than men) represent an incorporation within the physical structure of human beings of the effects of cultural conditions, an interpretation so profound that resulting activities are as direct and seemingly "natural" as are the first reactions of an infant. To speak, to read, to exercise any art, industrial, fine or political, are instances of modifications wrought *within* the biological organism by the cultural environment.
>
> This modification of organic behavior in and by the cultural environment accounts for, or rather is, the transformation of purely organic behavior into behavior marked by intellectual properties with which the present discussion is concerned. (Dewey, 1938/2018, p. 43)

In the late 1930's, philosopher John Dewey considered the relationship between organisms and their environments. By stating that man is a "social animal", he concluded that the environment of humans and animals is different, as the human environment is "culturally transmitted". For him, the cultural environment and the organic structures of a person are closely intertwined. He attributes great importance to an organism's environment, for the organism itself and its behaviour: the cultural environment has modifying effects and is even capable of altering the "muscular structures of individuals". Dewey's concept of the *cultural* environment reminds of the biological concept of the *epigenetic* environment. Both address questions of how individuals are embedded in environments, how environments shape their behaviour, altering structural properties of their bodies. While Dewey focuses on what he terms "cultural" aspects of that environment, biology attempts to describe how an "epigenetic" environment "talks" to our bodies and changes our biology. More precisely, biology assumes that this environment is predominantly harmful, affecting the body in a pathological way; a presumption that leads to a research focus on "stress" and its effects on our mental and physical wellbeing.

As I have previously shown in this thesis, researchers inscribe these assumptions of environment into the experimental arrangements with cell culture and mouse models, by re-enacting stressful experiences in cells and mice and measuring the epigenetic effects (with the exception of the social box-paradigm, where researchers aim to contribute to a better understanding of mental disorders by studying mice in an unstressed state). In the last subchapter, I will delineate and analyse the researcher's strategies for studying the stress response in human tissue. Therefore, in the following sections I will showcase researchers and how they articulate epigenetic accounts of mental health along three experimental arrangements.

First, several of the institute's scientists conduct research within clinical studies. In the institute's most important clinical study, scientists compare patients suffering from stress-related disorders to healthy individuals with the aim of identifying biomarkers for psychiatric diseases. In pursuing their scientific interrogation, researchers collect different kinds of human tissue, such as blood or saliva, and apply different levels of analysis: from measuring bodily functions, such as metabolic changes, to elucidating biological changes, such DNA methylation.

Second, and almost exclusively in cooperation with other, partly international, research facilities, the institute conducts several cohort studies. While the methodological approach is similarly broad as in clinical studies, in cohort studies, scientists frame their cohort by clustering individuals along shared experiences, such as childhood abuse. Here, the aim is to elucidate the molecular underpinnings for addressing the question of how early adverse experiences relate to later health outcomes. In the context of these collaborative cohort studies, the institute is in most cases the facility that carries out the epigenetic analyses. Within cohort studies, there is a line of research that uses human blood cell lines to study the connection between environment and epigenetics and its possible implications for mental health. The biologist Valentin uses such cell lines to elucidate the molecular and epigenetic underpinnings of individual responses to stress. Although he carries out his research in cell culture like Adriana and Emma (in a nutrient medium outside of the organism), his intention is, as we will see later, not to model brain-like structures but to investigate epigenetic changes in one specific gene locus in the used blood cells.

By analysing these different experimental arrangements with human tissues, I will revisit the crisis in psychiatry with which I have introduced this thesis. I will show how, along these experimental arrangements, environmental epigenetics is predominantly articulated as an answer and possible solution to this crisis. As we will see below, much like other research endeavours with neuronal cells and mice, research with human material is fundamentally embedded in the concept of "stress"; it emerges as a technical tool which facilitates epigenetic accounts of mental health conditions.

4.4.1 Studying mental disorders in clinical studies: epigenetics as the missing piece of an aetiological puzzle

Lost in diagnoses: revisiting the crisis in psychiatry

> Right now, as a psychiatrist, you're relatively helpless. So, we have an arsenal of medicines and an arsenal of psychotherapy… but many... many do not help. So, unfortunately, too many. There is certainly the problem that we still treat too few sick persons, but even... *even* if we treat the few that come to us... sometimes it works, but often it does not work fast enough, good enough, long enough and in some cases, we are just helpless and I think that's because we do not know exactly why someone has a psychiatric illness. (Stella, pos. 99)

The above quote from an interview with physician and neuroscientist Stella brings together several challenges related to mental disorders and clinical practice. Against the background of the limited

scope of therapy that she here mentions, the question arises as to why so few people consult psychologists or psychiatrists. This might relate to the ways that mental health conditions are currently being problematised by political leadership and the public. Is it considered a form of anti-social behaviour and thereby a modern myth (see for instance Szasz, 1979 on the medicalisation of emotional, behavioural and interpersonal problems)? A concept that stigmatises mental health patients as *enfants terrible*? Or is mental illness perceived as an uneconomic by-product of our contemporary societies? As social anthropologist Mary Douglas (2003) would have it, a *matter out of place*?

These questions are also related to the way the modern natural sciences and predominantly medicine as one of the most important institutions controlling our lives (Zola, 1972) understands mental health problems and their treatment. In the interview, biological psychologist Rahel pointed to the problem that, "we know in psychiatry, which is still a little bit the stepchild of medicine, that achievements in basic research are transferred very, very slowly into clinical practice. There is almost such a backlog of development" (Rahel, pos. 10). In this context, clinicians and mental health organisations call for the acceptance of mental disorders as phenomena that are real, despite the fact that they might not always have a physical, material cause like many somatic diseases. Those stakeholders urge for a formal recognition of the importance of mental health because of the fact that we still do not have the same scientifically profound understanding of mental health conditions as we do of cancer. And they demand that funding be redirected to mental health issues just *because* mental health treatment is, to date, limited: psychiatrists like Stella complain that current therapeutic measures do not reach enough people and do not have the anticipated curative effects.

But where does this helplessness, as the most obvious symptom of this crisis, come from? Why are many severe mental disorders currently considered un-treatable, despite the fact that there is a range of pharmacological and psychotherapeutic interventions? "I think it's precisely because we don't yet understand exactly enough *why* someone has a mental disorder" (Stella, pos. 99), Stella stated frankly. Biological psychologist Rahel also mentioned the insufficient knowledge of the pathophysiology of mental disorders – a lack in scientific knowledge that leads, in her perspective, to a tedious process of "trial and error" based on "arbitrary decisions" in current methods of treating patients (Rahel, pos. 134), rather than a directed therapeutic strategy.

But what is the reason behind this knowledge gap that permeates into clinical practice and produces a treatment plight? For a possible explanation for these uncertainties we have to work backwards, as it is not possible to address treatment before addressing diagnosis: clinicians derive treatment from diagnosis. This means that people with major depression might benefit from a different therapy than people with anorexia. In fact, the situation is even more complex, as most psychiatric patients suffer from more than one disorder, accompanied by somatic illnesses, such as cardiovascular or metabolic diseases – a pathological phenomenon termed "comorbidity". Even for lay persons it might be obvious

to discern that diagnosing mental disorders is therefore a great clinical challenge. Neuroscientist Lydia summarises her view of the diagnostic challenges as follows: "If you have cancer, you have cancer. It is diagnosed. It is treated in many cases. And then you are cured, and you forget about it. But with psychiatric diseases, it's never like this. People carry these problems all their life" (Lydia, pos. 28).

Today, there are two major manuals meant to guide clinicians in making a psychiatric diagnosis: the Diagnostic and Statistical Manual of Mental Disorders (DSM), published by the American Psychological Association and the International Statistical Classification of Diseases and Related Health Problems (ICD), published by the World Health Organization. The listed diagnoses are based on phenomenological descriptions of mental disorders: a range of possible symptoms or experiences is related to specific disorders. For instance, the experience of a threat of death, serious injury or sexual violence (APA, 2013), precipitates a PTSD. A definition known as "criterion A".

Recently, however, these diagnostic strategies have been criticised for their inaccuracy. For Rahel, the diagnoses that are listed in these clinical manuals are

> too far removed from any aetiological processes. So we have a purely phenomenological approach in psychiatry, so it's not about causes at all. And that was also important, at some point... it's a completely atheoretical approach and then... At the beginning of the 80's, it was transferred to the DSM, because at that time, the biggest problem in psychiatry was that we didn't have a common understanding about diagnoses. When you for instance worked in a clinic in northern Germany and then had to go to a clinic in southern Germany, it has happened that people have talked about different things, different phenomena, when in fact they have talked about a depression. Actually, every clinic had a different understanding of depression and at that time people said: ok, how are we or our patients to be taken seriously if... if we can't even define our diseases properly?" (Rahel, pos. 12)

While the development of the diagnostic manuals has been important to finding a common language to talk about mental health phenomena, these diagnoses are now criticised for being based on the patients' subjective symptom descriptions and the clinicians' phenomenological observations instead of on "objective", "measurable" and "generalisable" characteristics. As diagnosis and therapy are understood as gears that are intermeshed with one another, it is the current way of classifying mental disorders that is increasingly criticised for not being effective enough, for not being able to truly guide treatment. The crucial point is that mental disorders of different people may have similarities on the symptom level, while individual biological parameters may vary greatly: "I think it is clear that psychiatric disorders can look very similar on the symptomatic level, even if the biology behind them is very different" (Stella, pos. 99).

This is an assumption and a critique that contributes to the vision of personalised medicine. A current biomedical perspective that acknowledges that we are all unique and therefore moves away from a "one size fits all" approach to treatment and patient care. Instead, personalised medicine prioritises therapy tailored to individual lifestyles and environments to achieve the most successful results in the management of a patient's disease (Rüppel, 2019). Every disorder is considered to be different for

each person and always based on their biology. We can therefore observe a trend in psychiatric research towards understanding the biological underpinnings of mental health in order to develop more fine-grained, biology-based diagnoses. This trend gives rise to the idea of a novel taxonomy of mental illness – a taxonomy that is envisioned not only as reducing personal suffering, but also as lowering the massive costs of the health system (Rüppel et al., 2018) by moving away from symptom-driven diagnoses that have so far been not effective enough.

Establishing a new taxonomy of mental health conditions: the RC-study

The institute is also conducting research and studies to contribute to establishing a novel classification of mental disorders like the one mentioned above. Such a new taxonomy is no longer classified according to shared symptoms but rather based on shared biological marks. Therefore, the institute has launched a project to identify the biological and molecular underpinnings of mental disorders: the Random Clinical study (RC-study).[45] It is the institute's most important clinical study carried out by the collaboration of many researchers and clinicians that work at the institute. The study is made possible mainly by the infrastructure of the institute: besides its various laboratories and research groups, the institute also holds a day clinic and several outpatient clinics, such as a scientific-therapeutic outpatient clinic. This is also where the clinical studies are carried out. With this infrastructure, the institute aims to unite the triad of basic research, clinical research, and the treatment of patients under one roof.

In the RC-study, the study cohort mainly consists of in-house patients who suffer from stress-related disorders, such as depression, and of healthy test persons. In this context, healthy test persons ("probands") are regarded as unaffected by mental disorders and therefore are included as "controls". As controls, they are similar in all important respects (such as age, absence of serious internal diseases), except for the lack of a stress-related disorder. By studying individuals who suffer from mental disorders alongside individuals who do not, the scientists hope to be able to compare the biological differences between those two groups. Participants in the study are recruited through a call published on the institute's website and by informing the in-house patients about the possibility of taking part in the study. As we will see later, the phase of data ascertainment extends over several days, with the last survey taking place one year after the start of the study. As we will also see, environmental epigenetics plays a specific role, as here it is not the centre of the study; it is but one amongst the many forms of data collected. By drawing on important environmental epigenetic research from human and animal studies, the RC-study protocol states that, "epigenetic modifications are also increasingly being studied for their role in the development of mental disorders, with changes in DNA methylation being

[45] Pseudonym

described in relation to the HPA axis in depression and in PTSD" (study protocol, RC-study, p. 2; author's translation).

During my research stay at the institute, I had the opportunity to accompany the young patient Jakob Eberl,[46] who suffers from depression, through the first two days of the study.[47] These were two days of very different examinations and testing procedures, during which I followed Jakob through various laboratories and examination rooms both at the clinic and the research institute. Below are three field vignettes that reflect the versatility of this study.

Vignette #1

After the patient has answered several questionnaires concerning his psychological and physical state of health, among them one questionnaire for the external assessment of the severity of depression, the study-assistant Lara moves on to the second aspect of today's study day: the blood sampling. Despite several attempts, she does not accomplish the blood sample from the study participant. Therefore, she calls her colleague Heidi to help her. She's a rather small and older lady with a Swabian accent and also wears a white lab coat. She asks: "What's still missing? Is he a patient or a test person?" She starts stowing the blood for the blood sample and looks for an adequate blood vessel. In my impression, everything takes a very long time. "Is it still okay? I know, I stow very strongly," Heidi says to the patient. She also has troubles with hitting the vein and needs several attempts. … Finally, it works, the blood runs into the ampules. … "How many do we still need?", Heidi asks Lara. "This and the RNA and the DNA," Lara replies and holds an ampule in the air. ... After a couple of minutes, the two ladies have collected all the blood that is needed for the study. They thank the patient profusely for his cooperation and Heidi jokes: "As you see, we don't let anybody go without having their blood!" Everybody is laughing and the patient replies in a similar giggly tone: "I do not want it to be boring here either." (fieldnotes, 12.12.16)

Vignette #2

The next day. Again, I'm shadowing the patient Jakob who takes part in the study. We enter a room, where the PhD student Selia already awaits us. Selia and the patient know each other from yesterday, when the first part of this experiment was conducted. After they have taken a seat, Selia starts to place electrodes on the patient's face, the back of his hands and the palm of his hands. … After that, the patient has to put on a kind of backpack, but worn on the front of the torso, on the chest. Selia tells him to sit at the table and to place his chin onto a backing to keep his head stable. Selia changes the room and takes a seat at a huge desk on which three screens are installed. … The experiment starts: the patient has to fulfil several exercises. Selia monitors the experiment in the meanwhile. In a whisper, she offers me to ask questions. I want to know which data is measured during the exercises and Selia explains that the pupillary reflex, the eye twitch and the skin conductance response are measured by applying stressors such as a subtle electric shock or awkward noise. … "On a scale of 0-10 you could also assess the fear, but that's nonsense because that's not objective, unlike our measurements," Selia says. (fieldnotes, 13.12.16)

[46] Before we start the study day, I introduce myself to Jakob and explain my research project. I tell him that I am a social scientist and that I accompany the work of the employees at the institute, focusing on their work processes. After he has consented, Lara, the study nurse, begins to clarify the course of study. The same applies to others who I met during this survey phase (most of them I knew from previous meetings).

[47] In sum, for patients the study consists of five study days on which "examinations" take place. After four months and after one year, psychometric data are collected. Probands are only appointed on two consecutive days (study protocol, RC-study).

> ***Vignette #3***
> I accompany the patient to the next part of the study day: the fMRI measurement. I follow him down to the basement into a large, winding room with doors leaving to other rooms. It's a busy room with a few desks and many monitors. Employees stand together and talk, in the next room an investigation is currently taking place. We walk to the back of the room where the patient is already expected by a colleague – I think she's also a technical assistant. "Hello Mr. Eberl!", she greets him. … After some preparations, the experiment starts and the patient has to fulfil several tasks, such as solving calculations under time pressure while being monitored in the fMRI. In the meantime, the technical assistant is repeatedly taking blood and saliva. First, the patient is doing pretty well: on the screen in front of him, he gets positive feedback. Then he "miscalculates" increasingly and a senior physician comes in and speaks into a microphone through which the patient can hear him in the fMRI. "Come on, hurry up, the other participants did it much faster than you!" The patient is now always in the red area, which means that he is slow and also solves the arithmetic problems incorrectly. The study assistant tells me that the faster the patient responds, the more difficulty the arithmetic tasks will be and the less time will be available to provide an answer. So, the patient can only lose. (fieldnotes, 13.12.16)

Blood, data from the fMRI, pupillary reflex, skin conductance response, DNA, RNA, questionnaires – already on the first two days of the study, a large number of physiological and biological measurements were taken on the patient's body. First and foremost, these measurements reveal one major aim of the institute's biological approach towards mental disorders: to objectify subjective emotions and descriptions. By imaging methods, such as the fMRI, by behavioural and psychophysiological measurements, and by analyses of blood and saliva, the researchers intend to translate individuals' feelings, emotions, and affects, such as fear, into what Selia summarises as "objective measurements". To understand mental disorders within biomedically measurable frameworks is thought of as a *more profound* and *precise* understanding; a knowledge regarded as more reliable and target-oriented.

The idea of objectifying personal descriptions and displaying mental disorders in bodily processes is based primarily on the way neuroscience conceptualises stress, a phenomenon closely linked to mental health issues. As mentioned earlier, the experience of chronic stress is conceptualised as an experience often preceding the development of disorders such as depression. At the same time, mental disorders are most often understood as being related to an imbalance in an individual's capacity to cope with stress. Since stress is regarded as a reaction of the *whole* body to changes in its environment, mental disorders are assumed to be reflected in brain structures as well as in the body periphery through processes such as the metabolism or stress hormone circuits. Thus, the measurement of these biological and physiological variables is employed as a valuable pathway to assessing an individual's mental health status. The RC-study depicted in my field-vignettes addresses precisely the core of this endeavour, which we can observe as a general trend in psychiatry: making mental illness explainable within a biomedical framework in order to establish a new taxonomy based on shared biological markers instead of symptom-driven classifications. This "objective" way of knowing mental disorders involves the hope of finding the "right" diagnosis for a patient's self-recounted symptoms and finally developing a treatment-strategy considered suitable for the specific disease in question. In contrast to this

imagined targeted therapy, today "the choice of a medication is made primarily with regard to the expected side effects due to the lack of clear indications of individual effectiveness" (study protocol, RC-study, p. 1; author's translation). As we will see later, within this research endeavour, epigenetics is attributed a fundamental contribution. Before turning to this analysis, I will first delineate how stress is re-enacted in this study.

Re-enacting stress as a strategy to see biological difference and similarity

As we have seen so far, in clinical studies, stress plays a unique role in many ways. Similar to the other research arrangements with cell and rodent models, in the institute's quasi-experimental human studies,[48] stress is also the experiment's epistemic basis: it is applied in order to measure the bodily response to it through various parameters. The assessment and analysis of the stress response is considered to be a step towards the objectification of personal suffering; a step framed as necessary to improving the diagnosis and the treatment of mental disorders. But how is stress operationalised in the clinical study? How does it become part of research experiments and how do scientists re-enact stress in humans?

First and foremost, as described earlier, the study design is built to have a cohort of psychiatric patients. Only patients who suffer from a stress-related disorder (depression, affective disorders, anxiety disorders etc.) are included. Due to the mental syndromes of these individuals, researchers assume that they will respond differently to stress than healthy test subjects. This is an important distinction for researchers, as they are precisely aiming to be able to see and describe these differences in biological terms.

Furthermore, I observed quite different strategies of re-enacting stress and activating the stress-hormone-system in the participants of the study. First, stress in the participants is applied via physical penetration. In this context, a subtle electric shock or an unpleasant noise are induced to provoke a stimulus that is "unpleasant but not painful" (study protocol, RC-study, p. 2; author's translation). Additionally, an unexpected airflow is targeted on the throat of the participants and a short awkward noise is played over their headphones. This re-enactment of *physical* stress is conducted in two steps. On the first day, the participants are confronted with these stimuli in combination with specific geometrical figures shown on a screen in front of the participants. On the second study day, the participants are shown the figures again, but sometimes independently of the stimulus. During the

[48] The specific experimental arrangement of a quasi-experimental study does not provide control over all elements of the experiment as it compares "natural" groups of people. For example, no randomised sample selection is possible (Fife-Schaw, 2006).

whole experiment, peripheral vegetative parameters are measured via the skin resistance and eye blink reflex.[49]

According to the study protocol, these re-enactments are described as the "psychophysiological response to stress". What do scientists expect from this experimental arrangement? As Selia, a psychologist, explained to me, they intend to induce a fear conditioning in the participants on the first day. On the second day, they monitor possible fear extinction processes and aim to assess which individuals have been fear-conditioned, have "learnt" to have fear, and which have not. By measuring the bodily "startle effects" of participants, scientists are able to assess the stress response of these individuals. The idea behind this procedure is to model similar fear-conditioning processes observed in people who have experienced traumatic events. As Selia explains, "traumatised people suffer from constant stress, even if the stress-inducing moment no longer exists. They have been conditioned similarly to the participants in our experiment. Here, we want to measure the genetic similarities of people with particularly pronounced stress responses" (fieldnotes, 13.12.16). Hence, this experimental arrangement is an attempt to simulate a situation, a fright reaction, observed in human life worlds. In re-enacting stress as an experience that can have conditioning effects (in both patients and healthy test persons), the researchers aim to visualise genetic similarities and differences in responses to stress.

Second, in this clinical study, stress is also re-enacted via so-called "psychosocial" parameters, as is made apparent in the third vignette. Here, the participants are confronted with a dilemma: solving computational problems in a very limited period of time. In addition, they are being evaluated with negative feedback: their results are always shown as incorrect and their performance is also assessed as poor by the physician. This "psychosocial stress paradigm" (study protocol, RC-study, p. 4; author's translation) is regarded as combining naturalistic components of social evaluation and cognitive exercises. It is enacted with the aim of activating systems believed to be important for an organism's stress response. To measure this reaction, the researchers conduct physiological and endocrinological measurements in the fMRI. In this way, the stressful social situation is depicted in immediate neuronal signals (through the fMRI) and measured changes in the stress-hormone-axis (through the collection of saliva and blood samples).

Third, as in almost any experimental arrangement, in this clinical study dexamethasone is also used to induce an *in vitro* stress response. Samples of the participants' blood are needed to carry out the so-called "dexamethasone stimulation test". It is an experiment in which stress is re-enacted pharmacologically in order to measure the cortisol level of the participants in relation to this stressor. For this examination of the stress-hormone system, the patients' and probands' blood samples are mixed with

[49] The skin conductance response or ectodermal activity is associated with emotional-affective responses: the physiological arousal affects the sweat secretion which increases the skin's conductivity. It is considered to be a concise method of objectively measuring the human stress response (Boucsein, 2012).

the synthetic cortisone preparation dexamethasone and then examined for changes in various levels (DNA, RNA, proteins). The basis of this experiment is the assumption that gene expression processes in reaction to cortisol are different in patients with depression and in healthy persons.

As we can see from the various practices of inducing stress within the RC-study, stress is predominantly enacted as a comparative instrument for seeing both biological difference and similarity. It is rendered a tool to identify the physiological and genetic *differences* between individuals that are mentally ill – and who therefore already show a disturbed stress response – from those individuals who are considered to be healthy.[50] Additionally, stress is operationalised as a strategy to measure the physiological and genetic *similarities* of those who are supposed to be "baseline stressed": individuals who suffer from stress-related disorders. The aim is to identify biological markers ("biomarkers") shared by this group of people. As we will see below, epigenetics plays a significant role in this domain of the RC-study.

Environmental epigenetics as a means to restructure the concept of mental disorders

Having depicted how the scientists attempt to approach mental health conditions from physiological and biological perspectives, I will now delve deeper into analysing the specific role that epigenetics plays within this clinical study. As I have shown in the last pages, epigenetics is not the central element, discursively or materially, of the RC-study. This was very different from most of the experimental arrangements I analysed previously: both in cell models and in most animal models, researchers had a distinct focus on epigenetic processes. This may be mainly due to the fact that in these experimental set-ups access to epigenetic processes (in neuronal cells) in models of neuronal structures and in rodents is much easier than in humans. Therefore, in the context of clinical studies, epigenetics is enacted as a fragmentary piece of information that is added to the data portfolio made accessible to researchers for assessment. However, as we have seen, the knowledge that is used to make up said portfolios (before epigenetics) is now considered too insufficient to thoroughly understand the development of mental disorders. Biographical data in the form of psychological questionnaires, calorimetric, physiological, as well as metabolic information and results of imaging techniques are regarded as explanations for many aspects of mental pathologies, but not for all and especially not for the necessary *biological* aspects.

In the attempt to find a molecular language to describe mental health conditions, epigenetics in the form of DNA methylation is enacted as "additional information". As we can read in the study protocol of the RC-study, DNA and RNA are isolated from the leukocytes of the participants' blood samples.

[50] By inquiring about the medical history (anamnesis) of every study participant, scientists try to record life experiences that could potentially act as stress-exposures. This is one strategy to control the many parameters that are part of the experiment and to handle the "messiness" of research with living individuals.

"Since we assume that mental disorders as well as the positive or negative response to medication are at least partially influenced by changes in the genes, these investigations [analysis of epigenetic modifications in blood] should provide further information on this" (study protocol, RC-study, p. 16; author's translation). Physician and neuroscientist Stella summarises the significance of epigenetics in clinical research similarly as follows:

> And... and I think epigenetics is such a... an additional level that we're including now. We think it's an important level because it explains... so like I said... negative life events are the strongest risk factor for mental illness and I think we need to understand how that... how that happens and I think epigenetics is not the only layer, but it's an important layer. (Stella, pos. 23)

Judith, a psychiatrist, attributes an even more compelling significance to epigenetics in trauma research: "When researching trauma disorders, you just cannot avoid epigenetics, as trauma in childhood leads to hormonal and behavioural changes in adulthood which can only be understood with epigenetic knowledge" (Judith, pos. 78). Here, both researchers address a significant characteristic of epigenetics in the context of clinical studies: it is applied as a "tool" or as an "instrument" to produce additional knowledge on the development of mental disorders. At the same time, this additional epigenetic knowledge can never be considered in isolation but rather only in combination with other data.

Hence, in the context of the institute's clinical study, epigenetics is discussed as part of a specific molecular answer to the "psychiatric crisis" depicted earlier. Metaphorically speaking, it is in this vein enacted as one missing piece of a challenging aetiological puzzle: a component necessary to a full understanding of "why someone has a mental disorder" (Stella, pos. 99), and to establishing biology-based diagnoses in order to be able to improve treatment.

There are two crucial elements to understanding how and why environmental epigenetics is increasingly staged as a solution to psychiatry's aetiological puzzle. First, one requirement to solving this puzzle is the development of technological devices that allow for the measurement and display of epigenetic processes. The introduction of the Illumina-DNA-methylation-array is reported to be the technological "breakthrough" (Stella, pos. 10) for carrying out epigenetic research methods. The Illumina-DNA-methylation-array is a technological device that provides researchers with the possibility to analyse the human genome in relation to its DNA-methylation by high throughput.

Second, the metaphorical enactment of epigenetics as a precious piece of information is also part of the narration of the "case of the missing heritability", that Stella recounted in her interview. This "case of the missing heritability" is told as a story of biological aberration. Although researchers and psychiatrists observed heritable components in some diseases, they lacked genetic methods and strategies to explain this heritability. The Human Genome Project led to optimistic forecasts that specific genes would be found that would explain this connection. However, the hopes accompanying this candidate-gene approach were sorely disappointed. According to Stella, the first decade of the twentieth century was therefore a time when psychiatrists would have had the "frustrating" feeling of "missing" some-

thing, of not being able to "grasp" the hereditary elements of mental disorders with purely genetic approaches. This explains why the focus in psychiatric research was shifted away from classical genetic methods and towards the relation between genes and the environment, a topic in which epigenetics plays a significant role on many levels. Stella and her colleagues hope to be able to grasp the "thing" (mental disorder) itself. To formulate a novel ontology about how to understand mental phenomena.

As mentioned earlier, this novel ontology goes hand in hand with the attempt to turn subjective patient experiences into measurable and objective information, that is biological markers, including epigenetic modifications. As Selia explained during the experiment, "On a scale of 0-10 you could also do a fear assessment, but this is nonsense, because this is not objective, in contrast to our measurements" (fieldnotes, 13.12.16). Her comment illustrates how taking a predominantly biological view on mental disorders renders other methods for assessing emotions – by questionnaire, for instance – less valuable and hardly meaningful because they cannot be generalised. Epigenetic modifications and other biological markers are therefore rendered as novel objective diagnostic tools to curb the arbitrariness of current classification systems. These would sometimes hinder appropriate treatment, as physician Judith explained on the basis of her experiences in assessing the health status of patients:

> I have seen so many people who have suffered, although they have not met these... these, sloppy spoken, stupid criteria of these diagnostic catalogues, but who were just as sick, but they neither got a reimbursement... nor a therapy from their insurance – yes? – and that's crazy. And for this reason alone, and also to help people, we need a change in the taxonomy, in other words a re-definition of mental diseases. That's... that's what's gonna happen and epigenetics is gonna play a big role in that. (Judith, pos. 84)

The big role attributed to epigenetics is thus the objective visualisation of suffering, which should pave the way for equitable access to health care. This is made possible according to the imagination of researchers by epigenetics allowing them to talk about the same *thing* instead of getting lost in arbitrary symptom-driven diagnoses.

New ontology – new therapy?

In the above analysis, I have shown how the institute attempts to solve an aetiological puzzle by approaching mental disorders from a *biological* perspective and by adding epigenetic information to the way that mental health phenomena can be *known*. The RC-study is the most significant research project that contributes to establishing such a new ontology and a new taxonomy of mental disorders. However, many PhD and postdoc projects also to some extent strive for this objective. It is an endeavour that unifies nearly all of the institute's research activities: most of my informants talked about their attempt to re-think mental pathologies in a molecular framework and language, to establish a novel biology-based way of diagnosing mental disorders. While this endeavour is still in its infancy, some researchers already discuss how epigenetic knowledge might inform diagnostic manuals such as the

DSM with an understanding of mental disorders framed in molecular-biological terms. Neuroscientists Yehuda and Bierer (2009), for instance, indicate that with the integration of epigenetics into the clinical practice, the focus of the diagnosis PTSD will shift to the *timing* of the occurrence and "prior experience [will be permitted] to have a role in determining individual differences" (Yehuda & Bierer, 2009, p. 8). In the current edition of the DSM, the time in which the trauma took place has not yet been listed as a criterion for the diagnosis of PTSD. Judith speculates as well about how epigenetic knowledge, especially on the relevance of early life, might influence future conceptualisations of PTSD:

> What will change is not the concept of trauma, that can also be defined arbitrarily – the DSM-IV, the old diagnosis catalogue said, yes, trauma, one must have obligatory some feeling of... of detachment during the event. That is no longer necessary in the DSM-V, yes, my – and what will change is the definition of trauma sequelae and that is already changing... because of certain experiences, that one... until now one has called everything PTSD, no matter whether someone had an accident or was traumatised in childhood, but people who were traumatised in childhood have additional symptoms, which have not yet been reflected in the diagnosis catalogues. (Judith, pos. 87)

In addition to these speculations about how single criteria of diagnoses might change, how do researchers imagine that this new taxonomy might inform diagnostic routines, if mental health conditions are understood to be mainly caused by lesions in biology? In the interviews, researchers recounted their visions and imaginaries of what the therapy of the future, that is a molecular biologically informed treatment practice, might look like:

> So, it's going to be done like other illnesses, that you first do an examination, that of course you ask for the symptoms, but that you then... you also do an ECG,[51] you make a heart echo, you do blood tests and maybe anything else. And from this overall picture you say: ok, I think *that* is the problem – and then you treat the problem and you do not treat: I have a heartbeat – but you handle the problem. And... and I think we just have to move there in psychiatry. And... it becomes more and more clear that the... patients with mental disorders who had a childhood trauma are different and that... that just has to be queried and it has to be a diagnostic criterion. It is of course a sensitive topic, but it must be openly handled. It may well be that epigenetic tests also help us to objectify this. And... it's very clear that early trauma patients are simply at risk of having many more diseases, also physical ones and they also are less responsive to therapies. And I think that you might need different approaches again in order to know that from the beginning. (Stella, pos. 105)

As the above interview quote powerfully illustrates, not only is the way of *understanding* mental health conditions expected to shift from symptoms to biologies; the way of diagnosing and treating mental disorders, of "handling the problem", is also envisioned as being based on biological and physiological methods in the future. The information that is currently still gathered through a clinical conversation between therapist and patient and through specific questionnaires[52] is imagined to be predominantly carried out through specific examinations and measurements in the future: diagnosing ECGs, assessing the heart echo, conducting blood tests and measuring epigenetic changes – all are

[51] Electrocardiogram

[52] Currently, there are various questionnaires that are used to diagnose a specific mental disorder, such as depression or anxiety questionnaires. These are part of clinical interviews that are conducted with the aim of leading to a diagnosis (Strauß & Schumacher, 2004).

regarded as informing psychiatrists about their patients' mental health status. Again, this data is considered to be more accurate because it is "objective" and provides a standard against which to compare the measured symptoms in different patients, a strategy to truly access the *problem* and not the *symptoms* associated with the problem. Such imaginations of how to conceptualise and treat mental disorders in the future are also an important part of the following section, in which I address the ways that epigenetic approaches inform the institute's research with human cohorts. Again, I will showcase different researchers and their projects to show how adapting an environmental epigenetic perspective gradually leads to a molecularisation of trauma and early-life experiences.

4.4.2 Research with human cohorts: the molecularisation of trauma and early life

4.4.2.1 Approaching mental health in a human cell line: a story of adaptability

> As an organism, you are flowing – yes? You are not the same as you have been yesterday and you will be the day after tomorrow due to your experiences. How this is reflected in your body is of course completely different and... therefore – But I found it fascinating how adaptive we are as an organism and how... and how evolutionary, how that can change... how you can change. You are already very strongly determined by your genetic make-up, but how... how... what else... you can make out of it... and how the environment... how the environment has an influence on you, on your cells, because the... the cells, they are also quasi organisms in themselves. They just have decided to work together – right? – and each cell performs special tasks and sends signals to... to... and to, so to speak, to... and ... that ... I find that interesting and the molecular mechanisms behind it, that's very... very nice. (Valentin, pos. 30)

This metaphorical summary of how Valentin, a biologist, understands the significance of environmental epigenetics for human life hints at a fundamental epigenetic hypothesis: humans do not consist of cells that are meant to be fixed. Humans as whole organisms and as clusters of cells are not equipped with an immutable biological architecture, but rather respond to changes in their environment. They are plastic and malleable. In some cases, these changes in environments, when perceived as stressful experience, may lead to illness:

> Valentin: We [humans] have a physiology, the physiology works well and keeps us upright. … And this physiological network that keeps us going – that's just all the genes that work together and so – of course, when an environmental influence comes along that's kind of shaky – yes? – and so, if... at the beginning when you are young it is still relatively stable, and if you don't have any genetic predispositions everything is still relatively stable, but over the years of continuous psychological stress, if you for instance experience traumas, you just... you send out more and more cortisol – yes? – that is, this system, this physiological net is always strained, always under tension, and then it can happen that somehow... individual strands in this net break and if you... over the years, this network becomes thinner and thinner, at some point it collapses a little bit and that could trigger an exhaustion disease – yes? – So it's not a one-hit, everything is broken. But it's rather a wear and tear of the physiological system in... in the organism itself. Now, this is of course an explanation in very general terms. / Me: Yes / Valentin: Yes? With little genetic vocabulary.
>
> Me: And what role does epigenetics now play specifically for your project?

> Valentin: What role? It's the... really the core aspect in... [*amused*] in what I'm doing, because I have a gene... I'm relatively specialised on a locus in this gene … So, this... this lo... this gene is also very important in the stress response, because it sort of re-initiates homeostasis when you have been stressed – yes? – So it's a stabilising mechanism – exactly – a... so to speak a negative feedback – yes? You have stress, this gene shifts your physiological network back into your homeostasis. … And I look at the molecular epigenetic mechanisms: what happens? … And that gene is at the junction between the... physiology, between homeostasis. So, I'm interested in the question: what genetic variants are there in this gene itself? And what genetic variants in this locus lead to differently high responses to stress? (Valentin, pos. 51-52)

This quote from the interview with Valentin refers impressively to general concepts of stress and connects these to epigenetic research. The notion that an organism maintains a stable equilibrium, "homeostasis", and is activated by stressors, "allostasis", was first proposed by neuroscientists in the late 1980's. The idea that the physiological net, which keeps the body stable, can be damaged by excessive stress (a constant distribution of cortisol) is referred to as the "allostatic load". For Valentin, epigenetic processes are molecular information deemed appropriate to understanding how a single stressor can lead to different stress responses. It is a tool for seeing individual differences. Therefore, in his PhD project, Valentin focuses on a specific gene: the Trauma-Related Binding Protein (TRBP).[53] This gene is considered to be central in an organism's stress response as it is an important regulator of the glucocorticoid receptor sensitivity: it "effectively decreases glucocorticoid binding to GR, impeding GR translocation to the nucleus" (Yehuda et al., 2016, p. 373). Its clinical relevance lies in the observation that the TRBP gene expression is altered in individuals suffering from PTSD and MDD. By investigating its genomic variants, Valentin attempts to study what is called "risk and resilience". This pair of concepts is based on the observation that some individuals seem to be more prone to develop a mental disorder than others – despite the fact that they have experienced similar events. Against this background, scientists assume that there must be molecular differences that have either protective or pathogenic capacities.

What Valentin looks at specifically in this context is the biological phenomenon called "insertion" and "deletion". This conceptual pair stems from genetics and describes processes of genetic mutations. "Insertion" describes genetic variants in which additional nucleotides are integrated into the DNA, whereas "deletion" comprises the loss of nucleotides. All of these genetic processes are assumed to have effects on gene expression and hence on the protein product, thereby potentially leading to phenotypic abnormalities (Garcia-Diaz & Kunkel, 2006). Based on this assumption, Valentin's leading research question is how genetic variants of the same gene, when combined with stress, lead to different biological conditions for the organisms later in life: why do some individuals face a higher risk of developing a mental disorder while others seem to be more resilient?

[53] Pseudonym

To investigate this question, Valentin works with adult human cell lines derived from blood; they are not, therefore, of neuronal origin. In general, biotechnology differentiates between two types of cell lines: immortalised and primary cells. Valentin works with both types and explained to me that he isolated his cells from blood and "immortalised" them by means of a viral manipulation. This immortalisation gives the cells the property of being able to be proliferated (reproduced) indefinitely in a culture medium. In contrast, his primary cells came from *in vivo* tissue, isolated from the blood of volunteers without similar molecular manipulation (fieldnotes, 12.4.17).

Valentin has received his cell lines from the *1000 Genomes Project* and the *Grady Trauma Project*. The *1000 Genomes Project* was an international project, run for seven years by research institutes from many different countries, such as the United States, the United Kingdom, China, and Germany. Its main goal was to find the most genetic variants of at least 1% of the populations studied in order to understand genetic variation in the human population at large. The project could only be realised because the cost of sequencing entire genomes was drastically reduced in the 2000's. Within the *1000 Genomes Project*, the genomes of 2,504 persons from 26 populations across five continental regions have been sequenced. The scientists involved in the project derived a catalogue of human genetic variations from the sequencing data sets. The significance of the project today lies in its use as a database for scientists working with human tissue: it is openly accessible to scientists worldwide (Birney & Soranzo, 2016). The *Grady Trauma Project* is a US-American cross-sectional study that aims to determine the genetic and trauma-related risk factors for developing PTSD. As the project website informs us, to investigate these connections, researchers frame a highly traumatised, low socioeconomic status, minority urban population as a study cohort. It primarily consists of African-American subjects. An American-based biobank and medical research institute manages the cells of both projects and makes them available to researchers for research purposes.[54] In this sense, Valentin uses the project's infrastructure to receive human material for his research.

In general, Valentin's central methodological approach is fairly similar to the approaches of researchers who work with neuronal cell models. As Adriana with iPS cells and Emma with the cerebral organoids they study, Valentin too re-enacts stress by applying the pharmacological substance dexamethasone to his immortalised cell lines. The handling of the pharmacological substance appears to be standardised in the same way as Adriana's and Emma's uses of it. According to Valentin's research protocol, he stimulates his cells with dexamethasone by the following operational steps: first, dexamethasone has to be dissolved in ethanol, as it is a solid substance at room temperature; then, he manually administers dexamethasone on his cells by applying it with a pipette. He can adjust the duration of this "stressful" pharmacological event by the point in time at which he harvests the cells. In this context, a longer application of dexamethasone is assumed to lead to an enhanced glucocorticoid-response,

[54] http://gradytraumaproject.com/project/

which means that the GR is continually active and influences gene expression patterns. After administering dexamethasone as a stress paradigm, he therefore analyses its effects on gene expression patterns in the gene locus and its changes in the chromatin structure. As mentioned earlier, for the primary cell lines Valentin uses blood from individuals. This is a way to study the stress response in an *in vivo*[55] approach: in contrast to the immortalised cells, in the primary cells Valentin first re-enacts dexamethasone by letting volunteers take dexamethasone orally. Afterwards he collects the blood and analyses changes in DNA methylation patterns.

There are two main reasons for Valentin to look at environmentally induced epigenetic changes in blood for his project. First, as mentioned earlier he conceptualises stress as "tension of the physiology", leading to an activation of the glucocorticoid-receptor and to demethylation processes at the binding sites. Those normally go back to a baseline-methylation level after the stressful event, a process which can be also observed in the dexamethasone-model. However, when this epigenetic mechanism of the physiological net is broken, it can result in a progressive demethylation. In this case, the organism may fall mentally ill. Valentin concludes that these

> epigenetic layers [the DNA methylation] all react to the environment, so you can see, when you bring in the... when you bring in an environmental influence, that epigenetics adapts dynamically with this environmental influence. … So, you can see that we… we are responding... epigenetically to stress. (Valentin, pos. 57-58)

These demethylations have also been described in people who have experienced traumatic events and suffer from PTSD (Zannas et al., 2015).

Second, by resorting to human blood, Valentin assumes that the human organism functions as a "brain-body work" (Valentin, pos. 72). He investigates cells from a traumatised cohort with the aim of identifying biomarkers that may indicate a risk of developing a mental disorder. That is to say, by investigating stress responses in human blood, Valentin hopes to establish a "proxy" that displays processes that take place in the brain during or after experiences of stress. He elaborates on this connection in an interview:

> Me: So this is the essential groundwork you do to / Valentin: Yes. Exactly / then have a better targeted research?
>
> Valentin: Right, yes, right, right, yes. Because I'm not saying that... that what I see in the blood, that... the... the one and only factor that determines everything afterwards. But I mean, you can of course... that's why our body is a gene... a brain-body work – right? – and especially the stress system. These are signals that come from the brain, that go to our adrenal cortex and then go back again, so you see, it's a big interplay and in terms of biomarkers of course ... would it be very interesting if you could analyse in the blood: how ... yes, how strained is that ... is the physiology behind it, yes? If you could take that as a proxy, that would be interesting, yes. (Valentin, pos. 72)

[55] In this respect, Valentin's approach is distinct from that of Adriana or of Emma. While all researchers work with cells derived from humans and in culture, Adriana and Emma work with an *in vitro* model of neuronal cells.

Despite his rather global understanding of how stress affects the body, Valentin takes a very narrow approach in conducting his epigenetic analysis. By focusing on one specific gene locus in one gene that is important for the general stress response and by ascribing the power to influence an individual's health to changes in this gene locus, Valentin renders mental health into a highly fine-tuned logic. This associates mental health with small changes in an individual's biological architecture. It is important to note that Valentin is well aware of his radically reductionist approach. Yet, he regards it as a pragmatic methodological strategy that is necessary to conducting the experiment at all:

> I am quite specialised. I'm looking very focused on a certain thing... why am I doing that? Because I can better control my factors that I can change to really – it is very hard to achieve causality in psychiatric research, so causality as a mechanism-thought: this requires that. In order to achieve causality, you actually always have to keep relatively many factors stable except from one factor – yes? – and that's not always easy. (Valentin, pos. 66)

In the above quotation, Valentin refers to a general methodological challenge in psychiatric research that was in fact mentioned by all of my informants: establishing causality. According to Valentin, this limitation would be different in other research fields, such as cancer research: "You want to get rid of cancer, so you cut it out, you can examine the material – we can't do that – yes? – we cannot always access the brain" (Valentin, pos. 67). That means, Valentin's blood cell lines serve as a "proxy" for studying environmental epigenetic processes as such. He does not use the cells to model any neuronal or brain-like structure, but as a methodological testing ground to assess the feasibility of his specific approach: as already mentioned, he is predominantly interested in analysing the epigenetic changes after stress associated in *one specific gene locus*. Therefore, he is using cell lines derived from blood to first be able to experiment with different research questions and methods before entering into the material he is actually interested in: neuronal cells, which is a tissue far more precious and limited than blood cells. In the interview, he clearly states that "it remains to be seen whether it would be different in neurons, that would need further investigation, but at least I can take further steps forward – yes? – to further analyse it [the methodological feasibility]" (Valentin, pos. 68). Hence, his current project predominantly serves for testing fundamental methodological and theoretical repertoires in order to ultimately set up a research protocol for further research in other cell types than blood cells.

As epistemic objects, Valentin's cell lines entail different degrees of epistemological closeness and distance to one of psychiatry's main object of interest, the human brain. His use of *in vivo* material, the primary cells directly retrieved from blood, and of cells from a human traumatised cohort constitutes a certain closeness: these are *human* cells. At the same time, his approach entails some degree of distance (at least for now, until reliable biomarkers are established), for the very reason that they are derived from *blood* cells: they are epistemically distanced from neuronal cells, in which biology widely localises mental disorders. Therefore, when connecting experiences of stress to his research, Valentin uses a rather cautious language, detached from human life worlds. For instance, for him dexamethasone is a tool to induce a "change of the environmental situation and the cell reacts to it",

which is a rather topographic understanding of the environment. And he explained: "I have a substrate that binds to my glucocorticoid receptor and then the expression increases in this locus" (Valentin, pos. 56). In this context, the term "stress" is omitted from his vocabulary: "I would not say that what I do is negative stress. That's just another environmental situation [for the cell]" (Valentin, pos. 92). While this description may to some extent relate to Valentin's research personality, I also interpret it as bound to his experimental arrangement. It shows that research in human blood cells facilitates scientific hypotheses and claims that differ from research in models of human neuronal development. Speculations about the effect of stress on the brain and thus the whole organism seem to be more difficult to establish.

Interestingly, Valentin's imagined scenario of how knowledge produced in his research may leverage mental health to some extent also reflects aims that differ from those associated with Adriana's and Emma's neuronal cell models. While research with neuronal models predominantly targets a better understanding of early neuronal development via environmental epigenetic pathways, for Valentin epigenetics is knowledge relevant to being able to "increase the sensitivity of patients so that therapy can be more effective" (fieldnotes, 11.10.17). For him, it is important to understand a patient's "environmental sensitivity" – the ways an organism responds to external circumstances via epigenetic processes. In this imaginary, an assessment with dexamethasone could help to measure individual environmental sensitivity: "What is my patient like?... in terms of environmental sensitivity?" (fieldnotes, 11.4.17). In being able to change individual epigenetic profiles, Valentin hopes to also improve the ways patients respond to medication. Hence, in Valentin's experimental arrangement environmental epigenetics is first and foremost enacted as a story of adaptability: on the one hand, overly long phases of an organism's biochemical adaptations to stress via epigenetic mechanisms are rendered as potentially pathogenic. On the other hand, increasing an organism's capability to better adapt to psychiatric treatment, its "environmental sensitivity", is an imaginary therapy facilitated by Valentin's research approach.

4.4.2.2 Epigenetics as a "biological memory" for traumatic events

> When you think about it, when... when we act, feel and think, these are the three forms of human expression, so to speak, and the three functions that are superior to the brain. And we just want to examine the molecular basis of the disturbed emotional concept and the disturbed cognitions, this means thought structures, and the disturbed behaviour of trauma patients in particular. (Judith, pos. 66)

Judith is one employee at the institute who has a specific research focus on trauma and trauma sequelae disorders, such as PTSD. As the excerpt from the interview conveys, she attributes the consequences of traumatisation to molecular structures. Therefore, she tries to uncover this molecular basis of disturbed emotion and behaviour. As physician and neuroscientist, she knows the phenomenologi-

cal, clinical side of trauma as well as theories about what traumatic experiences do to the body. From her perspective as a trauma therapist, she states in a publication that so far, there are no drugs specifically effective against PTSD symptoms. Therapy specific antidepressants may be able to suppress a comorbid depressive syndrome, however, as her clinical observations of patients show, it has little effect on the occurrence of more trauma-related symptoms, such as agonising reverberation memories or avoidance behaviour (Judith, 2010). Against the background of this treatment plight, Judith aims to increase scientific knowledge on the health effects of traumatic experiences by including an epigenetic perspective. She even considers the importance of epigenetics to be absolutely necessary: "When you are researching trauma disorders, you just cannot avoid epigenetics as trauma in childhood leads to hormonal and behavioural changes in adulthood which can only be understood with epigenetic knowledge" (Judith, pos. 78). Hence, Judith conceptualises trauma as an epigenetic event having persistent biomolecular effects.

Cohort studies provide the necessary research infrastructure for her to investigate trauma and trauma-related health effects, such as depression or metabolic syndromes, although trauma can also be simulated in the animal model by using rats that had been raised under the adverse conditions of limited maternal care, a model for early childhood trauma (author X & Nadja). As we will see below, in comparison to research with cell and animal models, the cohort studies analysed in the following sections represent a specific form of experimental arrangement concerning experimental control: researchers are confronted with high complexities and a low degree of standardisation as they do not work with models built for laboratory research but rather study individual "life events". Therefore, the epigenetic accounts of mental health built on this research are much vaguer and more cautious than in the other experimental arrangements, as researchers "can only look in the blood or at most in the cerebrospinal fluid or urine and not where the... where the disease takes place, namely in the brain (Judith, pos. 54).

What these cohort studies have in common is their focus on a traumatic event, an experience cataclysmic for the experiencer. My informants often referred to trauma as a "maximum form of stress" (Judith, pos. 115), which is a scientific definition that mainly takes into account the bodily reaction to trauma and not the character of the adverse experience itself. It is a definition that makes trauma to some extent operationalisable and workable in the laboratory.[56] The DSM offers a spectrum of possible experiences that can be categorised as traumatic events. Basically, they are distinguished as directly experienced or witnessed traumatic events and can for instance include exposure to war,

[56] Based on imaging techniques, researchers have already made preliminary observations that the character of the trauma, for instance childhood abuse versus witnessing violence in childhood, leads to physiological changes in different brain areas. However, it is not yet possible to investigate how these different types of trauma might have different epigenetic effects, as scientists "do not reach these specific cells in the brain" (Stella, pos. 17).

threatened or actual sexual violence, natural disasters or severe motor vehicle accidents (APA, 2013). These occurrences are considered to possibly lead to a post-traumatic stress disorder and are listed as diagnostic criterion "A" in the current edition of the DSM published in 2013.

In general, Judith's research portfolio is very broad and ranges from clinical studies on biomarkers to cohort studies on traumatised refugees in Uganda, to find a non-European control group for genetic markers to "interventional stress studies". One of these interventional stress studies represents an interesting experimental arrangement as it illustratively displays the role of epigenetics in trauma-research as a form of biological memory. It also shows how different strategies of re-enacting or harnessing stress are used to investigate molecular differences in individuals.

In this cohort study, Judith and her colleagues investigate the stress response in "critically ill PTSD patients" and "healthy" individuals. As in the RC-study, this is a comparative approach in which non-traumatised individuals are considered a "control" group. It is a research design that should allow Judith and her colleagues to trace the identified differences back to the traumatisation. Both groups were subjected to two stress tests: the dexamethasone test and the so-called "Trier Social Stress Test" (TSST). Described as "moderate psychological stress in a laboratory setting" (Kirschbaum et al., 1993, p. 76), it is used to study the physiological effects of stress. Since the test's introduction in 1993, "researchers worldwide have used the TSST as a robust experimental protocol considered to produce reliable physiological outcomes" (Dickerson & Kemeny, 2004). Similar to the calculation tasks in the fMRI in the RC-study, the TSST simulates socially evaluative situations by inducing stress for approximately 15 minutes. In general, it models the stressful situation of a job interview and combines public speaking and mental arithmetic:

> The TSST requires participants to prepare and deliver a speech, and verbally respond to a challenging arithmetic problem in the presence of a socially evaluative audience. Social evaluation and uncontrollability have been identified as key components of stress induction by the TSST. (Birkett, 2011, p. 1)

Based on the stress induced by public speaking, a scenario that every human being is assumed to experience over the course of their life, the TSST is framed as an "ecologically valid stressor" (Allen et al., 2017, p. 115). Judith applies the TSST to see "how certain markers in the blood change, how certain hormones change, how the psychopathology changes through stress" (Judith, pos. 52).

Based on analyses of DNA methylation patterns in the blood samples of the cohorts, Judith identified two groups of "stress-types" that she traces back to epigenetic differences. These differences are also reflected in behaviour: "those who have been traumatised in childhood and adolescence are terribly upset by such a stress test" (Judith, pos. 52). Judith attributes the difficulty that these individuals have in coping with stress to the lack of a hormonal stress response: "the answer is, so to speak, extinct" (Judith, pos. 52). This means that such individuals are lacking a link between their mental stress

system and their hormonal system. If stress hormones are not released there is no increase in cortisone and the body cannot cope with stressful situations. Therefore, Judith classifies those individuals as "non-responders". In contrast to the "responders", the "non-responders" lack the ability to adequately respond to and deal with stress. Judith locates the core of this dissociation of the mental stress system and the hormonal system in epigenetic differences: the "non-responders" show aberrant methylation patterns in genes important for the stress response – epigenetic modifications that were not detected in the "responders".

While Judith applied the TSST in this cohort study to make visible the *molecular* and *epigenetic* differences between traumatised and healthy individuals, the dexamethasone as a form of pharmacological stress served as a tool to verify the results:

> And we then replicated this in dexamethasone – this is a different stress, a pharmacological stress – and all in all we found out that this stress response in the blood not only correlates with three epigenetic loci, but that this [stress] type can even be produced simply by switching it on and off. (Judith, pos. 72)

In sum, in Judith's experimental arrangement stress as a technical tool has taken different forms and made different things visible. First, Judith conducted her research with a cohort of highly traumatised individuals and non-traumatised controls to investigate the molecular differences between those two groups. Hence, she assumes that these traumatised individuals are to some extent "baseline" stressed and will show both a different biology and behaviour than the control group. That is to say, in this context she does not re-enact stress, but harnesses "naturalistic" experiences and life events for epigenetic research. In contrast to most other experimental arrangements, Judith does not work with "unstressed" research subjects, inducing the epigenetic changes she aims to investigate by applying stress. The epigenetic changes are already *there*, as a consequence of the participants' traumatic biographies. While we find a similar framing of the study subjects in the RC-study, the two approaches to forming the cohort also differ significantly. The in-house patients participating in the RC-study suffer from a stress-related disorder. They have presumably experienced some traumatic or adverse experiences at some point in their life, but this is not the inclusion criterion that determines whether or not they can take part in the study. It is the disorder – depression, anxiety disorder, etc. – that qualifies individuals as "adequate" study subjects. In the epigenetic cohort studies, however, cohorts are framed *along* traumatic experiences, this is the core inclusion criterion and at the same time a central object of investigation.

Second, within the context of this "naturalistic" and "ecological" stress harnessed *ex post facto* for the laboratory, Judith re-enacts stress "psychosocially" under laboratory conditions by applying the TSST. This stress test represents her actual research instrument for addressing the differences between the two groups of study subjects, to see what exactly has changed epigenetically on the basis of DNA methylation patterns in genes (in blood). Third, the pharmacological stress re-enactment through

dexamethasone is used to replicate the findings and increase validity. Here, the dexamethasone-paradigm seems to play a much smaller role than in other experimental arrangements, such as in cell culture where it is used to simulate chronic stress.

What we can observe in Judith's choices for her experimental arrangement and in her interpretation of her results is that epigenetics is framed as a dysregulation. A "mismatch" between an environmental change and the required behaviour needed to be able to "adapt" to this change due to (a) traumatic experience(s) in childhood. Stored in a form of biological memory, trauma in this context is translated into a *molecular event* condensed in epigenetic regulatory patterns. The effects of traumatic experiences, hence, are the result of a cascade of molecular reactions, in which "epigenetic mechanisms program body processes" (Judith, pos. 73). This interpretation sees personal experience as hardening into molecular structures, *molecularising* trauma as an element of personal biographies and as a potential cause for mental disorders. It was not least the technological progress that helped this idea to make its breakthrough, as we can read in one of the field's publications: it is only "in the last few years that we have begun to understand, through technological advances, how early traumatizations are physically written down and can affect different aspects of our behaviour and experience throughout our lives" (Brückl & Binder, 2017, p. 118; author's translation). Such a molecular perspective on trauma leads to a similarly molecular perspective on how we can understand mental disorders, namely as anchored into our biology:

> A mental disorder is nothing esoteric, it does not mean that God has not loved you, so to speak, and that you are not worth anything, but it is based on biological changes that are partly reversible and has a biological basis. And epigenetics, because it is just as vivid and vividly conveyed... explains that for some things you cannot do anything, but that you can still change them and that mental disorders have a molecular basis, and I find this very important. (Judith, pos. 95)

4.4.2.3 Representing life in the retrospective: the early-life paradigm

> And the way I personally came to epigenetics was that we saw a gene-environment interaction that just happened to be associated with trauma early in the... so the interaction is only if the trauma is early in childhood, but the genetic polymorphism affects our stress response in adulthood. So, it wasn't entirely conclusive as to why... why... why don't I see that interaction in adulthood trauma? And that's when we realised that there has to be another... somehow something different than the genetics to explain it. And then I just started talking to a... with one of my... my postdocs, we were thinking: ok, let's look at DNA methylation now, maybe it's really that we... that we have epigenetic changes in addition to genetics that only come when the trauma happens in childhood. And that's what it was really like. (Stella, pos. 4)

The relevance of early childhood has emerged repeatedly in the course of my analysis. Conceptualised as the early-life paradigm, it is harnessed for epigenetic laboratory studies, such as by applying dexamethasone to models for prenatal neuronal development. In cohort studies, the early life paradigm has the strongest clinical relevance. In the following section, I will show how the combination of the early-life paradigm with cohort studies becomes a research guiding construct. In this sense, it emerges

as a hub in which epigenetic knowledge seemingly accumulates – knowledge ranging from a better understanding of health trajectories, to the prediction of an increased risk of mental disorders, to ideas about how this knowledge could leverage the treatment of mental health conditions.

In general, the notion that early life *matters* for human development is an old assumption in psychiatry. However, the connection has far lacked a molecular explanation; an explanation that could only be revealed by epigenetic reasoning, as we can read in the following publication by Rahel and Stella:

> Childhood trauma is one of the most well-established risk factors for the development of mental disorders. Due to the availability of new technologies, we are now beginning to understand how early trauma gets under the skin and exerts a sustained influence on various domains of psychological functioning and health. [The authors] consider genetic and epigenetic factors as possible mechanisms mediating the biological embedding of childhood trauma. (Rahel & Stella, 2017, p. 118; author's translation)

In her research portfolio, physician and neuroscientist Stella investigates precisely this epigenetic link between early life and health trajectories in adulthood. As mentioned earlier, for Stella epigenetics is an important "additional layer" to be able to understand the relevance of adverse events in life as what Stella refers to as the "strongest risk factor for psychiatric illness". She continues: "and I think we need to understand how that... how that happens, and I think epigenetics is not the only layer, but it's an important layer" (Stella, pos. 26). This interpretation confers epigenetics the power as a tool that supports scientists in retrospectively investigating what has happened in individuals' early life, what molecular traces have been left by the trauma they may have experienced. As with the "case of the missing heritability", epigenetics visualises a phenomenon that was previously invisible or incomprehensible. This is a form of "molecular credibility" (Kenney & Müller, 2017, p. 38), as it gives life science research the power to demonstrate a molecular connection between early life and adulthood via epigenetic pathways, ultimately leading to a molecularisation of childhood trauma.

In this context, the TRBP emerges as one specific focus of Stella's research. As mentioned earlier, the TRBP is a gene that is believed to be a strong agent in an organism's stress response as it regulates the activity of the glucocorticoid receptor. In the last decades, it has emerged as *the* stress gene and much life science research has corroborated the hypothesis that individuals who have experienced trauma show molecular abnormalities in this gene. The TRBP is furthermore a fundamental biochemical agent for clustering individuals into cohorts, as trauma is considered to be "imprinted" in this gene: Stella and her colleagues postulate that people who have experienced some traumatic event have "significantly different epigenetic markings in this gene" (Stella, pos. 41). Therefore, those individuals who have experienced trauma in childhood or even before birth represent "explorable" cohorts. Localising childhood trauma to epigenetic processes and marks gives the researchers the opportunity to analyse traumatic experiences within the framework of biological exploration.

One cohort in which Stella investigates the effects of early-life stress is a sample of 1,000 pregnant women, in a study she conducts in collaboration with Finnish colleagues. In this study, the womb is conceptualised as an epigenetic environment and a potential mental or somatic disease in the mother is regarded as early, prenatal life stress for the foetus. This means that not only anxiety or depression, but also pathologies such as diabetes, are rendered as exposures that potentially leave epigenetic traces on the child's epigenome. Therefore, the researchers

> examine the methylome of the child at birth and in some cases [they] also have the methylome of the placenta and can really try to understand: ok, how does the very early environment affect DNA methylation and also in the interaction with... with the gene... with the gene variants?" (Stella, pos. 10)

For Stella, this is an approach that allows her to move away from studies in adults and rather towards studies that allow her to follow developmental trajectories, to investigate "how does this [epigenetics] also develops over time" (Stella, pos. 10). We can observe here the ways that the early-life paradigm is increasingly "expanding" into ever earlier, prenatal life phases. Thus Stella's scientific view is also increasingly expanding and is directed towards ever earlier, and at the same time longer, periods of observation.

In a study that looks even further back, she has conducted research on offspring of people who experienced systematic persecution: these individuals are framed as "molecularly altered" but not directly exposed to the traumatic event. Stella and her colleagues studied methylation patterns of the TRBP in the blood of those experienced such atrocities, their offspring and in non-exposed parents and their offspring who are nonetheless considered "demographically comparable" (Stella et al., 2016, p. 372) to the victims/victims' offspring groups. While the first two groups (victims and their offspring) are the "exposed" cohort, the latter two groups are regarded as "unstressed" control subjects. Based on DNA methylation analysis, the research group claims to have shown that those who have survived atrocity and their offspring have methylation changes on the same site in a functional region of the gene at question, the TRBP. The authors interpret these results as demonstrating an association of preconception stress effects with epigenetic changes in both exposed parents and their offspring in adult humans (Stella et al., 2016).

In this study, Stella and her colleagues not only suggest epigenetic modifications as a mechanism by which traumatic experiences are inscribed into biology. They go further, proposing a platform for discussing the mechanisms through which these traumatic experiences may be transmitted to the next generation. They introduce the concept of "intergenerational transmission of trauma", describing how the effects of traumatic experiences may be passed down from one generation to the next via epigenetic pathways. Hence, "early life" is moved even further into prenatal, even *preconceptual* life phases, reconfiguring the preconceptual maternal womb as the first epigenetic environment, which produces specific "pathways of epigenetic plasticity" (Mansfield, 2017, p. 361).

In this context, it is important to note that Stella re-narrated the story of the intergenerational transmission of trauma with much more reservation. In the interview, she clearly stated that they do not know where these epigenetic changes in the offspring actually come from:

> The adults whose parents survived systematic persecution, have significantly different epigenetic markers in this TRBP, but where does that come from now? Well, it's not from their own traumatisation, it's not from... from the parents' illness, the parents' mental disorders, but... but now what the mechanism was – so is it the... the mother's pregnancy? Is it early parental behaviour, this environment...? So, or is it actually something in the germline?... we can't measure that yet. (Stella, pos. 41)

The above quotation shows that due to the fact that epigenetic trauma research has to resort to peripheral tissue, cohort studies are an experimental arrangement characterised by much more vagueness and indeterminacy than cell or animal models. Establishing causality between epigenetic modifications found in blood and their relevance for the brain "where the disease occurs" (Judith, pos. 54) is recounted as the major analytical challenge and limitation. Despite these challenges in conducting and interpreting epigenetic research with human tissue, cohort studies are research arrangements in which the ideas about how epigenetic knowledge could be applied are most concretely formulated.

4.4.2.4 Applying epigenetic knowledge in the clinic: between prevention and intervention

As I have shown in the previous sections, the early-life paradigm and the TRBP are conceptualised and operationalised as "tools" that enable knowledge production on epigenetics and mental health. Beyond their relevance as epistemic instruments, they also give rise to imaginations regarding the leverage of mental health care. As we will see below, these imagined future directions oscillate between the prevention of mental disorders and the treatment of psychiatric patients.

Prevention: Who is at risk?

First, in elucidating the mechanisms of how traumatic experience can change methylation states in the TRBP, both in exposed individuals and in their offspring, Stella aims to provide insights into the molecular underpinnings of the phenomenological observation "that some people are simply resistant to trauma" (Stella, pos. 4). "So why," she inquires, "does stress have stronger epigenetic effects in some people... than others?" (Stella, pos. 103). The early-life paradigm is in this context rendered as a key concept to understanding how genes and environment "interact" to define risk and resilience. This is a clinical pair of terms that describes that some individuals develop a mental disorder while others do not, despite having experienced similar traumatising or stressful life events. While the question of risk and resilience also plays a role in other research arrangements, such as the RC-study, in cohort studies it is clearly one of the main research perspectives and clinical objectives. By analysing how early-life experiences impact DNA methylation and interact with different genetic variants, Stella and

her colleagues hope to be able to describe and *predict* disease trajectories. One of the anticipated aims in this context is to identify groups of people that are specifically at risk of developing or "inheriting" the possibility of developing a mental disorder some time in their life. The ultimate objective here is to assess who is in need of therapy or preventive interventions, to stratify populations into different risk groups along their epigenetic profiles. This is a specific imagination of how epigenetic knowledge could inform public policy and direct it towards leveraging earlier intervention in order to reverse risk trajectories and possibly prevent pathological health outcomes which also addresses economic and societal questions. As Stella puts it, "Who specifically needs interventions against the background that we as a society cannot afford interventions in all people?" (Stella, pos. 28). By drawing on the importance of early life, Stella emphasises the societal and state responsibility to identify who is most vulnerable and therefore might benefit most from early development support. For her it is important "to put money and social attention exactly there… to shape this environment positively" (Stella, pos. 28 & 52).

Intervention: how to better treat mental disorders

In the therapeutic imaginations, the early-life paradigm has a similar relevance. It is enacted as a paradigm with a twofold significance: first, Stella and her colleagues postulate that "negative life events are the strongest risk factor for mental disorders" (Stella, pos. 69) and that they also increase the risk of somatic disorders such as cardiovascular or metabolic diseases. Second, the early-life paradigm is also harnessed to speculate about the power of therapeutic interventions *at an early state*. This means, in this context, that researchers assume that the sensitivity of early-life phases to adverse experiences can also be extended to positive experiences and supporting interventions. Stella imagines the possibility to

> help children long lastingly. … And that's what I think I'm interested in, in epigenetics. So, of course psychotherapy helps, but the question is: can we assume that if we do that in... certain stages of development with certain methods, that we might have a change for the whole life? (Stella, pos. 60).

Early interventions that target epigenetic changes are in this context enacted as a beacon of hope that a long lasting and wide-ranging therapeutic strategy might be found. The novelty that epigenetics brings to this therapeutic scenario is the idea to not only treat the mental symptoms of psychiatric patients, but also the somatic disturbances that often accompany mental disorders. Here, Stella addresses the limitation of current therapies, such as psychotherapy, that might only target psychiatric symptoms: "but these children still have a higher risk of diabetes, coronary heart disease etc. [The question is, whether] we can influence everything through this early intervention" (Stella, pos. 62).

In the interview, Judith even substantiated the idea of an epigenetically effective drug therapy. The interview excerpt below illustrates how rendering mental health phenomena in a molecular biological framework also leads to favour a molecular biological intervention, such as an epigenetic drug:

> That's my favourite idea: that one day you will be able to make epigenetic changes with specific medications. That means apart from epigenetic marks predicting mental disorders, that you can also change this therapeutically. There's a drug that already does work epigenetically: valproic acid. But it only became clear later and you only found out later, the drug is older, that it makes epigenetic changes and I think that's a very interesting model and there are other – yes – drugs in development and of course that would be great if you... if you could do that specifically by changing epigenetic processes, that means methylation, demethylation, to combat a disease. So, this is my favourite idea, and I also think it will work. (Judith, pos. 82-83)

While Judith regards epigenetic effective drugs as an easy fix for mental health problems, this is an imagined possibility that is discussed very heterogeneously by my interviewees. Based on her "epigenetic understanding of what brain diseases are", neuroscientist Lydia renders mental health conditions as too complex: "So I see this completely not realistic to be that, with one drug, you will fix everything" (Lydia, pos. 30). Research group leader Lucas in turn regards current psychotherapeutic approaches as "being epigenetic in itself, as epigenetics is the principle underlying psychotherapy" (Lucas, pos. 32), and therefore does not need to be surrogated by other epigenetic interventions.

In sum, we can observe that research with cohort studies is an experimental arrangement which represents a discursive arena for discussing the clinical potential of epigenetic research. More than in the other research arrangements, epigenetics offers scientists a platform to speculate on its applicability. Yet these discussions are as heterogeneous as the research itself and oscillate between two visions of how to address mental health conditions in the future: either to prevent mental disorders even before they can fully develop or to treat a mental disorder in a targeted and rapid manner. Either way, epigenetics in clinical research is enacted as a beacon of hope that the treatment crisis in psychiatry will be mitigated or even solved. All of the imaginations constructed around possible applications of epigenetic knowledge are based on the notion that epigenetic modifications are reversible. In principle, the researcher's aim is to restore epigenetic plasticity in order to make prevention or intervention function. This is an idea we could observe in Valentin's research with human cell lines in which he highlights an organism's adaptability for health and well-being. Stella, too, elaborated on how she understands epigenetic plasticity. A concept, which she explains as being important to use,

> in a targeted way. … If you give stress hormones to people, you see that in certain stress-dependent genes, there are very strong changes in DNA methylation. However, these goes back to the original level – this means in healthy people, exactly. And the question is: If there was stress in childhood, why does it sometimes not go back to the initial level and what role do gene variants play in these dynamic changes? … So, it's certainly very important that we understand what the contributing factors are. And then maybe you can restore an epigenetic plasticity and... and I think you always have to combine it with... with... with other methods like psychotherapy, relaxation, anything else to restore the system, but maybe it's easier and faster when this plasticity is back again, on an epigenetic level. (Stella, pos. 33)

4.4.3 Coda

In this chapter, I have shown how epigenetic approaches inform clinical research on mental health conditions on different levels. In this concluding section, I will briefly summarise how epigenetic research is conducted in different experimental arrangements that include human tissue by addressing the challenges and limitations bound to these study designs.

Valentin's research arrangement is based on human blood samples with the purpose of studying both *in vitro* and *in vivo* stress responses. While he obtains his material from two cohorts, the individual biographies of those people who frame the cohorts seem to be of no specific relevance to him. By re-enacting stress through dexamethasone he measures epigenetic and biochemical changes in the TRBP, a gene highly associated with the human stress response. His experimental arrangement allows him, in the first place, to make claims about how the human stress response is a manner of adapting to "changing environments", measured by DNA methylation patterns in the blood cells. As he only investigates human blood, his approach is epistemologically rather distant from the human brain: Valentin cultivates his human cell lines in cell culture, therefore they are quite detached from the corporeality in which the stress response and the epigenetic changes take place. His reduced experimental arrangement and his "specialised" (Valentin, pos. 52) focus on one single gene locus is a practice and ability of directed perception ("gerichtetes Wahrnehmen"; Fleck, 1979). While this is a crucial scientific skill, it also excludes many parameters that might be relevant to an organism's stress response. Valentin, therefore, frames his approach as an attempt to establish a valid methodology before addressing his questions with the limited material of neuronal tissue (e.g. post-mortem brain tissue).

The institute's clinical study and the other cohort studies can be interpreted as an attempt to address this limitation. While the core objective of the RC-study is to establish a novel taxonomy of mental disorders, a new way of classifying and addressing psychiatric symptoms by means of biological epistemology, the cohort studies conducted by Judith and Stella aim at finding the *molecular* underpinnings of traumatic experiences. By allowing more diversity and "messiness", these experimental arrangements include at least some aspects of the study subjects' social realities. As I have shown, in the RC-study for instance many different data are collected, surveys are conducted and the cohort studies harness "naturalistic" traumatic events for epigenetic laboratory research. While including living humans in clinical research might lead to the most valuable or sought-after results – after all, the researchers are interested in how humans, and not in how mice, deal with stress – the loss of control is recounted as a challenge for the subsequent analysis. Therefore, Judith for instance frames soldiers as a collective, with which she can at least to some degree re-stabilise her research claims:

> Because they just... especially in the predictive marker area, it's a defined trauma. It's actually horrible when you think about it philosophically and ethically, that you send people there and know that a large percentage returns sick – yes? – but it is done anyway, regardless of whether we do the research or not. ... This is a collective that can be well researched – defined trauma – usually young

> healthy men. There are always covariates in research, even in the RC-study. If someone is 60 and has diabetes and all that, then you don't know what you have in their blood: how much is caused by glucose, by the sugar metabolism disorder, how much by PTSD? Yes, and with these cohorts of soldiers, they are mostly male and mostly physically healthy, otherwise they would not be sent to the front. Yes. There are several advantages to all this. Mm. (Judith, pos. 109)

While reducing possible covariates – that is, variables that are perceived as disturbing – is one of the means by which researchers attempt to increase the significance of their results, the establishment of causality is seen as another challenge in research arrangements that include living human beings. This is a characteristic of clinical and cohort studies that we cannot observe in the cell and animal models the same way and is closely linked to the very study design: conducting epigenetic analyses in blood, such as measurements of DNA methylation, to date are still regarded as a proxy for the biochemical processes that take place in the brain, where mental disorders are assumed to be manifested. The leading technical assistant of Stella's research group, Florentina, illustratively pointed out that

> to find a correlation in the field mental disorders at the level of genes and epigenetics may be difficult, but it... to show that this is causal, so that's even another... one more step... so... Attempts in the laboratory to prove that the calculated associations actually are also the case in the system... in the system – such as in a cell culture system or a mouse model. This only happened after Stella became director and we now really have a whole department and laboratories and staff that use different methods and different models, really from cell culture to mice and now the IPS cells and organoids and... Of course, all this in the hope that what is found genetically and epigenetically will be tested for causality. Exactly. And only in the last, let's say, three, f... three years ago, epigenetics really came into it, so before that it was more like genetics. (Florentina, pos. 32)

This quote from an interview with Florentina also powerfully illustrates how the various research arrangements – neuronal cell models, mice models, and clinical research with human tissue – are orchestrated so that they can interact. This is an approach to compiling the institute's numerous research projects in a general research choreography, which Stella calls "top-down/bottom-up" (Stella, pos. 24). In this way, Stella and her colleagues have also steadily approached a more profound understanding of the relevance of TRBP for humans:

> For example, this TRBP came primarily from human research, so ... we discovered this gene-environment interaction with methylation and then colleagues here in animal research took up this TRBP and also re-examined it in a kind of early stress model and are now trying to understand exactly which brain regions are important. And... and things like that. And with this knowledge, it is also possible to short-circuit this again with imaging studies in humans. Exactly. And then there was a... another... another possibility is that my colleague Noam, for example, they just looked: what is important when animals are especially afraid due to stress? And then they found a certain micro-RNA – which is also an epigenetic factor – that... which is important in stress and which also buffers this TRBP by chance. And then they did a lot in the animal model and also causally established the fact that you see exactly: if that is not there, then it changes – and then we went back into the human being and saw: ok, this micro-RNA is actually changed in people who experienced trauma in childhood and are regulated by st... is regulated by stress in humans. And... and so we just have the... the... the... yes, a... a better understanding, because we have found something in humans, but know relatively well how it should work in a ... in a mammal. (Stella, pos. 25)

As I have shown throughout this first empirical chapter, every research arrangement facilitates specific epigenetic accounts bound to the very research apparatus that is applied. However, what has become

obvious in this last subchapter is that only the *ensemble* of all of the different research arrangements permits the construction of a scientific picture deemed appropriate to make claims about stress-induced epigenetic changes in humans. Therefore, scientists switch between different research arrangements, collaborate with colleagues and at the same time attempt to make processes in the brain visible via "detours" and proxies, for instance via epigenetic marks in the blood. As long as they have not achieved this goal, they will fall back on the various models and research arrangements in the hope of circumventing the respective limitations that each apparatus brings with it.

5 Environmental Complexity Across Different Research Arrangements

In the previous chapter, I portrayed different scientists and their research projects. By analysing their research practices, I showed how the researchers re-enact stress in different experimental arrangements. Moreover, I discussed how these different strategies of re-enacting stress also facilitate epigenetic accounts of mental health conditions in relation to the chosen experimental design. The researchers I interacted with narrated these re-enactments of stress as more or less clear imaginations of how to conduct scientific practices (especially in cell and animal research). These are stories and imagined scenarios explaining how to simulate stress – as a form of environmental stimulus – *appropriately*. An appropriate way in this context follows specific experimental protocols that are regarded as being standardised, routinised manuals and which also feed the scientists' imaginations of how their experiments should run. In the chronic social defeat set-up, for instance, Nadja and her colleagues at the institute anticipate having a mouse with depression-like phenotypes after 21 days of defeat.

Since these re-enactments of stress are based on the way researchers frame and attempt to conceptualise human environment, in the first part of this second empirical chapter, I will delineate how they discursively approach environment. I will show what they discuss in *their* theory – that is hypothetically – as epigenetic environment: which different notions of epigenetic environments circulate within the institute? Afterwards, I will show how, in their research practice, the researchers I have followed only focus on certain aspects of this environment by choosing specific strategies of re-enacting stress: which environmental aspects are operationalised as accessible elements of epigenetic laboratory work?

In the second part, I will address the question of what lies *beyond* the researchers' imaginations and attempts to re-enact stress in a standardised way. Here, I argue that the laboratory is a space that is itself embedded in an environment, situated in a socio-material world. Therefore, despite the scientists' various strategies for establishing control over their epigenetic experiment, their practices are open to environments that are not planned as re-enactments – environments that are unintended and inevitably part of almost every epigenetic research endeavour. I will analyse how the scientists relate to those moments of epistemic openness and how they develop strategies to tame the messiness they suspect exists only outside of their "standardised" experiments but that in fact also interferes with their research.

5.1 What is discussed and re-enacted as an epigenetic environment?

> So, coming back to the question you've raised: why is environmental epigenetics interesting? Well, I think, because it connects two poles. Both those who said "it's just the environment" and those who said "it's just genetics". They're now connected. And you can no longer sustain this polarisation of mental disorders: "it's just the schizophrenic mother" or "it's just the genes you've inherited". (Lucas, pos. 40)

In epigenetic research, environment matters. As the interview excerpt above shows, environment is often seen as the antithesis to genes. In this juxtaposition, epigenetics is framed as the science that could finally mediate between these two diametrical concepts. Hence, environmental epigenetics is awarded the ability to solve the long-handed disagreement between the two disciplinary lines of argumentation by merging the nature/nurture-divide: environmental epigenetics postulates that the environment interacts with our genes through various biochemical processes. It thus proves to be a corrective that creates a counterweight to an earlier and now "outdated" perspective. Now, environment is endowed with the power to change seemingly hardwired biological processes that are carried out deep in the cell nucleus, such as DNA methylation. The environment thus also becomes an epistemic object of the life sciences. However, as I will show below, it remains a vague concept.

5.1.1 Environment as a blurry concept: how environment is encountered in the laboratory discourse

As the epigenetic scientific community has not yet offered us any conceptual work around environment as a human lifeworld, throughout my ethnography I tried to elucidate what my informants understood by an epigenetic environment: what makes up the environment that can affect the body epigenetically? The sum of these definitions gave a rather vague picture of how epigeneticists understand environment. Some researchers shared an idea of environment that represents a quite differentiated picture and at least tries to include the variety of socio-material aspects of human life worlds and lifestyles:

> Nadja: So what... what does the environment do with the genes? It's the interface, so what... the environment, so to speak, the environment precipitates itself via epigenetics with the genes and changes the phenotype.
>
> Me: What then is environment for you?
>
> Nadja: Environment is all kinds of things to me. The environment for me is toxins, whether I smoke or drink [*laughs*], whether I have stress, whether I take medication, my psycho-social environment, whether I have contacts that can absorb it when I am stressed, what I eat, what I can eat, because I can afford it, it's the economic environment in which I grow up, whether I'm abused in some way at home or whether I can go to school and have 13 years of school or 12 years of school and then get paid to study, that's all one... a hotchpotch of things. ... Actually, every... every activity I do – when I read something I also do something with my epigenetics, because then I learn something and that leaves its mark. Yes, that was very comprehensive now. But in fact, it's really all epigenetics. (Nadja, pos. 121-23)

The interview excerpt above reveals how Nadja approaches the epigenetic environment by embedding the human organism in a network of different socio-material aspects thought to, as a whole, contribute to its development. In her interpretation, literally *everything* is endowed with the power to affect our bodies on a molecular level. Environments become epigenetic events in themselves. In this way any form of environment and human life form is, so to speak, "epigenetised".

The technician Florentina approaches the epigenetic environment on a similar organismic level by stating that:

> Everything – as just said: as trauma is reflected [epigenetically], I'm sure that also positive experiences are reflected in our epigenome. But (.) where can you look for this, or... And I think that's actually for me a reassuring and courageous aspect (.) that just – yes – a nice walk in the sun can have effects that I can pass on to my children and not just the negative experiences. And that maybe this will somehow compensate, I mean, if you would then really sum up: yes, what have you done in your life, what maybe... what you do not want to pass on to your descendants? And I don't think that anybody can say: So, I have always made sure that... – right? But if you can say on the other hand: yes, well, I've been smoking for ten years now, maybe it wasn't really useful, or I parachuted three times a year, maybe it wasn't really risk-free, but I often laughed or I... – maybe it makes up for it or kind of balances out or... or... yeah. So, fantasies, right? [*laughs*] – so everyone makes their own... their world and their ideas how it fits for them and how they can live with it and it's certainly not static, but changes over the years in the course of time. People live in a certain context and in a certain time. (Florentina, pos. 70-71)

In contrast to Nadja, Florentina particularly emphasises an organism's potential openness to what she describes as "positive experiences", such as laughing or the feeling of sunlight, even though she admits that the effects of these positive experiences may not be easily visualised. In addition, she conceptualises the contexts humans are embedded in from a broader, developmental perspective. For her, the environment becomes a process that extends over the entire life span of an organism and ultimately represents a sum of experiences. In her interpretation, environment becomes a multiple phenomenon, at least discursively.

In general, the term "environment" is not used consistently throughout the institute. Some researchers speak of "environmental experience", some of "social experience", "environmental impact", "environmental situation", or "stimulus". The various ideas of what contributes to an organism's development, among them nutrition, toxins, psychosocial stress, or medical drugs are "lumped together as 'environment' and treated as a standard background that is not itself in need of explanation" (Oyama

et al., 2003, p. 1).[57] While environmental epigenetics *hypothetically* allows many notions of environment as crucial for our genomic structure, in the first empirical chapter I have shown how the researchers always channel their concept of the environment into the concept of stress. In their research arrangements, they therefore attempt to model forms of social or psychosocial stress by applying various experiments deemed appropriate for re-enacting these experiences. In general, I could observe two levels of how the researchers approach context as environment which they also build in their experimental design. A *cellular* or *genomic* context on the intra- and intercellular level, and an *organismic* and *environmental* context (Van Speybroeck, 2000) – a hierarchy that I will turn to in the following section.

5.1.2 Of SNPs and sabre-toothed tigers: how environment is encountered in the laboratory practice

Generally speaking, context matters on different scales within the institute. These scales can be categorised as "spatial" and "temporal". On the *spatial* or *topographic* level, some scientists analyse genomic neighbourhoods in relation to their effects on mental health conditions, such as schizophrenia. Rather few scientists I have talked to look at mental health conditions exclusively through this "genetically induced" (Joachim, pos. 15) angle. Research group leader Joachim, for instance, stated that "you indeed can observe differences in the epigenetic signatures of different cell types that are not necessarily attributed to environmental influences, but to genotypes" (Joachim, pos. 10). In this context, so called "single nucleotide polymorphisms" (SNPs), which are mutations that can increase the risk for specific diseases, such as schizophrenia, are considered to have epigenetic effects. In the interview, Joachim clearly demarcated these "genetically induced" changes resulting from "environmentally induced" changes:

> And from the... on the... from the background I was interested in the institute, where we look at two things: on the one hand epigenetic changes in psychiatric diseases, but we [Joachim and his re-

[57] In the environmental epigenetic attempts of clustering environment, we often can observe a demarcation between materiality and sociality while in the social sciences, this division of the human-life word hardly exists (any more). Instead of distinguishing between material objects, such as bridges, and social experiences, such as discrimination, as two distinct phenomena, social science theorists propose to think with "socio-materiality" (Latour, 2005; Law & Mol, 1995; Orlikowski & Scott, 2008). This theory allows for the scrutiny of processes as both social and material patterns, paying attention to the complexity of human life. One example of how the life sciences tend to neglect this complexity of the human world is how the paradigm of "low socio-economic status" (low SES) is modelled in research with rodents. Across different disciplines within biomedical research, lower socio-economic status is described as a crucial risk factor for physical and mental health (Fryers et al., 2005; Maselko et al., 2018; Marmot, 2017). Within this context, in one of the institute's special seminars, scientists that work with animals gave a talk on "mouse genetics" using animal models of stress. They for instance explained how they model low SES as a form of early life stress by providing "limited nesting material", rendering this practice as a "socio-economic model of poverty" (field-notes, 7.6.17). This method of building a mouse model for human experience powerfully illustrates how life science research simplifies complex socio-material phenomena by radically reducing them to one controllable paradigm.

> search group] don't focus on those that are environmentally induced, / Me: Ok / but we focus on those that are genetically induced, because a large part of the... when you look at normal people and... and not only psychiatrically ill people, but also others, then you can find differences in the epigenetic signatures in different cell types, which are not necessarily due to environmental influences, but to genotypes. In fact, a large part of the epigenetic variance between individuals can be explained by genetic factors, simply because different SNPs and different mutations are present. (Joachim, pos. 11)

Joachim's radical reduction of context to the cellular level is a methodological approach to understanding different "risk-bars" (Joachim, pos. 25) that can describe individual disease susceptibilities on a molecular level. By zooming in and focusing on genetic variances, Joachim's epigenetic research perspective stays within the body, analysing individual molecular differences and their association with mental health on an intracellular level. At the same time, this approach widely excludes environment as the context of the organism these cells are part of. For Joachim, conceptualising the epigenetic environment on the cellular level – that is to say, as an end point of a chain of reactions reaching the cells – is a meaningful approach as,

> at the end of the day, everything is at the cellular level. I guess, but... so the substrate of epigenetic changes are the cells, is the DNA or the chromatin. Those are the only epigenetic changes that exist and what we are looking at are mainly the genetically induced epigenetic changes whereas other people are looking at the environmentally induced epigenetic changes in different ways. (Joachim, pos. 52)

The idea that cells react or adapt to the topographic environment surrounding them through epigenetic modifications is also the underlying principle of administering dexamethasone in the *in vitro* cell model. In the interview excerpt below, Valentin summarises the essence of his dexamethasone stress-paradigm:

> I would... say that what I do... is just a different environmental situation. ... So it is simply a change of situation in this environment and the cell reacts to it. (.) So now in my sense: I have a... a... a substrate that binds to my glucocorticoid receptor and then that one just binds, the expression goes up there and that's it – yes? – but it is still very far from being a human being, this cell – yes? (Valentin, pos. 94-96)

In the models for early neuronal development at the cellular level, we can also observe how the property of "environmental sensitivity" in cells is instrumentalised for research: Adriana and Emma treat their cells (one- and three-dimensional cellular structures) by pipetting dexamethasone in liquid form *onto* the cells. In other words, they alter the topographic environment of the cells. Dexamethasone is therefore understood here as a signal to the cell to adapt to the altered environment via epigenetic changes. As I have shown in the previous chapter, this is conceptualised as "stress response in early developmental stages".

In contrast to this cellular scale of environment, researchers attempt to approach environment on the organismic level in the mouse models and in the clinical and cohort studies. The notion of adaptation also plays an important role here, however: as I have shown, researchers aim to investigate responses to stress regarding the organism as a system. They re-enact "psychosocial stress" by the chronic social

defeat set-up (Nadja, Julie), investigate how mice change molecularly within a "semi-natural environment" (Noam, Jano), and harness "naturalistic" traumatic events for their epigenetic analyses in research arrangements that invite living humans into the laboratory (Rahel, Judith, Stella). These organismic approaches towards environment are highly linked to the temporal dimension of environment or stress. In general, the researchers' experimental arrangements distinguish between developments in dependence on early and adult temporal levels. All stress experiments in mice are located in adulthood, investigating epigenetic changes of stress on the adult organism, while the cohort studies, as I have shown, predominantly focus on early life. As already mentioned, the conceptualisation of these life phases as "epigenetically sensitive windows" (Ho et al., 2012) is known as the early-life paradigm. Despite the fact that "stress can hit you in different stages of your life" (Noam, pos. 100), as research group leader Noam stated, the field strongly focuses on the early-life paradigm as a crucial figure of thought.[58] In this context, researchers state that the environment of the mother has epigenetic effects on the foetus' methylome: anxiety, depression or diabetes are for instance parameters that fall into this vein. According to the researchers' logic, the embryo's epigenome is programmed by the first environment it encounters: the placenta.

In the interviews, some scientists discussed the biological meaningfulness of an embryo being epigenetically shaped by environmental stimuli. In these discussions, the narrative of bodies being adaptive to their environments is a recurring discursive element which is related to an evolutionary temporal horizon. In this logic, it just *makes sense* that a foetus is, so to speak, "prepared" for the outer environment by being equipped with a certain epigenetic outfit. Research group leader Noam explains this by referring to people who are living in terrible environments, such as a war zone:

> I want you to think about the evolutionary point of view, so, you are pregnant and you live in a… in a war zone. You as a… keeping the next generation, you should transmit to your embryo the signal to make him or her fit the best the outside environment – yeah? So, if you live in an area that have missiles and you have to run, to shelter and it's very stressful – what signal is this telling your baby? Look, when you are now developing your brain and body, you should be better… you better be small and fast and quick – yeah? – you better be always looking for danger, always putting your attention to the surrounding, increase your vigilance. And we know from human data, that those kids who grow up in those types of areas are born earlier and smaller. … This is just the way he or she was designed. (Noam, pos. 104)

When those children then would grow up in a different environment, where they would have to go to school and sit quietly, their behaviour would be considered to be pathological, Noam elaborates in the

[58] The early life paradigm has a general core relevance in a vast range of epigenetic research endeavours. In drawing on Rheinberger (1997), Niewöhner (2011) therefore notes that the early-life adversity paradigm increasingly appears as an epistemic object, as it "provides a coherent interpretative frame that is able to harness at least part of this heterogeneity. It is at the same time an established concept anchoring ongoing research in relevant pasts and setting out a research strategy for the future that goes significantly beyond the current epistemic horizon by bringing the social and the material environment into molecular research" (Niewöhner, 2011, p. 288).

interview. He describes this as a "mismatch between the way he [the embryo, the child] was designed to the society he is living in" (Noam, pos. 105).

The biologist Valentin as well referred to this evolutionary biological narrative to explain why "wrong" epigenetic manifestations can lead to mental disorders, as a person's environment changes. Here, he uses the prominent metaphor of the sabre-toothed tiger:

> Adaptability is the most important thing for an organism. Back then [here he is referring to an undefined time in human history] it was a positive thing to decide as quickly as possible to run away and to have such a stress-system [that is active]. Today, as the sabre-toothed tiger is no longer chasing us it can be a disadvantage. … Hence, at that time it was an advantage, from an evolutionary point of view, nowadays, because our environment has changed, it might make you ill. (Valentin, pos. 104)

The institute's clinical and cohort studies can be interpreted as an attempt to investigate these adaptation processes *in vivo*, in the living organism. In this context, epigenetic trauma cohorts are framed as a group of "highly stressed" people, having experienced something cataclysmic: women that have experienced physical and sexual violence in childhood, individuals that have been involved in severe accidents, people who have fled form war, victims of systematic persecution, refugees, or soldiers are all, for instance, defined as cohorts. Hence, stress is not actively re-enacted in those individuals but it occurs more or less as a phenomenon that originates from real life socio-material environments; it is a "naturalistic" exposure harnessed in those studies as an experimental stressor comparable to applying dexamethasone to cells.

Recently, Stella and her colleagues have attempted to shift their scientific gaze from the question of the effects of single traumatic events in childhood to investigations that address developmental trajectories. In longitudinal studies that accompany individuals over several years, Stella tries to study the influence of environment on organisms over time, in a life course perspective, its "coming into being" (Van Speybroeck, 2000, p. 203) along a history of experiences. Bearing this in mind, it is important to note that the more complex the experimental level is, the more difficult it is to stage and analytically examine the environment. For example, for molecular biology it is easier to change the environment of a cell than to stage or research an organism in the world: "The higher one goes in the hierarchy, the harder it becomes to find experimental support" (Van Speybroeck, 2000, p. 196).

5.1.3 Coda

> And there was then about 15 years ago I would say, almost 15 years ago a ground-breaking work from the group of Michael Meaney... and... Moshe Szyf from Montreal, who had shown for the first time that in a rat model for different parental care, there was methylation of a gene, the glucocorticoid receptor, which is essential for behaviour, drive, and so forth. In other words, it was in itself a big surprise to us that DNA methylations cannot only lead to diseases in the form of hereditary patterns, but that they can also change depending on the environment, experiences and, in this case, especially social experiences. I think that DNA methylation can change in response to toxins or other physical, physical environmental stimuli, and I think that this too was already a feature of

> the field, and the step that Meaney and colleagues went further at the time was really that they said: social or even human psychological experiences can lead to these changes and then code for relatively long-term changes in behaviour. (Lucas, pos. 5)

The above interview excerpt, which refers to the often quoted work of Meaney and Szyf, impressively illustrates that environment has risen to a crucial or even one of the focal objects of scientific investigation in environmental epigenetics. The environment-molecular relation is staged as a highly sensitive construct, even taking (discursively) into account how everyday activities, such as reading, may impact our bodies on a molecular, epigenetic level. This means that some scientists approach environment from a rather holistic perspective and attribute literally *every imaginable* environment the potential to alter our epigenome – adverse experiences as well as positive environmental aspects. Bodies are increasingly understood to be porous entities within different environments.

In this subchapter, I have outlined what scientists at the institute discursively depict as an epigenetic environment. These narratives are predominantly based on subjective assessments and are very broad, including human activities as well as material and economic factors. To some degree, these discourses on environment also recognise a certain processual nature of the environment and describe individuals' lives from a developmental perspective. However, these environmental descriptions do not claim to be translated into practice. They do not constitute a kind of environmental theory for epigenetics meant to be put into operation in the laboratory. Because, as I have shown, these definitions we find in the discourse of the institute differ drastically from the way environment is actually brought into play in the laboratory: only very specific aspects of the socio-material world in which we live are harnessed for laboratory research, mostly subsumed under the category of "stressful experiences". The practices of harnessing aspects of human lives represent strategies for making life explorable in the laboratory and within a molecular framework; for making human life "researchable" through and in a life science methodology and logic. Most often, we find ideas of environment taking the form of a topographic model inscribed in these re-enactments. This understanding of the environment translates objects into clearly separable entities that interact with each other: organisms react to the environments surrounding them, and cells respond to changes in the environment directly surrounding *them*, as in the dexamethasone-stress-model.

From a social science perspective, an analysis of which environments are categorised as epigenetically relevant is interesting from at least two perspectives. First, analysing which aspects of human environments are re-enacted in the laboratory can reveal which social variables and aspects of human lives get scientific attention and which remain unperceived. This is specifically relevant in the context of what historian of science Michelle Murphy coined as "regimes of perceptibility" (Murphy, 2006; see also Shostak & Moinester, 2015). Drawing on the realm of regimes of perceptibility reveals "how the politics of knowledge production and the process of materialisation involve obscuring awareness of certain things in order to make others more pronounced, known, and thus controllable" (Garrison,

2014). That is to say, currently, we find a heavy focus on adverse experiences (for the reasons I have described throughout this thesis) – a research perspective that increases financial support while excluding other, positive environmental aspects (at least in the current epigenetic research landscape). At the same time, personal experiences, such as childhood abuse are included as important causes of illness in the aetiology of mental disorders and are subordinated to the molecular-biological order by epigenetic research.

Second, such an analysis is interesting as it uncovers an important divergence: while many researchers might speak and think of environment in the sense of life-worlds within socio-material factors that occur in certain ways (see above), in harnessing this environment for laboratory practice they translate it into environmental *factors*. These environmental factors are then operationalised as a trigger for the molecular mechanisms researchers aim to investigate. In other words, researchers might have ideas about what an environment might mean for an organism, but environmental epigenetics lacks a specific theory on environment. In this sense, environmental epigenetics renders some aspects of a human life *a priori* as objects of scientific investigation by operationalising them as stressors in the laboratory, as is the case, for instance, with dexamethasone.

From an STS perspective on scientific knowledge production, however, the laboratory itself can be regarded as a *body* embedded in an environment. Accordingly, it is not an empty space, not a vacuum. And even if scientists strive for maximum control and intentionality, they are not protected from events taking place that are not intended. Against the background of my first empirical chapter, which addressed the "standardised" practices of re-enacting environment/stress, in the following subchapter I ask: what is done with all of the environmental variables that are not defined as intended experimental elements? How do researchers relate to environments that occur inadvertently? I call these instances of epistemic openness *unintended environments*: they are not planned, yet are unavoidable events within everyday laboratory practices and impact the scientists' research to a greater or a lesser extent. *Unintended environments* can be exemplified by, and are symbolically condensed in the construction site in front of the laboratory: while I was conducting fieldwork at the institute, a new mouse house was built and I was able to observe how it gradually took shape. Despite the fact that it is spatially detached from the laboratory's inside, the construction site influenced laboratory life in several ways. In conceptualising it not as a puzzlement, as *aporia*, but as an *unintended environment*, I began to see the area as an informative field site for my thesis: it helped me to deconstruct the practices of environmental epigenetics in relation to its focal argument, the environment. In the following section, I will therefore address the epigenetic experimental apparatus with these questions in mind. In other words, I attempt to analyse the researchers' practices of including elements in and excluding elements from their scientific gaze.

5.2 The Construction site: a reference to bewilderment and distraction

FIGURE 22. Note at a balcony door of the institute requesting that the door be kept closed to reduce the noise from the construction site in front of the lab building (photograph by the author, June 2017)

I discovered this note rather accidentally on a rainy day early in the summer of 2017 while I was waiting for an interview partner. The balcony door is at the end of a corridor in which the researchers' offices are located. Here, the scientists read articles, analyse their data, prepare for meetings, think, discuss, and write papers – rather cognitive work in contrast to the more hands-on practices of the laboratory such as pipetting dexamethasone to cells. Since these processes of knowledge-in-the-making require a maximum of concentration, the scientists felt disturbed by the noise of the construction site which motivated one scientist to put up the above note in order to hopefully minimise the disruptive noise.

Indeed, the construction site in front of the laboratory emerged as a recurrent discursive figure during my fieldwork. Often, scientists referred to it in the interview or while I was shadowing them. And I myself also felt its presence: when I was in the institute, shadowing a scientist or attending a meeting, I frequently witnessed how the construction site vehicles transported building rubble or metal piers and produced noise, dirt, and vibrations. These were exactly the moments that drew my ethnographic attention and I asked myself: how is the laboratory as a distinct form of environment related to and

entangled with environments that are actually not acknowledged to be part of the laboratory's experiments? Though they are not intended, those environments do exist and impinge on the laboratory in manifold ways, like the noise from the construction site. During my fieldwork, the construction site therefore emerged as an additional important field site for my own research endeavour. It provided a vivid contrast to the rather clearly narrated imaginations of how to re-enact stress appropriately in the epigenetic experiment with the *de facto* practice of re-enacting stress. In other words, the construction site metaphorically indicates a divergence between the researchers' ideas about their practices for modelling stress and the actual feasibility of these practices, debunking these practices as not always fully controllable. But first: *why* was the construction site experienced as a distracting factor at all? I will address this question in the following subchapter.

5.2.1 Noise, dirt, vibration: problematising the construction site as a contingent environment

Nadja: …and the construction site out there.
Me: Is that an issue for you? Is it noisy or –
Nadja: It's incredible.
Me: Yeah?
Nadja: It is really hardcore!" (Nadja, pos. 210-214)

With this emotional reference to the construction site Nadja opened up the discursive arena for discussing those moments and instances, in which biological research – that is mostly expected to happen in a standardised and controlled manner – is unexpectedly bewildered by phenomena that "crash" into the research practices. As an environment that exists outside and is therefore presumably isolated from the scientific laboratory, many scientists spoke of the building site as negatively influencing research at the institute. But, why is it a problem at all and for whom? The answer to this question lies in the central hypothesis of epigenetic research: cells, organisms, and bodies are regarded as sensitive and adaptive to their environments and surroundings. Human beings are supposed to be molecularly impacted by material substances and by the events they experience at any time in their lives. Therefore, epigeneticists build experiments in which they aim to analyse those molecular processes by imitating certain environments. The researchers postulate that our cells can be influenced by external stimuli, such as stressful experiences. Likewise, they use dexamethasone to model these experiences in cell culture or they deploy mice in specific testing arrangements to study the molecular effects of psychosocial stress. In these experiments, the external stimuli under scrutiny are turned into accessible research objects. These are research methods meant to intentionally create certain environments in order to study their epigenetic effects. In this sense, epigenetic processes are described as a form of gene-environment interaction with clear and measurable mechanisms. However, the postulated malleability of cells and organisms suggests that the experimental design, too, is potentially influenceable by any imaginable form of environment (Niewöhner, 2011).

In the previous part of this chapter, I have shown that even for some researchers themselves practically *everything* can have epigenetic effects – from experiencing stress in childhood, to being exposed to toxins, to reading a book, even if the last mentioned experience is not (yet) part of the experimental apparatus. This is the point at which I would like to revisit the construction site and ask: what effect did this specific environment have on the experiments and on the research practices themselves? How can we interpret the phenomenon of the construction site for environmental epigenetic research as such? What is its relevance? And to begin with: what are the instances in which the construction site is a noticeable element of the "everyday doing of molecular research" (Niewöhner, 2011, p. 288)?

FIGURE 23. Picture showing the "swimming pool", as some of the scientists humorously call the construction site (photograph by the author, August 2017)

5.2.2 Porosity of bodies – porosity of laboratories?

First of all, I recognised that it was predominantly the scientists that conduct research in mice who worry about the consequences that the disturbances of the building site might have. One phenomenon that is directly related to the construction site's noise and vibration is that mice would not reproduce "normally" under such conditions. Valentin and Nadja reported this circumstance to me:

> "Mice don't breed when there is noise and vibration", Nadja told me while I was shadowing her. "Is that problematic?" I wanted to know. "Yes, sure, because we don't have mice for our experiments then. … I begged the mice: please breed at the weekend when there is no construction work done." – "And can you do anything about it?", I dug deeper. "Well, we don't have too dramatic bottlenecks, as we get mice also from our other lab in XY city." (fieldnotes, 24.8.17)

In this case, it is the predispositions for conducting experiments with mice that are in danger, as the construction site influences the mice's reproductive behaviour. Though this does not result in majorly

restrictive effects for the institute as a whole (the institute can obtain laboratory mice from its branch laboratory), for the mice that are actually bred in the institute's still existing mouse house the construction site has more profound consequences: almost all scientists that work in the mouse model stated that they would observe behavioural changes in the mice themselves. Nadja for instance told me, that "the mice that were born during the construction site are more anxious. You really can observe it. They kiss the floor with their bellies" (fieldnotes, 24.8.17). Julie reported a similar observation:

> Then – surprise! – again the construction site. This is "hell on earth for stress experiments with mice", Julie exclaims. I listen eagerly and am pleased that the construction site is once again the topic of conversation. There would be disturbing noises that we humans would not even perceive, however, they do stress the mice, says Julie. "How can I still trust my experiments?", Julie asks rhetorically. … "I still know the mice before the construction site, they were very different. … Today, my mice are baseline stressed. (fieldnotes, 26.1.18)

This excerpt from my research diary denotes a significant effect of *unintended environments* in environmental epigenetic research conducted within stress experiments: mice, as the "protagonists" of the stress experiment, are put under continuous stress due to the noise and vibration of the construction site. Hence, they are constantly "stressed". This change of organismic constitution shifts the unstressed/stressed-paradigm as the analytical basis of epigenetic research on mental health conditions (see Ch. 4.1) to a novel paradigm: baseline-stressed/more stressed. From the researchers' perspective, this implies that the mice's organisms are continually activated as they have to respond to the enduring stressful experience. The construction site could, hence, be interpreted as a "chronic stressor".

What is also at stake here is the scientists' certainty that they will be able to conduct neat biomedical research so that they can, as Julie put it, "trust" their own results. Here, it once again becomes obvious that the construction site interferes with the researchers' imaginations and strategies for re-enacting stress appropriately in order to investigate its epigenetic impacts. In this context, the question of *which* stressor is actually measured in the stress experiments that are conducted during the construction works becomes very salient: is it the stress that is intentionally enacted, such as restricting food or letting one mouse defeat another mouse? Or is it the vibration and noise that put the mice under stress and hence also influence the measurement results? Or is it a mixture of every imaginable form of stressor? Do these stressors mutually reinforce each other? How? And which stressor is finally responsible for changes in the epigenome or the metabolism of the "stressed" mouse? That means, *what exactly* do the scientists measure?

The challenge of disentangling these different environments and stimuli that come to matter in epigenetic stress research was also an issue for Mirena, head of the institute's biobank:[59]

[59] A biobank is a biorepository that stores, processes and distributes biospecimens and associated data for use in research and clinical care (De Souza & Greenspan, 2013). According to Mirena, the most central task of the institute's biobank is to formulate shared standards of how to collect and store data samples in cohort studies.

> Yes, and especially here at the institute, because we measure fear or the… the stress hormones … like cortisol for example. Yes, as I said, you want to minimise disruptive factors and then there is the drilling machine outside that crashes into your experiment. That is of course ... very unpleasant. (Mirena, pos. 102)

Of course, environmental factors like vibration and noise from construction sites would also bewilder genetic research on stress and behavioural research with rodents as such. However, in the case of environmental epigenetic stress research, these *unintended stressors* have a radically different significance, as the field postulates that cells, bodies and organisms are sensitively responding to environments. It is the field's epistemic basis.

Conversely, it is not only the experimental subjects that are affected by the construction site. It also impacts the scientists themselves and hence environmental epigenetic research practices as such. Once, Nadja and I were sitting in her office and she very impressively reported how the building site is distracting her actual laboratory work.

> We all work silently on our projects. At some point, there is a slight, continuous buzzing. I ask Nadja what that is and she replies that it is the construction site. The persistent topic here at the institute, I think to myself. … I say that I have already heard from other people here how obstructive the noise and the vibrations can be, especially during the lab work, which motivates Nadja to bring up a concrete example: "Yeah! Once I did injections into mouse brains and all of a sudden the whole lab bench began to vibrate because they dug such huge metal piers into the ground! You can never reproduce these results, as you'll never have these conditions again" she told me laughingly. (fieldnotes, 29.5.17)

FIGURE 24. The construction site from a bird's-eye view (photographs by the author, August 2017)

Even though Nadja reports the effects of the construction site with a sense of humour, the fact that a biomedical research laboratory cannot be completely disentangled from the world that surrounds it is a serious challenge in environmental epigenetic research that the scientists are confronted with. Again: what do they *really* measure in their epigenetic experiments? The intentionally re-enacted "stress" (e.g. chronic social defeat, restrainer) or the stress that penetrates the experiments (e.g. noise, vibration) and that is part of the actual socio-material environment of the research practices themselves?

Beyond those researchers who work in animal models, laboratory members that work in cell models also complained about the negative and restrictive consequences the construction site has on their everyday lab work. When I was once shadowing Adriana through her day, we were in the so-called "cell culture lab" together with a handful of other researchers. When the construction work started, the PhD student Romina, who was occupied with examining cells under the microscope and obviously annoyed by the disturbance, complained: "Boa, it's vibrating so much from the construction work outside that I can't take any really sharp photos" (fieldnotes, 2.3.17). Nadja even felt so heavily disturbed by the construction site that she for a certain period decided to work on the weekend or in the evening rather than during regular hours to avoid being confronted with noise and vibration. Against the background of these challenges, the construction site emerged not only as an extra stressor for the mice as research subjects. For the scientists themselves as well, it became a stressful environment that they could not withdraw from, alluding to the omnipresence of stress: not only is stress *the* institute's experimental basis – every research project aims to understand the epigenetic effects of stress for mental health outcomes – but the scientists themselves are confronted with situations or conditions which lead to a certain stress level. The researchers quite often reported how stressful their everyday work is. "As you might have noticed," Adriana once said to me after a colleague of hers was quite impolite with her, "a lot of people are stressed out here" (fieldnotes, 2.3.17). On another day, she continued talking about this topic, saying, "Working in the cell culture lab is mostly very stressful, as you have to do a lot of different working steps. Split the cells, stain them and you always have to adhere to certain timeframes, you can't just work at your own speed. This is really stressful for me" (fieldnotes, 14.3.17).

Of course, this is a rather metaphorical reading of the construction site and stressful working conditions, but it hints at how entangled different levels of stress are in the institute. Concerning stress as scientific tool to see molecular difference, it emerges as a coherent interpretative frame (Niewöhner, 2011). As phenomenon that has a long history as a research object (stress has emerged as a medical scientific idea since the second half of the nineteenth century, see Ch. 4.1), it is able to stabilise epigenetic experiments in the institute: the research community agrees on the causal relationship between stress experiences and adverse health outcomes, despite the fact that there exists a plethora of different stress theories.

The construction site (and all other *unintended environments*), however, may pose a potential threat to experimental stability. It symbolically alludes to the genuine *messiness* of the social world that contrasts the rather clear narrations of how stress research can be conducted appropriately. As events that are not elements of the research protocol, such as noise, *unintended environments* suggest a certain unpredictability of research practices: though research practices are arranged along a research protocol and are hence standardised, they are open for contextual surprises. In the case of epigenetic research,

the construction site furthermore directs our attention to the ambiguity that in addition to the enacted environments that are part of the research protocol, there are also not fully calculable environments that can have epigenetic or at least confounding effects which might be hardly disentangled in the analysis.

5.2.3 Conceptualising the laboratory as a laboratory-in-a-world

The construction site, so prominent in the institute's informal conversations, additionally symbolises the existence of different "layers" or "cycles" of environments that are interdependent and entangled to a high degree. In this sense, the laboratory, as an environment in and of itself, is not separated from the environment that surrounds it. In the same way, it is not separated from the time in which it exists; it is embedded in time and space. Thinking with sociologist Max Weber (1904), I argue that elements from the *real world*, such as the building site, are able to interfere with the laboratory environment as a supposed *ideal world* to several degrees. The *ideal type* is a concept from the Philosophy of Science and was introduce by Weber as an analytical instrument to order and record selective parts of the social world in order to make it explainable. Weber demarcates it from the *real type* that represents the empirically given phenomena. By understanding the laboratory as an *ideal type* and the world it is embedded in (and that it partly is meant to model) as a *real type*, and by paying attention to the effects of the construction site, we are able to take into account not only the socio-political implications of life science knowledge production, but also how the laboratory is itself affected by phenomena of the socio-material world.

The Austrian sociologist Karin Knorr Cetina conceptualises the scientific laboratory in a similar vein, allowing for the laboratory to be conceived of as part of society, rather than as a detached entity. By describing laboratories as "local contexts of action" (Knorr Cetina, 1988, p. 87; author's translation) in which scientists focus on certain processes in a specific manner, she thinks of laboratories as places of social condensation: "the laboratory appears as a place where social practices are instrumentalised for epistemic purposes and transformed into knowledge production processes" (Knorr Cetina, 1988, p. 87; author's translation). In this sense, the scientific laboratory is a specific reduction of the *real world*. Both spheres are still intertwined and entangled.

Thinking of the scientific laboratory as a condensation of the social world allows for the taking into account of the effects produced when objects that are articulated within the *ideal-typical* laboratory are released into the *real world* and vice versa. As I have partly outlined in chapter 2.5, the knowledge that is produced in research facilities such as the institute directly affects the way mental health conditions are perceived in society, how therapy is imagined, and how our lives are regulated by public health policy and medicine. However, as I have shown in the previous analysis, the epigenetic knowledge production itself is also impacted by elements that are part of the "messy" world outside of

the standardised laboratory environment. In the institute's epigenetic experiments, scientists analyse phenomena of the social world by reducing it to a few controllable elements, eclipsing the actual messiness of the social world. The main goal of this reductionist methodology is

> to arrive at a total understanding of complex life by analytically dividing up the organism into subparts (and the subparts into even smaller parts), thus allowing the characteristic features of the components of the organism and the way they interact to be studied". (Van Speybroeck, 2000, p. 193)

Biology's reductionism is therefore used as a methodological means to make social phenomena explorable. While this approach has produced important and successful knowledge, criticism of this reduced and narrow methodology is growing, from within biology itself as well as beyond the discipline. As I showed in chapter 4.3.3, the social box paradigm is an attempt to build a somewhat anti-reductionist model to study mental health conditions within a biological and epigenetic framework.

In sum, the construction site can be interpreted as a metaphor that both symbolically and practically alludes to the entanglement and enmeshment of different environments: the laboratory as a rather standardised, *ideal-typical* environment and the construction site as a proxy for a more messy, *real-worldly* environment. It even gets more complex than that: apart from the lab's direct external environment that is embodied in the construction site, contextual aspects within the assumed controlled and reduced lab-world also emerged as factors that can potentially bewilder epigenetic experimenting. Similar to the noise and vibration from the construction work, they are *unintended* and hence uninvited to the epigenetic experiment, though they remain unavoidable elements of research.

5.2.4 Epistemic complexities within scientific practices: the laboratory as an epigenetic environment itself?

5.2.4.1 Painting mice colourfully: when does environmental change become a "stressor"?

> It is April, 13 and I am shadowing the PhD student Jano today. He is going to colour the fur of mice together with the technician Iris. ... I take a closer look at the mice, which are housed in transparent boxes. They bustle about, seem a bit nervous, some sleep on top of each other. … I want to know where they got the mice from. "We have a branch institute in XY-city, which also belongs to us. The mice are bred there and then they are transported here once a week", Iris explains. She is already preparing the staining: she takes four mice out of a box, one after the other by grabbing their tails and placing them in a round glass container with a lid. "Sleep" is written on it in black: it is filled with isoflurane, an anaesthetic gas. Now, Iris waits for a while. The mice scurry around until they slow down and one after the other falls into a narcotic sleep. ... Iris takes two mice and places them on a heating blanket. She takes a brush and starts to paint one mouse red: the back, to the sides, the neck and a little bit from the head. When she's done, she puts the mouse to dry in a box on the right bench opposite. ... Once, a mouse from Jano starts to move. It twitches. "Oh no, don't wake up!", he says, adjusting the anaesthetic gas. ... I observe the freshly coloured mice, after waking up, diligently brushing themselves and recovering. Jano distributes the dry mice back to the larger cages, where they are either five or six. "Now we have to regroup the mice", he comments. ... The awakened mice are starting to scurry around, some are even fighting. They whine and you

> can hear them pushing each other against the cage bars and throwing up litter. "They have to re-establish themselves, because they smell differently now," Jano explains. ... Then, all the cages are stacked on a trolley to transport them to the little mouse house next door. Since the doorstep is slightly higher, Jano has difficulties pushing the trolley over it, causing the trolley to bang once very loudly on the floor. I scare and think to myself: the poor mice! ... Later, I ask Iris if the mice have already been stressed in any way. "No," she replies. "These are untouched mice, they have not been stressed yet, that will come later. They have only been painted." (fieldnotes, 13.4.2017)

This excerpt from my fieldwork diary vividly illustrates many interesting things about environmental epigenetic stress research in mice and *unintended environments*. During my research stay at the institute, I witnessed many anecdotal instances in which the complexity of the environment in some way influenced the research practices and the researchers themselves in peculiar and unintended ways. In those moments, the *unintended environments* occurred rather accidentally and within the laboratory setting itself (in contrast to the construction site as an environment the laboratory is embedded in), such as the bumpy transport of the mice from one room to the other. However, *unintended environments* often have to be accepted for the sake of the feasibility of a certain experiment: at the moment, colouring the mice is inevitable for behavioural experiments on a group level, as it allows researchers to distinguish the mice from each other. Sometimes, those environments are even unavoidable consequences of other *unintended environments*: due to the construction site, Jano and his colleagues have to receive the mice for their experiments from the branch office that is 16 km from the institute. The mice have to be transported, which might potentially be a stressful experience for them. Here, a concatenation of unintended environmental events becomes obvious.

While witnessing all of these *unintended environments* I started asking myself, what happens in the *ideal world* of the laboratory? Is the laboratory not also an environment for mice, cells and humans? Why is placing mice into a restrainer considered as a stressor whose epigenetic effects are worth analysing, while putting mice under anaesthetics and letting them re-establish the group hierarchy by fighting is not?[60] Why is restricting food availability categorised as valid stressor and hence part of the research protocol, while painting mice and letting them swallow chemical hair colour when they preen themselves afterwards is not classified as a potential stressor? How do the scientists make sense of their epigenetic experiments despite those environmental elements that more or less unpredictably clash with their research practices?

[60] Interestingly, in their paper on different identity domains in mice, Jano and his colleagues also mention the re-shuffling of mice into new groups, though, as part of the experimental arrangement and in support of their argument that identity domains are relatively stable, framed as "manipulations of the social environment". To test the robustness of identity domains (IDs), mice from 16 groups that had been assigned ID scores based on the 4-day baseline testing period were shuffled into new groups and were re-introduced to new arenas for another day of measurement. In the paper (Jano et al., 2019), the research group states, that for adult male mice, this is a relatively dramatic and stressful manipulation and causes significant changes in many behavioral readouts, especially those related to general locomotion and aggression, whereas the IDs remained relatively stable with the changing environments. In this conext, we can see that the re-shuffling is considered a "stressor", though it is not always discussed as such.

What I could observe in this context is that the scientists follow a selective mode of attention. Some forms of environment are acknowledged as being "biologically embedded" in the body while others remain unacknowledged for the sake of stabilising the experiment. The 16 kilometres that certain mice have travelled to reach the institute is for instance such an environment that has to be unacknowledged as it is currently outside of the scientists' control or intention. This demarcation work between purposefully enacting epigenetic effects and being aware of simultaneously producing conditions that might also affect the results (through the researchers' behaviour towards the mice, through the materials used, etc.) is what STS-scholar Martine Lappé (2018) conceptualises as a "paradox of care", defined as "the simultaneous *centrality of care to the study* and the *invisibility of many forms of care work* that make the science possible" (p. 700). She shows "how researchers working with model organisms acknowledge the impacts of experience on the body, but simultaneously limit what kinds of experiences can matter in the production of epigenetic knowledge" (Lappé, 2018, p. 700). This is done to maintain laboratory processes and produce sustainable meaningfulness in the epigenetic experiment. Simultaneously, these demarcations have to be done in ever novel contexts, such has handling the fact that mice have to be transported to the laboratory.

Finally, what the above excerpt from my fieldwork diary also shows is that *unintended environments* that might interrupt epigenetic research are not only elements outside of the standardised laboratory world, but are sometimes simply part of the everyday research practices within the laboratory. They might even be part of the experiment arrangement itself. Consider the following situation:

> I follow Jano and Iris on a different day. Again, both were busy with setting up a behavioural experiment within the social box testing arrangement. We are in the room next to Jano's office, where the "PhenoWorld" – which is the name the manufacturer has introduced for the multi arena cage system – is installed. It is a huge complex testing area consisting of several home cages, different social boxes and many connecting tunnels. While Jano and Iris are trying to program the system according to their protocol, one mouse gets stuck in a connecting tunnel on her way from the home cage to the social box, as the gate does not open. "Oh look! One mouse is stuck", Jano exclaims. And indeed, one mouse is trapped in the connecting tunnel between two gates. Iris opens the gate manually so that the mouse can go back to the other mice in the social box. "This was unintended," Jano explains. "We are trying to program the system so that the mouse is forced to stay in the home cage where we can measure different metabolic processes and accidentally we've started a session in which the gates close." … "Oh! There's an interesting event!" Jano shortly thereafter says to Iris. Now, two mice are in the home cage that is connected to the tunnel that has just been closed unintentionally. Iris comes over and explains that it is because she has opened the gate manually and has forgot to close it again: it was open the whole time. Now, the mice are starting to fight a little bit. Jano asks Iris: "How do we get them out now?" and Iris replies that they will solve it by themselves and in fact, the "foreign" mouse disappears after a few minutes and Jano and Iris continue their work. (fieldnotes, 28.9.17)

Why is this incident striking? To answer this question, I will necessarily revisit the reasons for the introduction of the social box system into the laboratory. This system is one response to the knowledge that reductionism as a method does not work (any longer) in some experimental contexts. In light of this, the social box paradigm can be interpreted as an experimental reaction to the inevitable

complexity of environments that some researchers do not see reflected in current animal stress tests. By an inherently complex set-up, it is supposed to include more different forms of materialisation or the embodiment of experiences that the reduced standard stress tests are incapable of showing: metabolic processes, behavioural patterns, molecular pathways, and so forth. In addition, it allows for the inclusion of a *group* of animals being tested over a *period* of time. Not least because of this, the social box is believed to allow for a more "socially sensitive" version of classical stress tests. This rather novel approach can also be regarded as an attempt to invite more complex contextual and social arrangements that are meant to allow for the mice to be tested in a more "natural" and "social" setting. This innovative endeavour to analyse stress-related disorders denotes the rising awareness in environmental epigenetic research that the body is increasingly regarded as porous, receptive to many different environments at the same time and in a complex way – just as the environment itself:

> Environment – again, it's very complex. You have stress [as an environment], of course. But it's also what you drink, what you breathe, what you smoke, or what you eat. It's all environment. Within the environment, stress… I cannot say is the most important, but definitely the most investigated environment or at least the one we have the most proof of and claim that it's affecting our chances to develop a disease – okay? So, these interactions, and here epigenetics comes [in] – okay? – so, when you say: okay, *how* does the environment, *how* does stress talk to our genes? – it has to be mediated somehow and probably one of the most prominent ways to do it is… is… via epigenetic mechanisms. And here you open a very big box. (Noam, pos. 7)

However, by opening the experimental arena to a myriad of environments, the social box paradigm also permits more *unintended environments* that are even partly produced by the system itself or by the researchers' conduct with the system. Here, I would like to return to the two incidents I encountered while following Jano and Iris. These *unintended environments* that in this context occurred uninvitedly are in other research arrangements enacted as a valid stressor, they are a stress-test in themselves. The first event (the mouse is stuck in a tunnel) is known as the "restrainer paradigm": it is a fixing unit used as a spatial stressor as the mouse is unable to move (of course, in the test this status is maintained over a longer period of time).

The second event (two mice in one home cage), when purposefully enacted, is called the "resident-intruder paradigm" and is described as "a standardized method to measure offensive aggression and defensive behaviour in a semi natural setting" that can be used "for acute and chronic social stress experiments" (Koolhaas et al., 2013, p. 1). Paradoxically, while both events can serve as single stress tests in more classical behavioural research, in the social box paradigm they merely occur as "by-products" that are caused by the system's complexity: Jano und Iris dedicated the occurrences no further attention and shrugged them off with a smile instead of discussing them as potentially impacting their results or at least as part of the experiment as a whole. Hence, on the one hand, the social box paradigm is built to allow more variance and unpredictable events. On the other hand, only certain kinds of events are acknowledged as being part of this novel way of studying complexity.

This stands in contrast to the painting of the fur, for instance, which is officially expected to have a small distressing effect on the animals by the *Animal Welfare Laboratory Regulation* (*Tierschutz-Versuchstierordnung*), published by the Federal Ministry of Justice and Consumer Protection. This state regulatory authority intends to protect animal law and to decrease the level of stress lab animals are exposed to. However, the Federal Ministry of Justice and Consumer Protection's perception of what is supposed to be stressful for animals must not be congruent with the scientists' perceptions. Thus, negotiations about potential stress experiences for animals is not only a matter of laboratory practice. It is something that comes to matter also outside of the scientific laboratory and is an issue that is subject to official regulation. By law, all animal experiments have to correspond with the statutory requirements of the *Animal Welfare Laboratory Regulation*, as conducting research with living beings is always an endeavour with potentially ethical concerns. Furthermore, every research project with living animals has to go through a regulatory approval process. For that purpose, the applicants have to display in detail the different operational steps of the experiment, including a report of all potentially stressful events and a list of all experimenters who will have contact with the animals. Then, the competent authority will respond to the application for the experimental project by approving it, demanding adjustments, or rejecting it. This procedure can take several years, especially when the applicants and the competent authority bargain over different definitions of stressful experiences.[61]

In the context of a project application to be approved by the Federal Ministry of Justice and Consumer Protection, *all* potentially stressful events are assessed in relation to the animals' potential exposure to them. This means that there is a general awareness in the laboratory of the possibility that events that are not classified as actual stressors within the experiment, such as painting mice or transporting them from one city to another, may also impact the behaviour and possibly the epigenetic processes that are at stake. In this context, the question of when (*unintended*) *environments* "start" to experimentally exist and thereby are significant to think with is an important epistemological matter. In one of Nadja's applications for approval for an animal experiment, I recognised a bar chart in which she had visualised the different phases of the planned experiment. Every chart exemplifies one phase of the research endeavour, amounting to 45 days in total: (1) dyeing the mice's fur, (2) first stay in the social box, (3) AAV-injection, (4) recovery phase and activation of the virus, (5) second stay in the social box, (6) restrainer, (7) third stay in the social box (fieldnotes, 29.11.17). What attracted my attention

[61] When I once shadowed Julie, I had the chance to look into a group's application for an animal experiment in which they aimed to analyse the role of RNA-modifications in the regulation of the central nervous system. The folder in which the proposal was filed was stuffed with different documents relating to the application process. The government's answers and comments mostly addressed the assessment of the level of stress exposure for the animals. In this context, the "forced swim test" that is applied in depression research, was evaluated as "moderate", the government however corrected the assessment to "severe". It took the group almost two years to get approval, Julie told me (fieldnotes, 26.1.18).

here was the fact that the temporal depiction of the mice's exposure to stress only starts with the dyeing of their fur. However, how do the mice get to the laboratory? Are they transported from the branch institute? Which events have shaped their lives before they are used in this experiment? And why are those not worth being reflected concerning their behavioural epigenetic effects?[62]

Interestingly, some regulations that should protect laboratory animals can also be experienced as *unintended environments* themselves, as they interfere with the proper operation of stress experiments. Julie, for example, once noticed that the government were meant to have introduced new cages for the chronic social defeat, since the old cages are considered to be too small. However, according to Julie, the new, larger cages would introduce the problem of providing too much space for two mice, resulting in the white mouse not becoming aggressive enough. The chronic social defeat set-up would therefore not work as it used to, the reason for it having become difficult to replicate lying with the government's new cage size requirements. As Julie explained, speaking of the results, "You can see it in the data as well: the phenotype is different. But there is still enough chronic stress visible" (fieldnotes, 26.1.18).

5.2.4.2 Environmental entanglements within cell culture: the "l-effect"

Due to the core postulation of epigenetics that organisms are highly sensitive to context, experiments in this field are particularly unstable theoretically when challenged with *unintended environments* internal to the lab. They not only interfere with the handling of mice in animal models, but they also impact the analysis of cells, however, to a different extent. Not every experiment is necessarily equally prone to such unintended influences. In July 2017 I attended the data club, a weekly meeting in which lab members present the progress of their work. It is Jano's turn to give an update on his PhD project. In order to analyse the underlying gene expression patterns after exposing mice with stress, he sequenced the RNA. One of his research findings leads to a lively discussion: something seemed to be controversial about it, but the problem could not be solved. Then, Nadja asks Jano when he has made the RNA sequencing. "It was last summer," he replies. Nadja seems confirmed in her assumption, as she quickly states: "Then it's totally clear. I'm sure [it was] 30 degrees in the lab as the AC doesn't work properly here. And RNA doesn't like these high temperatures. It needs a cooler atmosphere" (fieldnotes, 19.7.17).

Indeed, the laboratory temperature was frequently an environmental matter of concern as a lot of cells are highly sensitive to temperature changes. Once when I was shadowing the PhD student Valentin, he commented on his work jokingly, but still with a clear message, saying, "You have to think about whether it's not too warm in here for the experiments." Providing a stable laboratory temperature is in

[62] How this is later calculated, discussed and reported in the publications remains, so far, inaccessible to me, mainly as the study is not yet published.

this context considered to be a way of standardising genetic and epigenetic experiments and hence making them reproducible for other laboratories. The above anecdote about the not fully explicable result of the RNA sequencing also alludes to an epistemic practice that is of high significance for epigenetic research: making sense *of* environment and making sense of inexplicable results *via* the environment. As epigenetic processes are assumed to be highly sensitive to environmental context, some environments that are uninvited to the research are turned into a vantage point from which the scientists at the institute can reasonably (and gratefully) re-stabilise a faltering experiment. They provide, in this sense, a starting point for troubleshooting.

This "bias" that can be part of biomedical measurements was also an issue in my interview with biologist Valentin. At the end of our conversation, he talked about what kind of results are worth the most to be published: "And, ultimately, you publish those results, that you have often reproduced in your lab and that … others also have reproduced in their labs – yes? So, there is an 'l-effect', a 'lab effect'– you have the GxE.[63] But then, you can also have an LxG-effect or so, right? So, you really have a lab effect, yes" (Valentin, pos. 132). In this equation, Valentin refers to the bioscientific term of "gene-environment interaction" (GxE), which consolidates genotypic stability with genotypic reactivity to environmental stimuli and which also highlights the significance of both the genes and the environment for the individual development of human beings. As a mechanism for a "long-term integration of genes and environment" (fieldnotes, 31.5.17), epigenetics falls into the category of gene-environment interactions. Similarly, Valentin's neologism of the "LxG-effect" which, in analogy to gene-environment interaction comprises the "laboratory-gene interaction", alludes to a related phenomenon. He uses this term to summarise all of the instances in which laboratory environments – the lab temperature, the material used, or the handling of cells – can have an impact on the researchers' experiments and ultimately also influence their publishing practices.

Based on this assumption, the researchers themselves can also turn into *unintended environments* that might interfere with the epigenetic experiment (as described in the literature with regard to epigenetics in e.g. Lappé, 2018). Especially because epigenetic researchers often work with DNA or RNA to analyse, for instance, methylation processes, it is of utmost priority for them to not contaminate the experiment's DNA with their own or other "foreign" DNA. Once, Nadja prepared a solution for an injection into mice brains by diluting RNA with a transparent, reddish liquid and asked me "to temporarily breath less, because nothing may come in here" (fieldnotes, 29.5.17). And she added laughingly: "I would appreciate it if you would not spit into my tubes. So, please don't talk. After that, all questions are allowed" (fieldnotes, 24.8.17), while pipetting beads[64] to DNA samples of mice.

[63] Gene-environment interaction

[64] Beads are magnetic micro particles used to dissolve e.g. proteins by denaturising them.

Epigenetic experiments are described as being so sensitive that even individual working methods may be reflected in the outcome. Washing samples is a standardised procedure in the life sciences to remove proteins or other molecular structures that are not at stake in the experiment. The technician Jasmin told me that these washing processes can differ sensitively from technician to technician. A former boss of hers would have even distinguished after scanning the samples how attentively they have been washed. As Jasmin recounted, she would often ask jestingly, "So, have you chattered again,?" (fieldnotes, 31.1.17). Adriana also once regretted that some of her cell samples turned out to be no good. "Yesterday, I was so busy and hurried while washing, maybe I washed away too many of the IPS-cells" (fieldnotes, 2.3.17). With this additional level of interfering with epigenetic experiments, even aspects of the scientists' researcher personalities – such as working fast or working gently and carefully – turn into instances of how *unintended environments* become interfering yet ordinary parts of epigenetic experiments.

5.2.4.3 The pursuit of automation: reducing the "human" factor in research with human material

> In an ideal biobank, all processes would be automated, which means that when samples come into the lab, you put them into a robot where they are processed and continually marked with time stamps throughout the different stations, so that you can control everything better. It's about taking out the "human" factor. (Mirena, pos. 30)

The attempt to reduce the "human" factor in research with human material might sound like an oxymoron at first glance. However, given the fact that laboratories are highly artificial spaces and that humans are complex living beings that dwell in natural (to make the contradiction even more visible) environments, the endeavour mentioned by technician Mirena makes sense. Conducting research with human material involves a certain susceptibility to errors or environmental complexities as it means opening the laboratory to research subjects, something that cannot be controlled in the way inbred laboratory mice or induced pluripotent stem cells can be.

When studying humans, *unintended environments* can emerge even before the research project has started: Mirena highlighted that 65 per cent of all sources of error would occur in "pre-analytics" – the phase that precedes the processing and analysis of data. In this context, it is the research subject him- or herself that may occur as a distracting event. When collecting human blood, the patient's or healthy subject's behaviour is a decisive factor that can impact the ongoing study: whether they have drunk "too much coffee" or "smoked too many cigarettes" or whether they "have eaten" before the blood collection or "did sports" – all of these factors can have an impact on the research outcome (Mirena, pos. 64). In general, the individual's lifestyle is in this context regarded as a factor that has to be controlled or at least to be *known*, as "the worst thing you can do in the lab and in a biobank is to try… to cover up something with the hope that nobody will notice it" (Mirena, pos. 78). In fact, many of

these possibly bewildering parameters can even be measured in the samples themselves: hormones and metabolites can tell whether the patient has eaten something and "you can determine the drug mirror in order to assess which medication the patient or healthy subject has taken before. Even, if she did not tick any box on the questionnaire you can see it" (Mirena, pos. 84), Mirena explained.

Individual lifestyles and experiences emerge as the great unknowns in research with humans. The neuroscientist Zoe summarised this challenge as follows:

> I think that's a huge issue which the field is facing. … For example like here we do prenatal or early childhood stress and we do all different kinds of stress. … And … if you are studying someone in adulthood who had some trauma as a child, it's very unlikely that that was the only trauma that they ever suffered in their life. It's very unlikely, and so how do you kind of separate these mechanisms like: what… what is, what was caused when they were a child and what is like what they have experienced throughout their life? I think most people that have traumatic childhoods, they also have traumatic… adulthoods as well, because – you know – maybe they are in a lower socioeconomic – you know – lifestyle or whatever, where they are constantly exposed to all different types of stressful events. (Zoe, pos. 28)

What Zoe alludes to in the above interview excerpt is the dissonance between exposure and epigenetic effect. In contrast to animal or cell model organisms, the complexities in human life make it hardly feasible for scientists to distinguish between an effect being causal to one event or being just associated with it. This "association-versus-correlation dilemma" is specifically challenging in the field of psychiatric research on environmental epigenetics. As the human brain is not accessible in the living organism, the brain eludes molecular-biological analysis. Even in post-mortem brain research, which is an attempt to bridge this analytical gap, the complexity of *unintended environments* endures.

> And the other is that, because people are dead, is that we usually don't have very good measures of how those people were exposed to different traumas throughout their life and that's a limitation. When we are using post-mortem brain research, it's usually just looking at like how it has changed in psychiatric disorders, assuming that these people probably have had some traumas in their life, but not knowing exactly when. And so there are some groups … that do what they call a "post-mortem interview" where they contact the families and they are really extensively interviewed to figure out when they experienced major traumas in their life. But with the samples I'm working with, we don't have that. (Zoe, pos. 18)

The problem of association versus correlation is in fact the challenge that was most often recounted by scientists working with human material. Knowledge about the causal relationship between event and effect is particularly important in epigenetic research, as epigenetic changes are described as being cell-specific. The same epigenetic process may have different phenotypic outcomes in different cells, ranging from merely transient effects to pathogenic developments. Deploying animals is hence regarded as an attempt to gradually close this knowledge gap as in "animal models … you can really just like focus on one specific type of trauma at a time, or one specific type of stress and then you can really break it down into smaller… (.) areas" (Zoe, pos. 28).

What becomes obvious is that in the context of research with human material, *unintended environments* in the form of lifestyle and experience mostly occur in different temporal dimensions than the

actual research endeavour (in contrast to for instance the laboratory temperature affecting cell culture research). Despite being phenomena that emerge *before* the actual data collection and analysis, *unintended environments* may still impact current research. Hence, researchers and technicians are challenged with distinguishing and disentangling different environmental effects in the samples. As it was already made clear in the above paragraphs, for Zoe and her colleagues it is important to consider what has happened *before* the actual collection of the data sample, as the pre-collecting phase may include elements that potentially interfere with the analysis of the material. As Mirena stated in the interview,

> smoking can for example be a disruptive factor or when the patient has drunk too much coffee ... his ... way of life, although it's hard to define it because epigenetics just describes the environmental impact (.) and it's really very difficult to differentiate in a study to decipher what's the specific impact of the drug and which changes come from environmental stuff?" (Mirena, pos. 64)

In sum, the integration of epigenetics into different biological knowledge formations recurrently indicates the increasing awareness of both the need for and the difficulty to dissect different environments methodologically and analytically. To some extent, it also complexifies the artificially ordered laboratory world: environments can be reduced to single though not completely tamed aspects, and attempts to reduce the "human" factor may not always be successful because scientists cannot control their research subjects' behaviours. As Zoe expressed in explaining this scientific goal, in an *ideal-typic* scientific imagination, "it would be nice if … you could say that this [specific epigenetic change] is definitely a signature of this type of stress – and then you could look at the epigenome and say: well, this person was exposed to this, because I can see it in the epigenome" (Zoe, pos. 26). However, the epigenome describes the *entirety* of epigenetic states. It is thus supposed to gather the sum of human experience over space and time. As a dynamic structure, it still exacerbates the endeavour to establish causality in research with human materials.

5.2.5 Coda

> So DNA stays the way it is. Epigenetics results from an influence of DNA and environmental influences, whatever these may be. ... [*laughs*]. (Adriana, pos. 40)

Whatever these may be. What Adriana has added to her definition of environmental epigenetics with a laugh, as if it were apparently less important, is in fact a crucial complement to understanding epigenetic research practices in light of this chapter. As I have shown, environmental epigenetics supposes bodies to be open to context, to be potentially influenceable by environmental change; however, this postulated porosity may also apply to the epigenetic experiment itself. How then can we interpret the susceptibility of epigenetic experiments to their environment? What does the fragility of epigenetic experiments to both intended and *unintended environments* mean? What role do the researchers' individual working methods, potentially visible in the experimental outcome, play? How can scientists

be certain that they measure and analyse what they in fact intend to measure and analyse, when environments might enter into their epigenetic research *uninvitedly*?

As mentioned earlier, reductionism is one of the most important methodological strategies in the laboratory sciences. This reductionism is based on an ideal conception of how to organise and operate with experimental components. What the construction site metaphorically alludes to, however, is that "reality" cannot be fully excluded, reduced and tamed in the manner researchers imagine. It is to a certain extent *always* part of the laboratory, it cannot be ignored. Environmental epigenetic as well as genetic research projects are to some extent unpredictable endeavours. In this context, analysing the construction site's symbolic meaning is important to understanding what actually happens in the institute. It figuratively points to productive tensions between the scientists' imaginations of how to re-enact stress appropriately and the moments of conflicting powers and complexities that are inevitable elements of the everyday research practices at the institute. In other words: the artificial laboratory world as *ideal type* is built to model phenomena form the *real type* (see Weber, 1904). Against the background of environmental epigenetics, however, these attempts are susceptible to contextual change, which makes research practices even more complex. There exist environments that differ from those the scientists intentionally re-enact in their experiments. In addition to dexamethasone or chronic social defeat, noise, vibration or high temperatures might join the epigenetic experiment. Such environmental factors are *uninvited*, yet significant in implying that epigenetic research endeavours are open to surprising contexts, despite their reductionist intention. This to some extent forces the researchers to fulfil ongoing negotiation work about the impact of these environments on their experimental outcomes and about the ways their research practices can be further developed to re-stabilise the epigenetic experiment.

Though environmental impact also plays a role in genetic research, in epigenetics, as *the* science of how organisms molecularly react to environments, it obviously has another scope. Nicole Nelson (2018), who has written about the environment as a potentially distracting factor in genetics, describes those environments that are in fact not part of the experiment as "epistemic by-products":

> observations that researchers accumulate as part of the process of carrying out what they consider to be their main line of knowledge production work. Rather than defining epistemic by-products with respect to particular intrinsic features, I define them relationally, with respect to particular experimental aims and programs. This relational definition has the advantage of not fixing the value of particular observations—not only can what counts as a product or by-product vary substantially, but whether a by-product is considered waste or valuable depends on who is evaluating it, or the presence of technologies or markets that could transform it or facilitate its movement. (pp. 119-120)

Many of these things apply to science as such. What is specific for the context of environmental epigenetic research is that noise and signal have the same character, that is stress. That is to say, stress as an *unintended environment* is not only a disruptive factor, but another environment that is not part

of the research protocol but still gets involved here. As a consequence, scientists might potentially measure the "wrong" environmental factor. Hence, in epigenetic research hypothetically all "epistemic by-products" are phenomena to be negotiated, making the research question even more complex. After all, environment is one of the crucial research objects in environmental epigenetics. Intended and *unintended environments* are productive tensions as they give the scientists a basis for developing and refining their epigenetic research practices. They hint at the need for changing the scientific practice that potentially has to be re-organised due to the increasing relevance of epigenetic knowledge in current life science research.

Unintended environments furthermore have the power to teach us about general shifts in how our world and living-together is perceived. In this sense, the construction site stands as a symbol of the dichotomies that are becoming progressively porous: not only the body-environment demarcation, as the basic epigenetic argument, but also the environment-environment demarcation (*ideal type* vs. *real type*). These epistemic coincidences also symbolise how elements of the social world are entangled, enmeshed and not always dissectible with the biological. This is continuously reflected in the laboratory world, in which elements, such as the materials used, the animals, or the researchers themselves are intertwined, in conjunction with each other, always interacting. And even if the researchers deconstruct the environment and their research objects to a high degree, the laboratory remains a multi-environmental encounter.

So, do we have to read epigenetics and *unintended environments* as a story of mere overlapping and conglomerating objects, practices and human beings? When everything seems to be entangled, how can environmental epigeneticists then produce meaning in their experiments? How do they manage and tame *unintended environments*? How do they separate environments practically and analytically from each other? And how do scientists re-establish stability and trust in their epigenetic experiments? In the following sub-chapter, I will address these questions by turning to the scientists' strategies to encounter and handle *unintended environments*, that is to say, those *unintended environments* the researchers acknowledge as such.

5.3 Strategies of environmental containment

FIGURE 25. Artistic interpretation of the dynamic effects of DNA methylation and regulation of chromatin structure on cell-wide gene transcription. Acrylic-on-canvas painting by neurobiologist David Sweatt (retrieved from https://cdn.vanderbilt.edu/vu-my/wp-content/uploads/sites/2352/2017/04/14141347/Neuron-Cover-2007.jpg on 17.8.20)

The epigenome is described as a dynamic, plastic system. A system that can potentially be influenced throughout our entire lifetime. The notion that some parts of the epigenome can be actively shaped by therapy, physical exercise, or nutrition gives rise to hopes for harnessing epigenetic plasticity for therapeutic and preventive strategies. At the same time, this general openness of the epigenome to different contexts emerges as a fundamental challenge for the research process itself. As I have analysed in the previous chapter, research with cells, animals, and human material can be potentially bewildered by what I call *unintended environments*. The existence of this contextual "noise" denotes the very situatedness of laboratory research practices. Furthermore, it potentially initiates novel requirements of how to deal with research practices themselves.

One issue put forward in this context by one of the scientists I observed is trust. "How can I still trust my experiments?" (fieldnotes, 26.1.18), the researcher Julie once rhetorically asked, alluding to the construction site as an unavoidable disruptive factor. Most environmental epigeneticists are aware of the circumstance that "you don't have black and white, you have grey" (Valentin, pos. 73), concerning the ambiguity of some of their research processes. That is why Julie ascribes to environmental epigenetics a specific responsibility to reflect on these challenging entanglements. In her view, epigeneticists cannot ignore the existence of potentially disturbing environments that are inevitable elements of research, but "for us, who do research on epigenetics, it should be very important" (fieldnotes, 26.1.18).

During my research stay at the institute, I had the opportunity to observe not only the proper processes of knowledge production but also plenty of instances in which scientists attempted to stabilise and re-stabilise these knowledge production processes as such. The awareness of the importance of context in the laboratory grows proportionally to the increase of knowledge in epigenetics. Unintended context, however, might be an interfering factor in specific research endeavours. Therefore, scientists employ different strategies to contain undesirable environments. Attempts to make intended and *unintended environments* distinguishable from each other to re-stabilise epigenetic experiments are a challenge Emma, a postdoc researcher, described laughingly as "the bane of my existence!" (Emma, pos. 77). Some of these can be described as practices that are fundamental in every life science laboratory, while others are specific developments grown out of environmental epigenetic research.

In the following chapter, I will address the implications of environmental complexity for the field of environmental epigenetics. Furthermore, I will delineate how scientists are forced to continually negotiate the impact of environmental complexity. When are the unanticipated side-effects too invasive as to be accepted? How can scientists report the actual circumstances of an experiment properly? And how do they attempt to re-establish trust in their own experimental results? While these questions are important in all life science research, in the context of epigenetic research they appear to be most pressing, as they affect the very research object of the field: the biological effects of environmental experiences. And yet, as we will see, the field of epigenetic research does not yet have a basis for discussing these issues in the wider scientific community.

5.3.1 Keeping environments out: reduction as a method of control

Reduction as a methodological approach is a common practice in the scientific laboratory. As elaborated upon in the previous chapter, by reducing context scientists create an *ideal type*, a selective excerpt of reality. Reduced research conditions can be achieved by narrowing down the research focus on a specific gene, for instance, or a specific epigenetic process which is kept stable. This procedure can be regarded as epistemic reductionism as it limits the scientists' heuristic perspective to one defined phenomenon.

In the context of *unintended environments*, scientists attempt to produce reductionism by eliminating certain environments, or keeping certain environmental factors out of the lab – an approach in which I played a distinctive role. Once, Nadja denied me the observation of an animal experiment because she feared that our conversations would disturb the mice. Another time, I accidentally crossed a line that I was not able to interpret correctly.

> On our way to the lab, Nadja and me also pass the mouse houses. There are signs in front of the doors: "Please be quiet, experiment is running." Nadja pauses, then she says she has to take a quick look. She opens the door. The lower quarter of the door frame has a thin board – presumably to keep a mouse from running away, I think. Nadja climbs over that guard, steps onto a small mat just

> behind the door, and pulls on blue plastic protectors over her shoes. "These are the mice that I isolated in different cages yesterday," she explains. I nod and enter the room by climbing over the cover. "Ah!" Nadja exclaims. "You're not allowed in here. So, stay on the mat," she suggests. … Later that day, we again end up talking about the separation of the mouse house in the "blue" and the "red" area. Nadja says that it was already borderline this morning, actually I should not have entered the blue area. (fieldnotes, 20.5.17)

By regulating who has access to specific areas of the laboratory, such as to the animal cages, scientists attempt to limit possible exposures for their research objects. Against this background, research with animals requires specific awareness as mice and rats are very sensitive to changes in context. Even if new personnel would enter their mouse house this could lead to a potential level of stress, as the person smells differently than the persons they are used to. This "carefully cultivating consistent experiences for the mice" (Lappé, 2018, p. 699) is one way of preventing contextual noise and containing potentially disruptive environments in epigenetic research with animals.

A similar approach to keeping certain environments out is the establishment of specific closed working systems within the laboratory. By conducting experiments in a so-called "laboratory hood", researchers intend to prevent the entanglements of different elements that should not conglomerate. Here, they can for instance produce and analyse genome-wide maps of epigenetic mechanisms by using next-generation sequencing. Such a hood is separated from the rest of the laboratory environment and can be cleaned with ultraviolet radiation. The practice of disinfecting surfaces and equipment is a further standard procedure to not only keeping unwanted environments out but to destroy and incapacitate them. Besides ultraviolet radiation, substances like ethanol and chlorine bleach are used to remove foreign DNA, because "we don't want to mix it [our samples] with what *you* (pointing to a colleague) did before or what *he* (pointing to a man who is in the opposite room) did before" (fieldnotes, 24.8.17), as Nadja illustratively explained.

The wearing of protective clothes is another attempt in genetic as well as environmental epigenetic research to establish "clean" research conditions. Gloves, elastic booties, gauze gaps, masks and laboratory coats are tools used to install a physical barrier between researcher and research object. These items are intended to protect in two reciprocal ways: the samples are supposed to be kept from foreign DNA and microbial material. But the researchers themselves are also protected from harmful environments within the laboratory: Julie once told me that a lot of ethidium bromide is used to stain DNA. "But it also goes through *your* DNA. Well, best of all: don't touch anything. That's why we wear special gloves that are even more impermeable" (fieldnotes, 26.1.18).

5.3.2 Learning from environmental epigenetics: documentation and being attentive to the temporality of things

Since the early twenty first century, the ways of practicing data collection and analysis in biology have gradually changed. There was a turn from single-gene approaches (to identify particular genes that can be associated with human diseases) to an approach that assumes that a set of genes contributes in conjunction with many other factors to different mental and physical health states – a scientific turn that was largely made possible by the technological progress in genotyping based on mass-produced arrays. Environmental epigenetics is one element of this multi-dimensional perspective on the development of health and disease. This progress in analysing methods leads to an increasing endeavour to collect and store data on a long-term basis. Additionally, with an increasing group of scientists working with the same material, environmental influence is becoming increasingly complex.

Hence, novel institutional attempts to standardise research processes are emerging. The establishment of biobanks as research units that are specifically occupied with developing standardised methods for collecting and storing biological material can be regarded as a rational consequence of the requirements of modern biotechnology. In this logic, the biobank at the institute puts forward scientific strategies to (re-)establish control over entangled environments that might interfere with the research by for instance proposing how to collect blood. This is one attempt to tame *unintended environments*. In this context, Mirena, head of the biobank, and her colleagues have formulated directives that can help the study nurses and researchers to work under comparable conditions, so that the "biomaterial [is treated] in the same homogeneous form" (Mirena, pos. 22). For Mirena it is extremely important that the (research) activities be monitored during all working steps and, as a consequence thereof, documented. Important questions in this context would be:

> How long did it take to transport the [blood sample] to the lab? How long has it taken to refrigerate or freeze it? And how long was the sample stored? Under what conditions? What was the temperature? Then, the freezers also need to be monitored. (Mirena, pos. 22)

What environmental epigenetics has additionally "taught" the institute is the importance of *time*. In my first empirical chapter, I have already analysed how epigenetic knowledge has introduced novel temporalities into the field of mental health research and the life sciences in general. A range of life science publications suggest how very early experiences, even starting in the maternal womb, can affect later health outcomes (Kundakovic & Champagne, 2015; Maccari et al., 2017; Murgatroyd & Spengler, 2011), giving socio-material experiences a tenacious reverberation. Both the researcher Stella and the technician Mirena indicated that, with deeper knowledge into epigenetic mechanisms, it would have become clear that *time* also matters in relation to the measurement and analysis of DNA methylation. When Mirena started to work at the institute 20 years ago, blood was collected only once from patients and healthy subjects to analyse their DNA.

> At that time, we though that it would be enough for DNA to be taken once per person and then… we collected a large amount of blood, 30ml, so that you can get a lot of DNA out and in the old databases, for example, there was no box for time – yes? And it has now turned out that it's a pity that you don't have that, because at some point we have started to take DNA at several [different points in time] and then saw a certain development in the epigen- … in epigenetics. And this was – we also have learned here over time. And I can say that in some projects we did not consider that time perhaps was important concerning the DNA, we have missed it a bit. Well, we just didn't know it, in retrospect, it's a pity, but that's how we learn. Exactly. (Mirena, pos. 56)

It becomes obvious here that environmental epigenetics has led to the practice of concretising experience in accordance to a timeline: what happened before the collection of the biological material and at what point in time? The question is raised so specifically that even the time of day when blood is collected is documented. This "time management" is assumed to contribute to a better matching of epigenetic modifications with socio-material experiences and is an attempt to assess DNA methylation as a dynamic process. Against this backdrop, a standardised documentation of the date and time of blood withdrawal as well as detailed questionnaires of the research subject's behaviour could help to map environmental experience and (epigenetic) effect on a more reliable basis. With this method, environmental complexity can be disentangled only to a certain degree, as the individuals' behaviour before the sample collection (drinking coffee, smoking etc.) is beyond scientists' control.

In research with animals as well, being attentive to the research object's temporalities is one way of domesticating unintended environments. In contrast to several other laboratories, Julie always runs her behavioural experiments with mice during night. By so doing, she attunes the stress exposure as one epigenetic environment to the rodents' natural day/night rhythm to avoid uninvited stress that might expose her mice even more.

5.3.3 Creating a level of comparison: controls and replications

> *Control* in the sense of a check or comparison ... appears in all experimentation because a discoverable fact is a difference or a relation, and a discovered datum has significance only as it is related to a frame of reference, to a relatum. (Boring, 1954, p. 589)

Nearly every researcher mentioned the same basic strategy to distinguish noise from signal: the use of control samples in their research projects. However, this strategy takes on different levels of complexity. In cell culture research, the endeavour to contain *uninvited environments* appears to be rather simple, at least at first glance. All cells can be "fed" with the same culture medium, they can be stored under similar conditions, they do not move, they can be fixed on a plate. While environmental contexts may change, controls are assumed to be capable of re-stabilising the experiment:

> We're going back to the lab where Nadja's bench is located. It's very cool here. "Whoa, cold!" I say. Nadja answers: "Yes, that's the way it has to be. But the air conditioning isn't that good, it's just a circulator." – Why is that so?", I would like to know. She explains that at the time when the building was constructed the installation of a proper air conditioning system, which ensures stable

> conditions, was not yet standard. In the laboratory where we were before, the NGS[65] laboratory, it was actually too warm, so they "only" do PCRs[66] there. "I once worked in a laboratory where there was no air conditioning at all. We needed different incubation times in summer than in winter," she says laughingly. "And how did you know how to adjust the times?", I want to know. – "You can see that. That's experience. And you have the controls for comparison," Nadja says. (fieldnotes, 24.8.17)

The above excerpt from my fieldnotes makes clear the fact that Nadja applies a very individual strategy to make the changing temperature, an *acknowledged uninvited environment*, manageable: she uses what she refers to as "experience", a learnt implicit knowledge that is not objectifiable and hardly verbalisable. Here, the control samples appear as additional back up, as both the actual research samples and the controls have been exposed to the same environment that gives Nadja a standard against which to compare.

Emma, who is working with organoids, has a very interesting perspective on the feasibility of differentiating environment/stress as signal from environment/stress as noise in cell and in animal models:

> Environment is huge, but with the animals, they are living beings, so you can kind of see... you... they can tell you a little bit if they're distressed – you know – if they are hungry, if they are... whatever, the lights bother, they may make noise about it. These organoids don't tell you anything and so you... so the... the way you can make sure that this doesn't affect your results is, that you build controls. So, you have your treated versus untreated organoids and they have lived in the same place, so if the temperature went down for ten hours last night that nobody knew about, at least they both had that stress. Of course, it's not perfect, because somebody – you know – an organoid receiving dexamethasone versus one not receiving will respond to that stress maybe differently, but at least – you know – you can control some of that. (Emma, pos. 77)

For Emma, behavioural change in the mice resulting from stressful contextual change is a chance to re-adjust environmental aspects to the mice's needs. The mice "tell" the researchers which aspects they experience as stressful. This means that Emma to some degree assumes that the control animal can reveal "'environment' where there is presumed to be none of consequence" (Landecker, 2013, p. 4). Emma interprets the circumstance that mice can "communicate" as an advantageous hint that intended and *unintended environments* of the experimental arrangement need to be modified to stabilise the research. Cell model organisms, in contrast, cannot express stressful states. They remain silent, something that Emma interprets as a drawback. What is interesting in this comparison of how to re-establish stability in two different model organisms, is that Emma does not reflect on environmental changes as having an effect on the experimental outcome in mice. They remain unacknowledged. Why is hunger or harsh light in this context not worth being reflected as environments having an experimental effect?

However, the employment of "unstressed" controls also can have epistemic limitations. Of course, scientists assume that "parallel controls at every step" provide them with a level of comparison

[65] Next-generation-sequencing
[66] Polymerase chain reaction

(Emma, po. 78). Indeed, my question regarding the impact of accidental environmental changes on research objects was often answered with a similar self-explanatory argument: *In the end, you have your unstressed controls as comparison*. However, what counts as "unstressed" in this context? Can we assume that organoids that receive dexamethasone versus organoids that do not receive it "respond" to a change in temperature because somebody, for instance, leaves the door of the incubator open in the same way?

In addition to such "technical" controls, researchers use "biological" controls – deploying mice that are genotyped, for example. According to Julie, this is another strategy for *pre*-establishing control as the mice would have different genetic conditions in one litter, which would be normal in keeping with the classical inheritance theory of Mendel. By providing the "same maternal care and environment" (fieldnotes, 26.1.18) for these mice, researchers could make the outcome more valid, as Julie says. But, how can scientists be sure that a dam cares for all offspring in the same way – with "maternal care" being one of the most researched epigenetic environments?

Even if the effects might not be as sturdy, the awareness of *unintended environments* can have important implications for the field of environmental epigenetic research. The last method for containing the effect of uninvited environments that I would like to delineate is the argument of replication under different conditions. Valentin and his colleagues regard the constant repeating of an experiment, to validate robust effects and to make the experiment replicable for other laboratories, an important strategy to produce results that can be considered reliably significant. In the interview, I asked him how he assesses the influence of unplanned environmental changes and how he deals with them in experiments.

> Me: I'd be interested to know how... how you get that into the experiment, how you can separate it, to see: okay, the effect I'm seeing now I can trace back to what I was doing – like that? I'd just like to know how that works and/or...
>
> Valentin: So... that's a statistical consideration. You do repetitions. (.) You have to... the effect must be robust enough that you do multiple repetitions, that if on a day like today, when it started snowing so beautifully... and if the sun is shining the next day, then... I do it again to see if the... the snow that fell outside, if it had an influence, now in a very abstract way – yes? That's why you have to do it again. Good science also relies on repetition and reproducibility. (Valentin, pos. 129-30)

Replication and reproducibility of experimental results are considered essential elements of the scientific method. Emma has mentioned a similar connection between replication and validity in the interview:

> You repeat the experiment multiple times with the same controls – you know – so that if in the month of June the humidity was different than in the month of January, at least you... and if you get the same result between the two, you can trust it. Yeah. (Emma, pos. 79)

In both quotations it becomes apparent that the scientists assume that reproduction confirms their assumptions, that reproduction makes the data more robust. This is an approach that stands in contra-

diction to Karl Popper's maxim that theories can never be proven, only falsified (Popper, 1959/2005). Valentin, Emma and some of their colleagues rather follow an abductive reasoning, which starts with an observation and then tries to derive the most likely conclusion from this observation. As I have delineated in the first empirical chapter, the starting point of Valentin's project is the observation that traumatised people with PTSD show demethylation in the TRBP. His intention is to replicate this observation in his project to make the observation more robust.

Moreover, this is not only about local repetitions in one and the same laboratory. Only if another laboratory can confirm the results are they interpreted as assured knowledge and valid data, as research group leader Joachim explained:

> So if a completely separate laboratory can reproduce a finding – this need not be the same gene locus, but can confirm the principle that environmental experience, social experience can lead to such changes – then that in itself was now more than enough evidence that there is a point. (Joachim, pos. 8)

Here we see a clarification of the claim by historian of science Lorraine Daston (2002) that modern molecular biology is a science that predominantly works with law-like rules "according to which life at the molecular level unfolds" (Niewöhner, 2015, p. 229). Only when results are confirmed by others, preferably by a "completely separate" laboratory, are they considered to be molecular rules. The separation described here is interpreted as additional significance, as a neutral, unbiased way of confirming laboratory results. The basis for these law-like replications are the publications of the methods and results, the exact research practices that were used – that is to say the principles of science communication.

> Reproducibility is a keyword: what if you change something now, yeah? Sure, that shouldn't have any influence, I have to show that reproducibly, I have to show that by means of reproducibility. ... When you repeat an experiment, you generate evidence, of course, yes? And that will then be published and recited in the literature and that's why our communica… Science communication is also based on the – yes – impact. This is how our science is controlled, but then the system has to really work, yes. That what you publish there is valid. Through peer reviewing and so on. (Valentin, pos. 132)

Against the background of my previous analysis, I would like to raise an interesting and important question: *what* in fact is and *can* be communicated to the scientific community as a basis for replication and as a basis for molecular biology's search for law-like rules? Does the current publication system allow the scientists to provide a comprehensive inventory of all environments that have been elements within an epigenetic research project, whether they be invited or unintended? What is about environmental changes that happen when scientists are not present in the laboratory? And how can scientists communicate when they have to face *unintended environments* they are incapable of changing? Revisiting the construction site: does the current system of publication allow for the recording of the construction site as an event that potentially effected the research result? In this context, Julie noted that "we don't write that we had so much construction noise that… You can't write that you do

not trust your own experiments any more, the reviewers would never let that pass" (fieldnotes, 26.1.18). This exemplifies a very significant theme, as it is a challenge of how to communicate research output to the scientific community and also to policy actors and ultimately to the wider public. What Julie criticises is that the proper research conditions, including challenging and maybe not explainable environmental complexities, cannot be reflected in the publications to an adequate extent. For epigenetic research, she is demanding a stronger focus on describing the circumstances under which experiments have been conducted in order to produce a truly replicable basis for other laboratories that either verify the results or produce new approaches. However, as Julie once expressed, "Often, there just is not enough room in the Materials & Methods-section. Yet, it's so important to us who are doing epigenetic research" (fieldnotes, 26.1.18). Emma similarly expressed her own opinions on the topic:

> Me: Is there room or space in the publication to discuss these issues for example?
>
> Emma: Yeah. You usually would put it in the methods, but ... there isn't enough space for it, so for example journals that really are... allow you to have a lot of supplemental material are great, so they... This is a discussion we had recently, because we are... we are trying to write this paper that is kind of a short... a small story, so we were thinking of writing it as a letter, but some journals don't ex... don't accept supplemental with their letters. So for us, the stuff we are doing, there is so much to say, in order to allow somebody else to repeat the experiment, that you really need that space, yeah. And so... yeah, exactly, that's... that's a big issue and that's why now you see papers that are... – you know – maybe they are like seven pages in print and then 35 pages in supplemental. And all these controls you have done, you put them there and you say: okay, we did check for this – you know – we did check for the... we repeated it five times, I'm only showing you one, but we repeated it five times – you know, this kind of stuff, yeah. Yeah. (Emma, pos. 78-79)

Both researchers speak to specific scientific conventions that potentially narrow an authentic discussion of the conditions and limitations of environmental epigenetic research as *local* and *situated* research practice. Against the background of these constraints, it is important to ask what in fact is replicated when publication systems do not allow the researchers to recount the *whole* story. Hence, in a sense Julie's and Emma's criticism calls for a rethinking of what an adequate research ethos for this specific scientific field could be. This could include, for example, being able to describe what happened between "black" and "white" in the "grey" domain of knowledge.

5.3.4 Coda

This subchapter was about environment. More precisely, it was about scientists' ways of dealing with environmental change; their strategies to contain environments that they acknowledge as not being part of the research protocol and that therefore might interfere with the epigenetic experiment in an unforeseen way; their laboratory practices in coping with epistemic complexity in order to produce significance or meaning. While some of these strategies can be regarded as parts of a more or less standardised repertoire of today's scientific culture, the existence of *unintended environments* also

reveals that environmental epigenetics demands new ways of approaching and communicating experimental practices. In this context, the increasing awareness that some biological processes, such as DNA methylation, are dynamic and have their own temporalities can be described as a central aspect that only gained relevance through epigenetic knowledge. This awareness has also changed scientific practice, especially in regard to documentation.

Employing unstressed controls was mentioned as a standard answer to my question of how the researchers can be sure to measure the intended, re-enacted stress and not an artefact due to an *unintended environment* that emerged as accidental stressor. As I have outlined, biology proposes stress as a cell's or an organism's ability to adapt to changing environmental structures. Against the background of the noise and the vibration from the construction site, do animal researchers still work with "unstressed" controls? How can we interpret the shift from the unstressed/stressed paradigm to a paradigm that can be denoted as baseline-stressed/more stressed? As Landecker (2013) writes:

> The main function of the control animal is to pick up biological outcomes that might result from extraneous elements of the experimental protocol, rather than arising from the experimental intervention being tested or the mutation under study in the experimental animal. (p. 1)

Given the circumstances – that all mice are "stressed" – what, then, is the function of the (presumably) "unstressed" control mice, the relatum? Has the construction site turned the controls into the actual experiment (Landecker, 2013)?

Notably, environmental complexity was mostly discussed as a phenomenon that *precedes* the experiment, a challenge that precedes data collection. This might be different in other laboratories. Based on his ethnography on the research practices of an epigenetic laboratory that works with mice, Niewöhner (2011) states that the group uses specific layers of analysis and interpretation to produce significance, which is not based on pure statistics. He argues, for instance, that "variance [in environmental epigenetics] needs to be contained post-hoc through building thick significance" (p. 288), for the same reason my informants told me that environmental epigenetics produces results that are not as determinate as in other research areas, such as cancer research. As can be seen in my material and my analysis, however, during my research stay I observed very few discussions about how to deal with ambiguous, "grey" research *results*. My interview questions in this regard were also partly in vain. This may have two reasons: first, as I have outlined in chapter 3.3), researchers often excluded me from their desk work, and thus also from their thought processes and their analysis of the results. In other words: while I could often observe how scientists deconstruct their research objects, their strategies for reconstructing the results – that is, putting together the individual elements of an experiment in a meaningful way – remained largely hidden from me. Secondly, the institute is very hypothesis-driven and has a certain "cultural focus on positive results" (Zoe, pos. 35). In this context "negative", "grey", or ambiguous results are mostly handled as scientifically less valuable than results

that support the hypothesis – as results, in short, not worth discussing. One might be tempted to state, though it would be a mild exaggeration, that the institute has a negative attitude towards negative results.

6 Discussion: How Scientists Produce Bounded Imaginations

6.1 Setting the scene: scientists' imaginations of scientific practice and its actual feasibility

In my empirical chapters, I focused on three cases of laboratory work to provide an in-depth analysis of how researchers explore environmental epigenetics within the psychiatric institute: research with cells, with animal model organisms, and with human tissues (clinical studies and cohort studies). I showcased different scientists and their various research practices to demonstrate how epigenetic knowledge is both mobilised and produced differently according to each research arrangement. My predominant aim in so doing was to analyse how environmental epigenetics deals with and applies *the researchers'* notion of environment to their experiments, how they translate it into research practices and with what effects. My detailed description and analysis of the research practices themselves allowed me to demonstrate how the scientists re-enact social adversity/stress differently, thereby also making different epigenetic accounts of mental health. The chapters show a specific divergence between researchers' imaginations and the actual performativity and feasibility of those imaginaries through the research practices they develop and are able to carry out, which I will explore in more detail in this concluding chapter.

The first aspect of this divergence consists of the researchers' attempt to reduce the social world they study to a few controllable parameters by stabilising as many experimental elements as possible. In this context, they focus exclusively on one specific gene or one specific epigenetic mechanism – by isolating them, for instance, from the "corporeality within which they take place" (Beck & Niewöhner, 2006, p. 223). In the framework of their research approaches, this means that they aim to disentangle their research object from its wider social and biological context, which they perceive to be epistemically "superfluous". This disentanglement is a way of building boundaries around the specific objects of investigation which, in the case of epigenetic research within psychiatry, are mental disorders. Mental disorders, here, are mechanistically broken down into very specific epistemic elements, such as the TRBP gene (see Ch. 4.4.2), isolated in a clearly defined rational framework. This specific form of "pragmatic reductionism" (Beck & Niewöhner, 2006) guides the researchers' imaginations and assumptions of how to conduct epigenetic research that is clean and clear, pure of disturbing "noise". Most readers will know that biological sciences always work with reduction and that the scientists are most often well aware of their reductionist approaches. As I will later show, in epigenetic research context reduction can lead to particular effects which are different from those brought about by context reduction in other research approaches.

Yet, these *ideal-typical* imaginations of scientific practices are disturbed by, amongst other things, the construction site in front of the institute – both symbolically and metaphorically: different phenomena that might be uncontrollable, such as noise, vibration or high laboratory temperatures, can impinge on the scientific experiment, potentially altering its progress and outcome. Thus, the construction site reveals the extent to which the scientists' reductionism is a fragile construct: it often cannot take these phenomena into account as further epistemic objects within the epigenetic experiment. This raises important research-related questions, such as: why do the scientists acknowledge the placement of mice into a restrainer as the simulation of an epigenetic environment, while neglecting to name noise and vibration from the construction site as stressors with epigenetic effects? Here, I introduce the term *unintended environments* to draw attention to this incongruity between the researchers' imaginary scientific practices and the actual feasibility of these ideal circumstances: epigenetics acknowledges some specific environments in *theory*[67], while neglecting others in *practice*. *Unintended environments* thus allow us to discuss what it means to conduct epigenetic research today: how do *unintended environments* force us to rethink the scientific imaginations and the scientific accounts and stories they imply? And with regard to the increasing importance of epigenetic perspectives for different fields of biomedical research, how can we conceptualise the modern laboratory as a space with boundaries that are in fact more open and porous than they are currently thought to be?

In what follows (Ch. 6.2), I will revisit each of the cases individually and identify how environmental epigenetics is enacted differently by applying specific forms of pragmatic reductionism. Afterwards (Ch. 6.3), I will summarise why and to what extent *unintended environments* seem to matter (or not) in these research constellations. In the subsequent concluding chapter, I will elaborate on the question of what the existence of *unintended environments* can teach us about epigenetic research practices and practices of telling responsible (scientific) stories – both for molecular biologists as well as for our own scientific accounts. Before elaborating on these aforementioned elements, let me briefly restate what I define as *unintended environments* and why I regard them as a useful concept in thinking within an STS approach towards epigenetic research.

[67] By "in theory" I mean hypothetically. Against this background, I would like to repeat that environmental epigenetics so far has not provided us with any conceptual framework of what constitutes the epigenetic environment. As I have demonstrated in chapter 5.1, while epigeneticists might informally think of environment as *lives as lived*, they deconstruct environment (in the sense of milieu or ecology) into parts of presumed molecular relevance that fit into their experiments. Philosopher of biology Linda Van Speybroeck (2000) formulates in a similar way the need for "epigenetic research ... to indicate those factors at the organismic level which will turn out to be crucial for further investigation" (p. 206).

Unintended environments: highlighting the distinction between factor and actual environment

As I have repeatedly shown throughout the empirical chapters of this text, the environment is one of the crucial epistemic objects in epigenetic research. Within psychiatric research, adverse socio-material experiences are conceptualised as constituting the epigenetic environment. Subsumed under "social adversity", experiences such as maltreatment, neglect, physical abuse or trauma are operationalised within the epigenetic laboratory via various strategies of re-enacting stress in research objects: adding dexamethasone to cell organisms, providing mice with few nesting materials or instructing test subjects to perform calculations under a time pressure. As *intended* environments, they belong to specific research protocols that should guide the researchers through the different stages of an experiment (here, the duration of a dexamethasone intervention for example is determined). I have demonstrated throughout my empirical chapters how the researchers' re-enactments of stress translate environment into factors or signals intended as triggers for the mechanisms under scientific investigation, such as transcription processes. Environment, so to speak, is "factorised" into components of presumed molecular relevance. These factors can be interpreted as the result of what Landecker (2011) calls the *molecularisation of the environment*.

In every research laboratory, however, environments also emerge that exist without the researcher's deliberate contribution, environments that nonetheless can have significant effects on the scientific practice, as I show in my second empirical chapter. Here, I propose the term *unintended environments* to categorise the sum of these environmental aspects that might affect the epigenetic experiment in unforeseen ways. These are the actual environments of experimental systems, understood as socio-technical practices, that need to be situated somewhere. From my empirical data, I draw two different types of *unintended environments*. First, there are site-specific *unintended environments* that result from the construction site or other circumstances specific to the institute, like vibration or variant room temperatures due to damaged air conditioning. These site-specific *unintended environments* remind us that scientific practices, no matter how sophisticated and routine, are always influenced by the context in which they are carried out. They most often result from the fact that the laboratory is itself embedded in environment; it is a *laboratory-in-a-world* in as much as the organism is an *organism-in-the-world*; a notion we can find in Developmental Systems Theory, a philosophical approach that accepts the organism as a dynamic process (Van Speybroeck, 2000; see also Oyama et al., 2001). In my analysis, I identified a second type of *unintended environment*, which is a product of the scientists' practices of reduction. This includes for example the transport of mice to the laboratory, which scientists do not acknowledge as a stressful event, hence neglecting this displacement as a possible epigenetic environment.

As my empirical data and my analysis show, these *unintended environments* are never elements of the research protocol. Often they are not acknowledged as part of the experiment at all. And still they are inevitable components of every scientific laboratory with effects that are worth being discussed and being taken into account. As we will see below, *unintended environments* matter to different extents in each research approach. In the context of research with rodents, for instance, my informants clearly state that the noise and vibrations from the construction site as a specific form of stress change the mice's behaviour, while research practices in cell culture appear, at first glance, to be mostly unaffected. While scientists often perceived the construction site and other phenomena as disturbing factors, conceptualising them as *unintended environments* turns them into productive tensions and provides an interesting vantage point from which to reflect on contemporary scientific practices.

6.2 Revisiting the scene: different research arrangements and their social and political implications

6.2.1 Practices of reduction in research with cell model organisms

In general, model organisms are supposed to help scientists to create scenarios empowering them to make claims about human mental health without accessing the human brain itself. In the context of cell model organisms, induced pluripotent stem cells are currently the most significant biological research tools within the institute and modern biotechnology at large. Their major advantage is their pluripotency: they can be differentiated into whatever cell type might be needed for conducting scientific experiments (see Ch. 4.2).

At the institute, scientists apply a specific form of reductionism within iPS cell research. First, they focus solely on neuronal cells. As I have outlined earlier, in today's science and society, mental disorders are commonly understood as brain disorders (Rose, 2019). Ultimately, mental health conditions are assumed to be understandable and explainable by investigating brain and neuronal structures. This is why psychiatric research focuses heavily on neuronal cells as objects of investigation. Such is also the case in most of the institute's research projects. As I mentioned earlier in this thesis, within an epigenetic approach towards human development early-life phases are framed as sensitive developmental windows (Waddington, 1942; Nagy & Turecki, 2012) – a postulation that is conceptualised as the "early-life paradigm". Hence, scientists assume that they will be able to deliver valuable insights about an individual's future mental health status by producing knowledge on *early* brain development. This is one of the crucial reasons that most of the cell experiments I have witnessed aim to model neuronal development in the foetal stages of life.

Given this reductionist approach, the scientists intentionally omit several elements that, in general, might also be crucial for an organism's development. First, they exclude the effects of stress on other

human cell types that, in an organism, are described as being intertwined processes (consider for instance blood cells that reach all organs and tissue). Second, they do not pay attention to metabolic changes resulting from stress experiences. Third, in focusing on early-life phases, the scientists preclude any temporal dimension that would account for the development of an organism *over the course of its lifetime,* how an organism comes into being along manifold interactions. The scientists' pragmatic reductionism therefore is predominantly directed at stabilising the components of their research projects by bounding their approach to one single cell type: neurones – and more specifically, neurones that are believed to model foetal brain structures. This is a way of making their bounded imaginary manageable.

From an STS perspective, this performance of reductionism is interesting to investigate, as biology and psychiatry in general conceptualise stress as a phenomenon that affects the *entire* body. The body responds physiologically to stress by releasing different hormones that initiate various bodily functions, such as an increased heart rate and breathing frequency, or dilation of the pupils. Hence, by reducing their research approach to a single cell type, scientists isolate the stress response from the corporeality within which it takes place (Beck & Niewöhner, 2006). Yet, what is happening with different "degrees" of outside? In other words: cells have other cells around them; then, we reach the level of the organ; then comes the organism; and finally we arrive at the actual environment in the sense of matter surrounding that organism. So, what does a cell without a body mean?

Second, the experience of social adversity is narrowed down to one pharmacological substance in all of the experiments: dexamethasone. Using dexamethasone allows the scientists to operationalise and access a complex social phenomenon in the laboratory. It is a way to access social adversity by means of the materials and logics of modern biology. In this context, scientists are interested in the potential effects that experiencing stress can have on the cellular level. More specifically, they aim to investigate the effects of the cell's stress response on the epigenetic level with the aim of making claims about the human organism as a whole. As the researchers clearly state themselves, they cannot offer a neurone an equivalent for social stress. They therefore use dexamethasone as a pharmacological proxy. The suitability of dexamethasone as a model for (social) stress is grounded in its chemical properties, which are similar to glucocorticoids – molecules important to an organism's stress response. Thus, dexamethasone is applied to induce a cellular stress-response in *in vitro* models of early brain development.

This series of reductions is one integral method and practice in cell culture research, used to understand the causal relationship between stress exposures and their epigenetic effects on the cellular level. This is an important achievement as, in research on human cells as in other biomedical fields, establishing causality is still one of the major challenges of epigenetic research:

> In humans, through our genetics, gene expression, and epigenetics studies, we can find things that are associated with certain changes in brain reactivity, psychophysiology, symptoms and maybe we can better characterise these patients. And then of course we want to understand: ok, now is this just an association, or is there a causal link? – and of course, we may be able to find the causal link … in the cell model. (Stella, pos. 23)

Despite the pragmatic background of this disentanglement, the reductionist approach also canalises the way complex social phenomena, such as experience, can be understood: experiencing stress is bound to applying dexamethasone as a message to the cell to initiate gene-transcription processes, epigenetic changes included. That means, "social interactions and material cultures are increasingly understood as biologically consequent environmental signals" (Landecker, 2016, p. 79). From a historic point of view, conceptualising experience (which is a specific form of environment) as "signal" is part of a post-cybernetic vocabulary. This vocabulary alludes to "the vast technical and conceptual infrastructure of … transducers, receptors and signal cascades … . A cell-signalling infrastructure makes contemporary epigenetic relations between bodies and environments possible, shaping talk of detection, reaction, input and reception" (Landecker, 2016, p. 80). That means, within epigenetic cell culture research modelling foetal development, cells are regarded not only as reacting to external stimuli but as *processing* environmental information (dexamethasone/stress) to the epigenetic landscape. In this context, experiencing is no longer regarded as something active and as an interactional process between the experiencer and their environments, as articulated, for example, by philosopher John Dewey (1958). It is rather conceived of as a passive phenomenon, something that "happens" to the experiencer and that makes the recipient disappear. Within this perspective, environmental epigenetics is enacted as a biological connection between the inside and the outside of an organism, between the genome and the environment. More specifically, its function is regarded as mediating between exposure and its specific cellular effect:

> Well, I think... so we think of epigenetics as the link to the environment and so – you know – now, with the epigenetic mechanisms we understand more about how certain environmental things are leading to those and then for the epigenetic mechanisms we understand a bit about how they lead to other things happening in the cell and so... so they are kind of the... the bridge. Yea? So... so in that sense it's really helpful, because psychiatry is a lot of environment – you know – and that's why we have such heterogeneity. (Emma, pos. 43)

This interview excerpt vividly illustrates how epigenetic mechanisms in cell culture research are positioned as an interface between translating information into the molecular architecture of cells and ultimately into an organism as a whole. Even if the focus on environment seems very narrow here, different layers and scales of environment in which the stress response is coordinated can be found even in the cell model: the cell itself also serves as an environment to other processes, for instance, to chromatin structure.

Especially within the model organisms of foetal life, such as iPS cell systems, the foetus is framed as a mere recipient of its mother's experiences due to the conceptualisation of the womb as its first epigenetic environment:

> What I would like to contribute is really an understanding of stress during brain development, what... how – you know – what is that doing to the individual, what... what the individual becomes? And are there places where we can intervene? (Emma, pos. 63)

Reducing the complex relationship between environment and genomes in the logic of signal chains allows only certain notions of the womb and of the mother herself: the motherly womb is no longer understood as a protective space and the mother is turned into an intermediate figure, passing her own (stressful) experiences onto her unborn child (Kenney & Müller, 2017). Against this background, Emma's question of *where we can intervene* is indeed a salient inquiry. Such a reduced perspective on human experience runs the risk of either favouring interventions that target epigenetic changes as an easy fix and disregard approaches that would problematise structural conditions as possible pathogens, or it might make, and has historically already made, only certain groups of people accountable for the health of future generations, leading to a gendered responsibility in society (Richardson, 2015; Kenney & Müller, 2017).

6.2.2 Practices of reduction in research with animal model organisms

Rodents, such as mice, are yet another group of model organisms that play a crucial role in basic research. They are regarded, in psychiatry in particular, as a valuable model because they give scientists access to the brain in a living organism. Modern life science has developed various strategies for manipulating rodents, ranging from genetic modifications through dietary changes to psychological hardship. Besides, scientists can draw on a plethora of different rodent testing arrangements, such as the open field test or the behavioural despair test. In the experimental arrangements with mice that I witnessed, I could observe how the scientists' approaches differed in the degree of reductionism they incorporated: some experiments implied a rather reduced perspective (such as the chronic social defeat set-up) while others allowed a specific openness (such as the social box-paradigm, see Ch. 4.3).

The most obvious strategy of reductionism in research with mice is their genetic homogeneity. All laboratory mice that are used in a project have the same genetic background, they are all inbred. Based on this genetic homogeneity, scientists assume that all of the mice they use, like monozygotic twins, are, at least theoretically, biologically uniform. Scientists assume that, in the same environment, they will develop in genetically and epigenetically identical ways. Therefore, the scientists postulate that a change in behaviour and/or a change in neuronal structures can be related to the stress they have re-enacted in the experiment. Finally, the mice's genetic homogeneity warrants a sufficient level of comparison for the validity of the experiment by excluding any form of genetic variability and heterogeneity, which is an essential feature of living organisms outside the laboratory.

To say that the scientists apply certain strategies of reductionism does not mean that their models and their methodologies are equally reduced. In contrast, as I have shown in my first empirical chapter, scientists work with rodents that are genetically manipulated in various ways, ranging from the knock-out of specific genes to rodents with a specific phenotype, for instance one that leads to a low metabolism. Therefore, mice that are used in the laboratory context are highly different from wild-type mice, a difference that makes them "a crucial part of the machinery of contemporary biomedicine" (Nelson 2018, p. 2). In addition, experiments with mice are characterised by a high degree of complexity. This complexity is visible for instance in very sophisticated experimental set-ups that recently even test mice in a non-isolated format in groups with other laboratory mice; it is also visible in the model organism, the mouse itself. Compared to cells, mice allow the researchers to investigate stress responses on very different levels: in their blood, in their metabolism, in their adrenal glands, in their brains. Given this context, mice experiments carry much more ecological validity than cell models.

Despite or perhaps because of this complexity, stress in a series of mouse experiments is re-enacted in a rather reduced form: scientists sometimes narrow it down to the pharmaceutical dexamethasone. Depending on the research question, scientists apply different strategies to administer dexamethasone to mice, such as orally via their drinking water or intraperitoneally via an injection into the body cavity. This is, again, a pharmacological manipulation with the aim of releasing a stress response in the mouse. One important reason for scientists to use dexamethasone is based on a pragmatic decision: as it is an artificial chemical substance that is applied by the scientists themselves they can control the duration of the stress response in the mouse by adjusting the dexamethasone concentration. Longer durations release a different stress response from shorter durations. In any case, modelling stress pharmacologically narrows down the stress experience to its purely molecular components. Following this logic, the scientists aim to produce a status in the mouse that simulates human depression or anxiety on a molecular level.

Within stress testing arrangements that use physical or "psychosocial" manipulation, such as the restrainer or the chronic social defeat set-up, we can observe another level of reductionism that seemingly allows some degree of complexity and openness. The significance of the chronic social defeat experiment is the relative absence of the scientist. Stress is enacted by letting two mice fight – the only intervention that the researcher directly carries out is putting the mice together in a cage and observing the defeat. This means that, while the researcher can control the duration of the defeat, the manner in which the defeat is performed is not subject to their control. In such classical and established stress test arrangements, scientific reductionism is performed by focusing on specific sections of a mouse's life which are placed at the centre of scientific investigation. Most often, this is the time shortly before and after the stress exposure, when the mouse's behaviour is observed and when it is ultimately sacrificed so that scientists can access its brain. From a more holistic perspective, we can

ask how meaningful such snapshots of a mouse's life are. How does the mouse behave when scientists are not looking? Or what potentially stressful experiences does the mouse have in the absence of the researcher?

Strategies of reducing complexity in animal research allow researchers to operationalise and model human mental health in the laboratory. By a series of reductions, some of which I have summed up above, researchers aim to enact epigenetics as a specific form of mouse behaviour. They relate a behavioural change to a molecular change. Stress is then assumed to be reflected in a specific mouse phenotype, driven by epigenetic changes such as histone modifications. A phenotype that for instance leads to neglect of grooming or social avoidance, as the neuroscientist Nadja described in the interview: "Sometimes they [the defeated mice] neglect their grooming and they also change their social behaviour: the stressed mice are not up for social contact any more. Things, that you somehow can observe in humans [with depression] as well" (Nadja, pos. 50). As the scientists assume that they can see such behavioural changes in the molecular profile (interview Nadja) environmental epigenetics is enacted as something observable from the mice's movements and performances. The basic scientific idea in this context is: acute or chronic stress experiences, either induced by pharmacological substances or physical interventions, lead to molecular changes in the brain that result in a change in behaviour. This is a rationality that translates a great deal of power over behaviour to biology and that localises states presumed to model mental health conditions in legible organismic structures.

6.2.3 Practices of reduction in research with human tissue

In comparison to the research approaches with cells and rodents, the practices of reductionism within research using human tissue are very different. This is mainly due to the specificity of this research approach itself. It is an approach in which scientists predominantly do not work with model organisms but try to access the human body and the human brain itself. The latter, apart from imaging technologies, is only possible in the dead organism. This means that scientists in this context do not simulate a specific disease or human development by means of cells or mice, but rather invite humans, as the object of their investigation, into the laboratory.

This research approach entails a maximum degree of complexity. In contrast to cells or mice, when humans participate in cohort studies by donating tissue (such as saliva or blood) or participating in medical examinations they only are present in the laboratory during the time of data collection and analysis. Nothing that happens before the assessment can be controlled by the scientists. They for instance cannot control whether their study participants smoke cigarettes nor can scientists influence what participants may have eaten before donating blood. Although they can ask study participants about their childhood experiences, they cannot rule out with certainty that they have had experiences

that they may have repressed. To repeat: in contrast to mice that spend their whole live in the laboratory, humans come to the laboratory only for a very limited period of time.

Hence, in research with humans, the application of reductionism as a primarily epistemic perspective is quite different from animal research, as there are many aspects scientists cannot reduce or stabilise. As a scientific practice, reductionism is for many scientists a strategy employed to establish a certain causality between stress exposure and stress response. Therefore, research with humans is described as "un-purified" or "unclean" in contrast to a mouse model, which is

> very clean [as] you can tell exactly what kind of stress it had. And so you can... if you now compare a mouse that had chronic stress with a mouse that had acute stress and a mouse that had no stress at all and you see drastic changes in the blood, in the brain and so forth, then you can say with certainty that it is due to this stressor. … In the mouse it is simple, very simple, in humans it is very difficult". (Judith, pos. 123)

That is to say, what scientists can measure in mice, they can only approximate in humans. In the following section, I will therefore delineate how they attempt to apply reductionism as a means of assembling boundaries around human tissue as their objects of investigation.

As I have shown in my first empirical chapter, scientists at the institute conduct epigenetic research with humans within clinical and cohort studies. In such studies, scientists analyse human tissue and bodily functions, such as blood, saliva, metabolic changes or, rather rarely, post-mortem brain tissue. As I have outlined, the search for biomarkers to identify psychiatric disorders with the goal of establishing a new taxonomy is the institute's core scientific study, the RC-study.[68] In the RC-study, scientists compare patients who suffer from stress-related disorders with healthy individuals. Within this research endeavour, scientists literally "invite" psychiatric patients and healthy subjects to the institute.[69] Here the assumed molecular and epigenetic differences of sick and healthy people are central experimental elements.

In the institute's cohort studies, the situation is somewhat different. These studies are always conducted in collaboration with other laboratories and scientists from different disciplines; in most cases the institute is responsible for the epigenetic analyses. Data is not collected in the institute itself, but the scientists to some extent "follow" their object of investigation, which is the experience of social

[68] The institute conducts several other cohort and clinical studies that I did not witness. They, for instance, investigate the biological efficacy of psychotherapy or psycho- and pharmacotherapeutic treatment in individual patients.

[69] The institute recruits possible study participants through information on its website as well as information sheets distributed among psychological practices.

adversity or different forms of trauma, such as systematic persecution or childhood abuse.[70] In both studies, scientists also perform practices of reductionism to access their research object. As we will see, in contrast to cell or animal models, research with humans allows for much less of such practices and the scientists have to accept much more "messiness" in their research projects in order to conduct epigenetic research at all.

First, the circle of possible study participants in cohort studies is usually bound to specific pathophysiological preconditions. Therefore, scientists formulate distinct criteria of inclusion and exclusion. In the biomarker study for instance, only humans with specific clinical phenotypes are considered appropriate test subjects: besides healthy test persons as controls, only patients with stress-related disorders, such as depression or trauma-associated syndromes, are included. However, patients who suffer from severe neurological or internal disorders are explicitly excluded. The reason for this strict focus on functional mental health conditions (in contrast to organic and neurodegenerative disorders) is the scientists' attempt to reduce as many confounding factors as possible, as it is methodologically challenging to disentangle what scientists find in the blood of the test subjects. For example, an increased glucose level can result from both sugar metabolism disorders and trauma. Factors, scientists define as "covariates". Hence, scientists attempt to research stress-related disorders in as "pure" a form as possible. In clinical practice, this is a major challenge given that many psychiatric patients suffer from comorbidities. Somatic diseases such as cardiovascular disorders or diabetes frequently accompany mental health conditions.

In this context, one cohort study conducted by some of the institute's scientists can be regarded as a rather radical and at the same time bizarre approach: the physician Judith and her colleagues sample soldiers as a study cohort. According to Judith, soldiers are a group of people with a "defined trauma", a "collective that can be researched well" (Judith, pos. 109). This good "researchability" is attributed to the fact that soldiers are often young, male, and healthy and do not suffer from high blood pressure, diabetes or other somatic diseases – health conditions that are framed as confounding factors. In addition, as they are sent to the same war zone, they also experience comparable traumatic events. In the scientists' perspective, this represents an additional level of comparison. Based on these strategies to reduce as much disturbing context as possible, Judith and her colleagues examine the soldiers before and after their military intervention to investigate the molecular underpinnings that in some

[70] In both research arrangements, it is not the methodology that is different, but the starting point and the experimental basis of the study and the way in which the study participants are considered. In the RC-study on biomarkers, researchers focus on specific, stress-related disorders, such as depression. This means that the cohort is sampled along the pathologies of patients; the stress-related mental disorder is the study's experimental basis. In the cohort study in contrast, we can observe a distinct focus on the stress event(s) and trauma. Here, the cohort is sampled along groups of people who have undergone the same or similar biographical events: survivors of atrocties, soldiers, or a minority urban population living in a highly dangerous neighbourhood.

traumatised soldiers lead to a PTSD and in others not. The scientific goal is to find epigenetic marks that can be used to predict who has a molecularly based increased risk of developing trauma-related diseases and therefore to find vantage points that lead to the prevention of mental suffering.

A second practice of reductionism in this strand of research is the focus on specific genes, molecules or molecular mechanisms as objects of investigation. In much of their research, neuroscientist Stella and biologist Valentin for example predominately target the TRBP gene. This gene in particular is described as an important player for human stress-related disorders, such as trauma or depression, as it regulates individual responses to stress. Stella works with different (partly multiple) traumatised cohorts, almost always focusing her epistemic gaze exclusively on the TRBP gene: people who experienced childhood abuse, who have witnessed a murder or have been raped. By following this gene through different groups of traumatised people, Stella is pursuing the goal of finding causal links between variants of that gene, epigenetic changes in this gene and the traumatic event. These are links believed to provide molecular insights into individual disease risk trajectories that follow a stress exposure. The idea is to identify individuals with a specifically higher risk of developing a mental disorder in order to find out who would benefit most from interventions, both from a therapeutic and an economic point of view. Other molecules or genes are intentionally omitted.

Again, in general scientists allow for, or rather have to accept, much more "messiness" within clinical research than in the other approaches. Here, they are confronted with the complexities of every individual's life, with the possible non-compliance of study participants, and with the genetic variability of humans, all of which are factors much easier to control in cell or animal models. This is also reflected in how environmental epigenetics is enacted here: in every research project that I have witnessed, it was articulated as a significant though not unique piece of information; clinical researchers never rely exclusively on epigenetic data. They always collect other biological and physiological data as well, which is then arranged with the epigenetic data: behavioural and psychophysiological measurements, biographical data in form of interviews, or the results from brain-imaging technologies. In this context, environmental epigenetics is enacted as a missing piece of an aetiological puzzle, more precisely as a missing *molecular* bit of information that is needed to respond to the crisis that psychiatry currently faces. Many psychiatrists experience this crisis as making them "helpless" due to the fact that they currently do not know exactly why some people develop a mental disorder while others do not. However, to date, scientists do not yet know the distinct role epigenetic data may play within these assemblages of knowledge, as epigenetic research in humans still is in its infancy and clinical applicability lies in the distant future. What scientists currently hope is to be able to develop a more precise understanding and classification of mental disorders on the basis of epigenetic knowledge and vocabulary – a novel taxonomy that is anticipated to guide treatment better than current classification systems.

Interim summary: different apparatuses of knowledge production engender different epigenetic configurations

In the previous part of this discussion, I have shown that scientists at the institute produce epigenetic knowledge through multiple steps of reduction. These reductions lead to different enactments of epigenetics according to the different research approaches in question. Given this context, I would like to emphasise that these different enactments are not bound exclusively to one single research approach. Instead we can observe several overlaps of how environmental epigenetics takes on meaning. Yet, in my empirical chapters, it becomes very impressively clear that the choice of the research approach and arrangement (cells, mice, or humans) makes a specific meaning of epigenetics particularly relevant – more so than in the other research arrangements. Drawing on feminist theorist Karen Barad (2007), I interpret these different research arrangements as apparatuses of knowledge production which allow certain enactments through their specific material arrangements.

As I have shown, through research with neuronal cells as models that represent early brain development, environmental epigenetics is enacted as a new connection between cells and their environments, which also materialises on a new semantic level: through advances in research with cell models, epigenetics has become a new way of speaking about environmental factors, which gives the researchers a scientific language and method to talk and study environmental experiences and their effects on cells and bodies. Moreover, it is a way of connecting these environmental factors to biochemical responses and changes in (neuronal) cells that could not be materialised before. In that sense, cells can be interpreted as material-semiotic actors (Haraway, 1992) which allow new scientific statements about how stress is *processed* on the cell level, namely through epigenetic changes.

In contrast, the material arrangements in animal models primarily enable a different configuration of epigenetics. In fact, the chemical reactions to stress are also measured here; but these changes are almost always placed at the beginning of behavioural changes: epigenetic changes are presumed to alter phenotypes and thereby behaviour. This means that only the animal model allows for the establishment of a causal relationship between exposure, measurable molecular change and observable change in behaviour, because the stress response here takes place in a corporeality that cell models cannot provide. Ultimately, environmental epigenetics is enacted as a phenotypic change observable in the behaviour of the tested mice. Additionally, research arrangements in animal models work with adult organisms and do not prioritise early-life phases. This research perspective emphasises the plasticity of the adult organism, focusing on the effects that epigenetic changes caused by acute or chronic stress can have on the brain and the organism itself throughout development.

Research arrangements with human tissue are apparatuses of knowledge production in which the epigenetic configurations of other research approaches seemingly accumulate. On the one hand, researchers direct their scientific attention towards cells and for instance analyse DNA methylation

patterns in blood. To some extent, therefore, we also can observe an epigenetic enactment that focuses on the cellular representation of stress experience. On the other hand, researchers study how these cellular changes through stress materialises in phenotypes, such as depression or PTSD, and therefore mediate behaviour. In addition, we can observe another enactment through with epigenetics takes on meaning and that is bound to the specific research arrangement itself – or more precisely to its limitation: in clinical research, epigenetics is always enacted as one piece of molecular information believed to be necessary to a full and more profound understanding of mental health conditions. It is described as a *crucial* layer of information, yet not one that can be taken alone. Researchers therefore always have to integrate results from behavioural observations or metabolic examinations as well. But even this is not always considered to be completely sufficient, because – and here we come to the limitation of clinical research mentioned above – these measurements hardly establish causality, as the human brain is not accessible. Hence, scientists supplement measurements in human material with mouse and cell models where possible and useful. They jump back and forth between different research arrangements, test hypotheses, take up observations in humans and search for the molecular basis in the mouse, "tinkering" to make their research object – mental disorders – as tangible as possible. Here it also becomes clear how the various research arrangements (should) interlock and thus produce the most accurate picture possible of mental health conditions.

6.3 Un/intended environments: between re-enacting and neglecting stressful events

6.3.1 How indented and *unintended environments* come to matter in the epigenetic laboratory

In the epigenetic laboratory, re-enacting stress is an intended practice. As I have shown in detail in my empirical chapters, in all of the research approaches described the scientists either apply specific forms of stress or sample specific population groups as stressed cohorts. In cell model organisms, applying dexamethasone is the most prominent strategy for inducing a stress response in the cell. This is regarded as a pharmacological intervention. Scientists who conduct research in animals often draw on physical or psycho-social manipulations. Therefore, they for instance put mice into restrainers where they cannot move, or allow two mice to fight with each other in order to simulate the human experience of being subordinate (see Ch. 4.3).

In research with human tissue we can observe two different ways that stress becomes a technical instrument. First, in this research approach stress is also deliberately enacted by scientists. In the institute's biomarker study for instance, scientists intentionally induce stress by letting study participants perform calculations under a time pressure. Second, scientists draw on naturally occurring events that are supposed to have traumatising effects on individuals, such as experiencing abuse in

childhood or experiencing war. As I have shown in my empirical chapters, even if scientists do not actively re-enact stress in these approaches, they perform practices to operationalise such experiences as objects of investigation in their research – they harness biographical events as laboratory stressors with high ecological validity.

In all of these imaginations of scientific practice, *intended environments* are rendered as a central means to the production of epigenetic knowledge. In all research arrangements, stress is (re-)enacted or regarded as the core technical instrument to produce knowledge. It is thus supposed to activate epigenetic mechanisms considered important to elucidating the mechanisms by which mental disorders develop. As *intended* epigenetic environments, practices such as applying dexamethasone are always elements of the study protocol the research projects and experiments are based on. They are standardised and widely established laboratory methods and they are a result of a series of reductions. These practices of performing reductionism are always bound to the specific research arrangement. While research with cells or with mice allows scientists to engage in more practices that reduce context and therefore to narrow their focus on the object of investigation, in research with human material reductionism of environments is a much vaguer practice. This is the price of ecological validity, so to speak; scientists have to accept more context and more "messiness". By focusing on very specific, predefined epistemic elements and by acknowledging only certain forms of stress as epigenetic environment – namely those forms that are *intended* – they are creating specific epigenetic accounts. In creating these epigenetic accounts, on the other hand, they create a bounded imagination of their own scientific practices, their imaginations of how to conduct environmental epigenetic research.

However, I also witnessed a series of stressful events that were not listed in the research protocols and occurred unwittingly, without the scientists' deliberation. And still they contributed to the research outcome. This means that epigenetic research also is vulnerable to unintended and unplanned instances. As we will see below, these *unintended environments* can be interpreted as productive tensions. They reveal a divergence between theory and practice that draws attention to important questions of contemporary life science knowledge production: how can we conceptualise the contemporary, epigenetic laboratory? And what does it mean to conduct epigenetic research today? Before I address these questions, let me first briefly summarise how *unintended environments* come to matter in research with cells, mice, and human tissue.

Unintended environments are part of literally every research endeavour, though their effects may vary. In this context, *unintended environments* seem to be closely linked to the possible degree of reductionism and therefore to the complexity that is incorporated into the research approach itself: in research with cell model organisms, I did not often witness discussions around what I term *unintended environments*. They seem to be less present than in research with rodent organisms and human tissue. At

least at first sight. As I have shown in my second empirical chapter, research with cell model organisms just presents a different way in which *unintended environments* come to matter. They do exist, but as we will see in the next paragraphs their effects can be handled, or ignored, much more easily than in the other research approaches.

This is related, in the first place, to features of the model organism itself: cells are often rather easily reproducible. Cellular experiments that do not conform can therefore be easily dismissed. There seems to exist a specific mentality of "starting over again", a certain disposability. Of course, this does involve a specific amount of financial expenditure. However, the institute has such solid financial support that the director has even once "taken a loss of 5,000 euros with humour" due to a mistake made by one of her employees. Biologist Valentin also very calmly spoke to me about "mycoplasmas", small, independently reproducible bacteria that can contaminate the cells under investigation: "Either I have to throw the cells away or I can treat them" (fieldnotes, 16.4.17). As long as the institute is equipped with enough identical samples, the experiment can easily be repeated.

Second, research approaches within cell model organisms usually do not imply any ethical conflicts and do not therefore have to be approved by an ethical commission. This distinguishes them very clearly from research with animals and humans in which every single research project needs ethics approval. These are negotiation processes that can sometimes take several years. In sum, research with cells models seems to need less degrees of investment.

Third, the fact that *unintended environments* are not very openly discussed within cell culture research is also related to the very specificities of the research institute. Due to a very well-funded financial structure, as the neuroscientist Zoe told me, the institute can follow a "positive results only" approach: only positive results that support the initial arguments are disseminated. Negative data, that might not be considered as proper results as they do not verify the researchers' initial hypotheses, however, are discarded and scientists move on to another project. This does not mean that the institute upholds a policy of data manipulation, but that the institute can afford to publish only those results for which a high reputation can be expected. This is a specific publication culture that focuses on "positive", rather clear results that we can observe to a certain extent in many molecular biology laboratories (see also Niewöhner, 2011). As a result, when *unintended environments*, such as unanticipated changes in room temperature, impinge on the research project, the scientists can in theory repeat the experiment and thereby balance out the unintended effects (given that they have enough time) without publishing their "negative" result and without contextualising the result to decipher its significance (interview Zoe). This is a focus on positive results that Zoe calls the "file drawer effect": "a lot of people will have negative results, that they just put in the drawer and never look at again. ... They just ignore the negative results" (Zoe, 34). As the effects of *unintended environments* within cell research approaches

are rather easy to manage, they were rarely elements of the laboratory discourse and were only rarely discussed.

In research with rodents, however, the construction site and some – not all – other *unintended environments* were often a topic of conversation. In this context, the construction site impinged on everyday laboratory practices, and thereby also on the specific practices of scientific reductionism, in different ways. First, the scientists' own practices were directly affected by vibrations arising from the construction work. Routine practices such as injecting substances into mouse brains turned into tasks requiring the highest degree of tact and sensitivity. Second, the inconvenient side-effects of the construction work also had effects on the research subjects, the mice. These were put under continuous stress, especially when taking into consideration that rodents are nocturnal creatures that normally sleep during the day when work is done on the construction site. A shift in the basic constitution of the mice can be considered as the most severe consequence of this: they were, as neurobiologist Julie stated, "baseline stressed". As I show in detail in my second empirical chapter, there are various other *unintended environments* that, while they are existing elements of research, are not acknowledged as objects of the experiment: the 16 kilometre long transport of the mice to the laboratory, the painting of the mice under anaesthesia, or unexpected events within an research arrangement, such as when a mouse unexpectedly got stuck in the experimental set-up.

Here I ask: why are these cases of potential stress not adequately discussed? By adequately, providing a basis for really reflecting on and negotiating their effects and the signals scientists ultimately measure – both in the laboratory and in their publications. At the end of my second chapter I discuss how the scientists reacted to those of my questions that targeted these issues of negotiation between "valid stressor" and "unacknowledged stressor". Most often, my informants replied that in many experiments they had "unstressed controls" as a level of comparison. These are used with the aim of controlling and containing the effects of *unintended environments*. Having unstressed controls is an established laboratory practice. Though, as my analysis reveals, by using unstressed controls scientists still do not or cannot be attentive to all *unintended environments*. For instance, when a mouse that is deployed as an unstressed control gets stuck in the experimental set-up can it still function as such? Or has, as Landecker (2013) puts it, the control become the experiment? How can we understand "unstressed controls" in the presence of environmental epigenetics, an approach that postulates a maximum plasticity of bodies to their socio-material environments? Against the background of the assumption that the handling of rodents can have measurable effects on the methylome in their brains, how can scientists ensure that the control objects have grown up under exactly the same conditions as the intentionally stressed animals?

Furthermore, I critically investigate the rationalities of how administrative authorities regulate the use of stressors in animal research. In that context, my analysis reveals that only some and not all possible

events are conceptualised as stress exposures. The *Animal Welfare Laboratory Regulation* has released a list assessing the potential effects of stress testing arrangements and laboratory practices based on their expected stress level for the mice. This means that there are official regulations that categorise different stress exposures according to their severity. However, these regulations only record stress as a distinctive laboratory practice and neglect stress experiences that arise form real-world phenomena or from epistemic by-products, such as the individual housing and handling of animals (Nelson, 2018). In this sense, painting mice for experimental purposes, for instance, is listed as a mild stressor, but a noisy building site remains unrecorded.

In research with human tissue, the existence of *unintended environments* gets even more complex. Here, individual lifestyles and experiences emerge as known unknowns: the researchers *know* that their test subjects' experiences and behaviours influence the study results. The range of (acknowledged) *unintended environments* is conceivably huge: smoking or drinking coffee before examinations, genetic variability, or biographies with many different traumatic experiences are phenomena known to affect genetic and epigenetic measurements. However, it is not possible to record all of these *unintended environments* and unlike experiments with cells or mice, the lives of individuals participating in the studies cannot be controlled in a similar way. Against this background, scientists attempt to collect as many live events as possible, an endeavour that is however only regarded as approximation as sometimes people cannot remember traumatic experiences, something the DSM-V even considers a symptom of PTSD (APA, 2013). Therefore, in research with human tissue, scientists are confronted with a maximum of complexity and heterogeneity and a minimum of environments that are intended.

As pointed out at the end of my second empirical chapter, the scientists do have methods and practices directed at containing unintended effects, managing complexity and taming the messiness. What I also show, however, is that the (epigenetic) scientific community to some extent is not (yet) fully prepared for a critical reflection on and discussion of these scientific inevitabilities; the risk of those papers not being accepted is still considered to be too high and the current publishing ethos often does not provide enough space for a thorough discussion of the actual socio-material experimental conditions of the presented results. In what follows, I wish to suggest possible ways of productively reflecting on these issues and challenges. By drawing on my empirical data and my analysis of *un/intended environments*, I would like to propose vantage points for engaging with questions that refer to laboratories as specific spaces of knowledge production and their significance to the currently increasing impact of epigenetic research approaches. My aim is to respond to conditions and challenges of contemporary scientific knowledge production by suggesting ways of discussing the effects of *unintended environments* as constructive entities instead of as elements that should rigorously be excluded from scientific scrutiny and discussion. I suggest that they not be considered as waste but as valuable data. To this

end, I will put these key results into dialogue with discourses on scientific responsibility and accountability within the feminist STS literature.

6.3.2 How can *unintended environments* turn into vantage points for discussion? Two suggestions

6.3.2.1 Extending the scientific gaze: working beyond the divide between the laboratory and its environments

What is a laboratory? This simple question is surprisingly difficult to answer. Yet, how we conceptualise laboratories also has effects on how we can interpret and evaluate the role of contemporary knowledge production for science and society. These important questions are focal analytical points of laboratory studies within STS that started to emerge in the 1970's (see Ch. 3.1). These studies not only emphasise that scientific practices are situated and embedded within local and cultural circumstances but also deconstructed the assumption that knowledge "from the lab was apolitically, asocially, transtemporally, translocally true" (Doing, 2008, p. 279). I would like to take these analytical points one step further and suggest that even the very site-specific situatedness – the socio-material environment the laboratory is embedded in – contributes to scientific specificities bound to the laboratory itself. Not every laboratory necessarily has its construction site, but every laboratory and its scientific members are entangled with the environmental factors outside of the laboratory's walls. It is exactly this entanglement that scientists attempt to deconstruct, to dis-entangle, by applying their specific strategies of pragmatic reductionism. The scientific laboratory can therefore be understood as a condensation of social and material phenomena with the aim of purifying them from their complexity and investigating them as isolated from one another, reconfiguring their components in a novel logic (Knorr Cetina, 1999). In this vein, sociologist Knorr Cetina regards laboratories as spaces that "allow natural processes to be 'brought home' and to be made subject only to the conditions of the local social order" (Knorr Cetina, 1999, p. 28).

My project to some extent challenges this conceptualisation of laboratories as powerful institutions eager for "taming" natural processes for the sake of scientific claims making. As I have shown, the scientists' practices of working with extracts and the purified versions of natural objects sometimes remains a fiction. Scientists who work with environmental epigenetic research approaches apply specific practices to keep this imagination alive. They build research arrangements that explicitly target the accessibility of social phenomena in and with methods bound to the laboratory. As Knorr Cetina writes,

> there are at least three features of natural objects a laboratory science does not have to accommodate: first, it does not need to put up with an object *as it is*, it can substitute transformed and partial versions. Second, it does not need to accommodate the natural object *where it is*, anchored in a natural environment; laboratory sciences bring objects "home" and manipulate them on their own

> terms, in the laboratory. Third, a laboratory science need not accommodate an event *when it happens*; it can dispense with natural cycles of occurrence and make events happen frequently enough for continuous study. ... [I]t should be clear that not having to confront objects within their natural orders is epistemically advantageous for the pursuit of science; laboratory practice entails the detachment of objects from their natural environment and their installation in a new phenomenal field defined by social agents. (Knorr Cetina, 1999, p. 27)

In that sense, the biological laboratory is well-equipped with techniques for manipulating cells, genetically altering mice or inducing stress in humans to accommodate stress-related mental disorders as objects of investigation within its rational framework.

What my analysis has also shown, however, are the limitations and conditions of these research practices, which visualise the particular circumstances and effects of the research *environment*. For geneticists, environment is rather a confounding factor, for epigeneticists it is *the* research focus. Not only is it the object of epigenetic investigation, it is an actor that engages with the experiment in an often-unforeseen way. My research therefore reveals the need to rethink the boundaries of experiments and laboratories. Environmental epigenetics essentially proposes that bodies are sensitive to their environments. They are plastic and porous, they can be affected by experience and exposure on a measurable molecular level. But, as the construction site reveals, laboratories cannot completely be closed off either. The sensitivity of bodies to their surroundings might also be indicative of the sensitivity of laboratories to their surroundings. Resulting from this, the scientific gaze should perhaps not only focus on what happens *inside* the laboratory. In the light of my observations, expanding the perspective to also include what happens *outside of* or *in front of* the laboratory could be advantageous for the progress of scientific claims. Therefore, I suggest not only that close attention continue to be paid to what happens in the laboratory but also that it not be forgotten that the laboratory itself is embedded in a very concrete world, in a specific time and place – that scientific knowledge not only enriches and informs sociality, but that sociality may also enrich and inform scientific knowledge. As Fleck already stated in 1935, scientific practices are *social* processes.

Such a perspective could acknowledge the construction site as a potential *real-world* model of stress. In this sense it serves as a model for environments under *real-world* conditions, or as a test site worth being taken into account to at least some extent – not necessarily exclusively in terms of design, but above all in the way research practices and the actual (environmental) conditions of epigenetic research are discussed. Bearing this in mind, I would like to recall briefly two basic principles of the biological laboratory. First, every laboratory strives to maintain a maximum level of control – this is the aim of the researchers' pragmatic reductionism. And a maximum level of control is also achieved by excluding and ignoring such aspects as a noisy building site, because their disorder, if taken in to account, would have to be acknowledged as destroying the order of the laboratory.

On the other hand, the aspect of ecological validity also plays a role: how generalisable are the results of maximally reduced or controlled experiments? This means, what can the simulated stress-phenomena in the laboratory say about actual stress-phenomena? What can the laboratory stress-experiment that excludes elements like the construction site say about human stress experiences that are entangled with manifold other environments (Ingold, 2000)? In other words, ecological validity refers to the question of "whether or not one can generalize from observed behavior in the laboratory to natural behavior in the world" (Schmuckler, 2001, p. 419). In general, experiments that are "closer" to real phenomena are characterised by a higher ecological validity. Experimental research is therefore always dependent on weighing ecological validity (the generalisability of results) and control (as a basic principle of the molecular biology laboratory, as opposed to field research in ethology, for example). The experimental design is a trade-off between maintaining scientific control and simulating real-world phenomena in such a way that it is as "true to nature" as possible. How ecologically valid can research results be that are based on customising objects of investigation (Knorr Cetina, 1999) to whatever extent necessary so that they "fit" the social order of the laboratory?

The second basic principle of biological experimenting is the notion of replication and repetition, which I have addressed in an earlier chapter (Ch. 5.3). Research results are considered valid if they can be confirmed by other laboratories. The more often a phenomenon can be described in a similar way, the more reliable the scientific knowledge about it is considered. It is therefore less a matter of finding generally applicable laws, but rather of providing precise descriptions of individual cases. These descriptions are based on re-narrating the nature of the experimental setting, explaining the exact scientific procedure and recording all elements involved into the experiment (ranging from the material used to the analytical strategies applied). However, what does not currently have a place on this list are the actual socio-material conditions of the epigenetic experiment. Aspects that could possibly act as additional stressors, such as the construction site subjecting mice to a continuous baseline level of stress, are excluded from these descriptions. This begs the question, on what basis are the experiments actually replicated, then? Of course, a construction site cannot be replicated, but how can we evaluate the results of research that repeats experiments which cannot actually be exact replications?

Against this background, I would like to suggest that ways be found to discuss and reflect on these elements of scientific work – but not in the sense that epigeneticists should completely abandon their scientific control. Rather, particularly with regard to environmental epigenetics, it seems essential to think about how environment is modelled in the laboratory and with what consequences, where the scientific gaze falls and where it draws artificial boundaries around objects, disentangles them from their actual environments and what effects this might bring along. Then, instead of resignedly stating that the institute's mice are "baseline stressed" (fieldnotes, 26.1.18), the scientists could or should pay attention to this (or these) shifting feature(s) of their research subjects. After all, the construction site

and other *unintended environments* do exist and have real consequences for research, whether the researchers ignore them or pay attention to them.

Crucially, expanding the scientific gaze beyond the laboratory walls – to conceptualise the laboratory as embedded into a socio-material environment – would allow researchers to pay attention to the fact that what is included in or excluded from the apparatus of knowledge production is a deliberate decision, an active demarcation, an agential cut (Barad, 2007). Such an interpretation takes into account that the scientists' agential cuts not only represent an independent reality but that phenomena only become relevant through the specific material (re)configurations of the world. As mentioned earlier, I interpret the three research arrangements I have witnessed (cells, mice, humans) in the Baradian sense as apparatuses of knowledge production in which epigenetics is enacted differently in each case. Environmental epigenetics as a phenomenon is realised through the decisions of the researchers, through their agential cuts. As these agential cuts are socio-political practices (Barad, 1999 drawing on Foucault, 1980) we should reflect on what makes up the apparatus. Where does the apparatus "end" (Barad, 1999, p. 6)? Explicitly accounting for the practices that enact a specific cut and for "what is excluded from mattering" (Barad, 2007, p. 178) would require an extended equipment list or a Material & Methods-section that can represent the research process in such a way that it is made reproducible and/or truly comprehensible for other researchers and laboratories.

This would include, for instance, a discussion of the construction site as an element of the apparatus of knowledge production, as an environmental aspect that was part of the experimental set-up. It would also include a taking into account of the scientists' very individual research practices, their very individual ways of approaching and taking care of their objects of investigation[71] – a recognition of their bodies as constitutive elements materialising in their research results. In this spirit, Barad shows us how the researchers' habits can influence the research process. She uses the example of an experiment on space quantisation that worked for one researcher (Walther Gerlach) and not for another (Otto Stern). The reason was the different composition of their breath. Both smoked cigars, but not the same cigars as their salaries were different. Stern's cheap cigars contained more pollutants, including sulphur which interacted with the silver film in the experimental set-up on which the signal was located. This did not happen in Gerlach's experiment because of his less sulphuric breath (Barad, 2007, pp. 161ff.). It would therefore be fallacious

> [to] tak[e] for granted that the outside boundary of the apparatus ends at some "obvious" (visual) terminus, or that the boundary circumscribes only that set of items we learn to list under "equipment" in laboratory exercises in science classes, trusting our classical intuition, our training, and everyday experience to immediately grasp the "apparatus" in its entirety, makes one susceptible to illusions made of preconceptions, including "the obvious" and "the visible," thereby diverting at-

[71] In that context, Nelson (2013, 2018) shows that in genetic research the technicians' handling can also possibly alter anxiety levels in mice.

> tention from the reality of the role played by smoke and mirrors (or at least smoke, glass, and silver atoms), where the "smoke screen" itself is a significant part of the apparatus. (Barad, 2007, p. 165)

Thus, acknowledging *unintended environments* as elements of the scientists' material-discursive practices that contribute to establishing environmental epigenetics as a phenomenon would also emphasise apparatuses as a "dynamic set of open-ended practices, iteratively refined and reconfigured" (Barad, 2007, p. 167) and rule out the fiction that they are static experimental set-ups.

6.3.2.2 Data vs. noise? Negotiating objects of investigation

Identifying data from noise is one basic technical challenge within environmental epigenetic approaches and biological research in general. Much of this practice is characterised by managing epistemic uncertainties and negotiating and deciding upon what can be counted as a valuable research result. Within these processes, epigenetics is a special case as here, data and noise have the same character: environmental factors and "stress", respectively. Acknowledging the construction site as data or at least part of the experiment instead of as a disruptive factor would imply taking into account all of the other *unintended environments* as part of the experiment as well. From a social science perspective, it is productive to bring into question why some forms of stress within epigenetic research are treated as technical tools or even as epistemic objects[72] providing valuable data while other, unintended forms of stress are discarded as noise and epistemic waste. This question is anchored in concrete research practices I have observed in the institute: the scientists intentionally induce stress in mice by for instance putting them into a restrainer, but leave the transport of the mice to the institute literally undiscussed.

In this context, I argue that *unintended environments* are highly political phenomena that remind us how the epistemic, ontological, and ethical are always intertwined (Barad, 2007). Especially with regard to environmental epigenetic research, I suggest that it would be productive to reconsider the practices of negotiating between objects of investigation and noise, the drawing of boundaries between *intended* and *unintended environments*. I interpret these *un/intended environments* as part of doing reality: they turn environmental factors, such as childhood abuse, into objects of scientific investigation. In that vein, *un/intended environments* mobilise certain research constellations in which relations are assembled in a specific way and objects, subjects, and locations are ordered. Thus, *unintended environments* emphasise performativity. In that sense, *unintended environments* are only meaningful as part of a practice; they are not pre-given but have to be actively acknowledged as an element of scientific knowledge production, they have to be re-enacted as such, for instance as stress-exposure

[72] In his book *Toward a History of Epistemic Things*, Rheinberger (1997) discusses how the two structures of epistemic things and technical objects are interwined and are often difficult to distinguish. Epistemic things can also become technical objects.

within the chronic social defeat. Only then will they get funded as epistemic objects of scientific practices.

Revisiting *un/intended environments* or noise/data from this perspective reveals that these phenomena are part of "ontological politics." As Annemarie Mol (1999) writes,

> the reality we live with is one performed in a variety of practices. The radical consequence of this is that reality itself is multiple. An implication of this might be that there are *options* between the various versions of an object: which one to perform? (p. 74)

In this sense, environmental factors can be either performed as data and as epigenetic environment or as noise and as *unintended environment*. It is part of an active decision, the distinct choice of a scientific community (including many different actors, such as researchers, reviewers, funders) to regard environmental factors – intended or not – as worthy of epigenetic scrutiny.

Such agential cuts (Barad, 2007) can have far-reaching socio-political implications, as they contribute to stabilising certain knowledge claims. Only those environmental factors that are acknowledged and stabilised as epigenetic environments are disseminated to the wider scientific community as potentially having (negative) health outcomes. By this, only specific environments are regarded and claimed to have lasting influences on our bodies on a molecular basis, while others remain obscured. Drawing on historian Michelle Murphy, STS scholars Sarah Shostak and Margot Moinester (2015) contextualise such scientific techniques of making specific factors visible within the concept of regimes of perceptibility. Embedded in a framework of "a *political economy of perception* ... [it] may favor particular conceptualizations and operationalizations of the environment", thus having "consequences for what dimensions of the environment are perceived as more or less real and actionable." (pp. 217 & 222).

For example, it is striking to take a look at who is considered to be disadvantaged, traumatised, or stressed in many epigenetic cohort studies. Through their specific study design, these studies most often suggest that emotional hardship only happens in certain pre-defined population groups, such as low SES households, uneducated families or ethnic minorities. While this is part of scientists' pragmatic reduction (to only focus on some groups, representations, and problems) it disregards that social adversity occurs across population strata (see Müller et al., 2017). Hypothesising that some groups are biologically imprinted due to their experiences is a research approach that may imply the risk of discriminating and pathologizing groups (that are framed as a cohort) based on particular biological and epigenetic marks. Surprisingly, despite also working with cohorts (namely individuals who have experienced some forms of stress and therefore suffer from stress-related disorders) the institute's biomarker study seems not to be embedded into a similar *political economy of perception*. This is mainly related to the anticipated research goal and how it is framed. Many cohort studies focus heavily on shared biographical events and therefore attempt to find molecular tags that reveal that some groups of population may be biologically impaired (very visibly so with, for instance, such language as

"Biological underpinnings of trauma and PTSD" (Ryan et al., 2016)). In contrast, in the biomarker study scientists clearly state that they pursue the goal of finding novel ways to classify mental disorders. In this case personal biographies are, at least discursively, placed less in the foreground.

Thus, *un/intended environments* are also political in the sense that they contribute to what society considers to be "true" – they "shape, form and diffract reality" (Law, 2011, p.5). In that vein, it is imperative to critically consider what scientific "truths" epigenetic research reveals for society by for instance rendering specific groups of people as explicitly vulnerable to mental disorders based on particular biological and epigenetic marks. In this context, it is my concern to not undermine the importance and meaningfulness of such research. With my analysis of *un/intended environments*, however, I want to point to the political character of epigenetic research, as far as such research always only casts light on some versions of an object (Mol, 1999), rendering them as data and others as noise.

The attempt to also acknowledge *unintended environments* as possible data within epigenetic research could lead to a more authentic dissemination and discussion of research practices and results. This would most probably imply two main shifts in the way (epigenetic) research is currently carried out. First, it would entail allowing for more ambiguity in the scientific laboratory, which is generally a place that actually targets the opposite: maximising certainty by keeping complexity out through pragmatic reductionism (see above). Yet, as pointed out by one of my field informants and also by other epigenetic research groups (Niewöhner, 2011), in environmental epigenetics there is no black and white: researchers are rather confronted with *grey* results which I believe also deserve discussion so that they be accepted and adopted as exactly that. Given this context of *grey* results, Barad speaks of "indeterminacy" (Barad, 2007), a term that conveys the notion that there is no such thing as scientific certainty; that certainty is a very fragile concept. Instead, scientific results are always to some extent indeterminate as the materialised knowledge always depends on the apparatus of knowledge production and the scientists' agential cuts.

Even if science in general strives for the unambiguous, indeterminacy should not be interpreted as having a disruptive effect on producing knowledge. Instead, it can be productive as it "makes room for the unexpected and lets the new enter through the cracks in the wall that seemed impenetrable" (Nowotny, 2015, p. 8). Metaphorically speaking, *unintended environments* can be interpreted as an invitation to scientists to, by a multidisciplinary approach, integrate them into their research instead of only striving for a purified ideal of their scientific practice bounded to their own imaginaries,[73] an

[73] In stating this, I am well aware that the culture of knowledge production always is highly intertwined with the politics of knowledge production and that scientific practices are subject to the pressure of publication.

invitation to not be overwhelmed by the heterogeneity but to embrace the messiness.[74] This is not to suggest that indeterminacies be responded to with experiments designed to be indiscriminately more open to the *real world*, but rather that indeterminacies be discussed as generative when and where they occur.

Second, and as a consequence thereof, such an approach would also imply developing strategies to manage indeterminacy and credibility in new ways. This is, as Lloyd and Raikhel (2018) speculate, "somehow distinct in the fast-moving, data-rich research that characterizes environmental epigenetics, in which key concepts and assumptions are rapidly stabilized and destabilized" (p. 756). In fact, environmental epigenetic research is an approach characterised by multiple unknowns that have to be managed by the scientists. One strategy could be an ongoing re-negotiation and discussion about what can be regarded as epigenetic data and what not. Some of these epigenetic data might have been "there all along" (Llyod & Raikhel, 2018b, p. 755) but not recognised as such. Drawing on ethnographic observation in a laboratory that conducts environmental epigenetics on suicide risk, Lloyd and Raikhel show how a specific type of methylation, namely CH methylation, was transformed from an anomaly to a discovery. In the relevant project, CH methylation was perceived, but the researchers "considered [it] relatively unimportant, and more commonly considered [it] a particular kind of anomalous data resulting from normal variations in the quality of the laboratory methods used in this type of research" (Lloyd & Raikhel, 2018b, p. 747). This was because they oriented their scientific gaze towards a different type of methylation, namely CG methylation, which was at that time the only type studied in the lab. Some years later an article brought to the fore the significance of CH methylation for mammalian development, an observation the group had failed to publish for various reasons (for instance, this would have jeopardised the credibility of some of their other findings) even though the data was actually there.

A similar re-interpretation of the significance of data can be observed in N^6-methyladenosine, a specific messenger RNA modification investigated by a group at the institute. Its role as a dynamic regulator in epigenetic processes was long misunderstood and only recently (Yue et al., 2015) emerged as an object of investigation within the institute and other psychiatric research using epigenetic approaches (see Ch. 4.3.4). If we understand epigenetics as a specific thought style (Fleck, 1979), the epigenetic research that I have observed can be conceived of as the result of the activities of a specific research collective. Epistemic theorist Ludwik Fleck points to a loss or a blind spot that might be cultivated throughout the research practices of a research collective: the ability of directed perception

[74] The idea of intentionally turning to heterogeneity also seems to be emerging in the field itself. Psychiatrist and neuroscientists Vaishnav Krishnan and Eric Nestler, for instance, invite their colleagues to explicitly address "the polysyndromic nature of depression and use a multidisciplinary approach to explore the neurobiological bases for depression's many subtypes" (Krishnan & Nestler, 2008, p. 1643), instead fo being intimidated by the disorder's heterogeneity.

("gerichtetes Wahrnehmen") is a crucial scientific skill, but can also lead to an inability to see contradictions within the research process. Thus, the above examples reveal that we have to acknowledge the highly dynamic character of environmental research in order to be attentive to elements that might turn out to be insightful epistemic objects, to acknowledge that managing epistemic indeterminacy and producing credibility in environmental epigenetics research has a very complex character (Lloyd & Raikhel, 2018b).

Against this theoretical background, casting "negative" results as limitations of the model organism employed itself, or as a methodological weakness, is a frequent practice in research with cell or mice models. As neuroscientist Zoe told me

> if you are using an animal model and you find a negative result, people usually blame the model and say: well, there must have been something wrong with it – you know – it's a limitation of the model, that we didn't see the effect, that we are expecting to see. (Zoe, pos. 34)

However, such a scientific habit runs the risk of narrowing a well-balanced discussion of the research output as it underestimates the significance of *unintended environments*. Perhaps it is not the model that contains an error, but rather the scientific view that is misdirected because it only takes into consideration what it is looking for. Here, I would like to suggest instead that critical attention be paid towards the dynamic processes by which phenomena are stabilised as scientific facts or categories. Such an approach could contribute to the handling of some of those phenomena as something other than artefacts or meaningless anomalies, to an encountering of them with constructive impartiality. As historian of science Hans-Joerg Rheinberger (1997) writes regarding "unprecedented events" within experimental systems, that novel phenomena "usually begin their lives as recalcitrant 'noise,' as boundary phenomena, before they move on stage as 'significant units'" (p. 21). Such open discussions on *unintended environments* as phenomena with their own scientific temporalities could lead to a more realistic image of the field's current challenge: to deal with indeterminacy, to produce credibility, and to faithfully report on the scientific practices to the scientific community and the wider public. As we can trace of much of Rheinberger's analyses, indeterminacy and imprecision can be particularly productive.

Ultimately, this could maybe mean the introduction of a third category, additional to "signal" and "noise" – a category that includes and mirrors the very indeterminacies that accompany epigenetic claims making. Here, I suggest a category such as "productive idiosyncrasies". With such a term, we possibly could reflect the complex terrains of stabilising scientific knowledge and point to the fact that molecular biology and epigenetics is always a science-in-the-making, shaped by a variety of negotiation processes. It would critically emphasise that a signal is not data *a priori*; a signal is data because scientists enact it as data by making agential cuts; it is a signal only in *relation* to a specific organism or even to a specific mechanism. Such a notion on signal/stress/environment is pretty much connected to ethologist Jakob von Uexküll's (1940/1982) theory of *Umwelt*, in which he sets out to comprehend

how the world exists *for* organisms. In his theory, an element of the environment can under certain circumstances "change ... its meaning" (von Uexküll, (1940/1982, p. 27). A stone, for instance, incorporated in the country road, serves as a support for the walker's feet, while the same stone, picked up, may function as a missile for an angry human (von Uexküll, 1940/1982).

The relational understanding of environment performed as *signal*, *noise*, and/or *productive idiosyncrasies* in the epigenetic experiment can also be discussed against the backdrop of what feminist STS scholar Donna Haraway (1988) conceptualises within her *feminist objectivity*. Separating noise from signal leads to objectivity in the sense of universal truth "from nowhere" (Haraway, 1988, p. 581). Feminist objectivity in the sense of Haraway, however, cannot be about fixed vision, but is something she denotes as situated knowledges. A core aspect of situated knowledges is thus the fundamental contextual approach to any research question. Thinking of productive idiosyncrasies in this sense could be in favour of an "argument for situated and embodied knowledges and an argument against various forms of unlocatable, and so irresponsible, knowledge claims. Irresponsible means unable to be called into account" (Haraway, 1988, p. 538). Establishing a third category, therefore, would mean to re-open the scientific gaze and be attentive to the "life cycle" (Star & Gerson, 1987, p. 152) of (novel) phenomena. To not get stuck in binarity but to *stay with the trouble* (Haraway, 2016).

7 Environmental Epigenetics as a Specific Mode of Scientific Knowledge Production: Concluding Remarks on Telling Responsible Stories

What I hope has become obvious throughout my dissertation is that how we *do* and how we *know* mental health matters. It matters because this scientific knowledge might permeate the epigenetic laboratory, informing what science and policy defines and problematises as mental disorders. What I also hope has become obvious throughout my dissertation is that the existence of *un/intended environments* and their implications for concrete practices of scientific knowledge production are closely tied to much broader ideas on a general accountability of scientists: to tell responsible stories. With her concept of *ontological politics* (see above), Mol (1999) reminds us to consider (scientific) objects not as objects that are merely discovered but as objects that are actively enacted. In my reading, this enactment implies a specific version of the object that is *performed*; a specific focus that is *chosen*; a specific "truth" that is *disseminated*; a specific story that is eventually *told*. These ideas reveal, that scientific inquiry is "an important and non-innocent world-making practice" (Kenney, 2015, p. 749).[75]

These practices of scientific storytelling are responsible practices. They are reflexive and relational, "forging connections with words" (Kenney, 2015, p. 758), as feminist science studies scholar Martha Kenney writes. Especially within the modern life sciences, accountable and careful storytelling is of unique significance as contemporary Western societies grant them huge authority and interpretational sovereignty. Today, the life sciences are epistemologically dominant (Kenney, 2019): most often, phenomena only become socio-politically relevant when they can be explained in technoscientific or molecular frameworks. In this vein, epigenetic research within psychiatry is thought to reveal the *molecular proof* for a phenomenon that has long been known in psychology but that has so far lacked a profound explanation: the causal connection between early-life hardship and negative mental as well as somatic health effects in adulthood (Brückl & Binder, 2017). Environmental epigenetic papers that lay claim to having closed this knowledge gap lend this phenomenon *molecular credibility* (Kenney & Müller, 2017), making it more "true" or "relevant" than before. This is a specific mode of objectivity as it makes something visible that has long been known, though in a different mode.

Thinking with Barad, everything is entangled with everything else. As discussed earlier, acts of observation hence make "cuts" between what is included and excluded from scientific consideration. Agential cuts are temporary stabilisations of objects and parts of apparatuses of knowledge production. As she writes:

[75] In the original publication, with this interpretation, Kenney specifically targets *empirical inquiry*. Though, as my argument shows, scientific inquiry as such bears a certain responsibility.

> phenomena are not mere results of laboratory exercises engineered by human subjects: rather, phenomena are differential patterns of mattering ("diffraction patterns") produced through complex agential intra-actions of multiple material-discursive practices or apparatuses of bodily production, where apparatuses are not mere observing instruments but boundary-drawing practices – specific material (re)configurings of the world – which come to matter. ... [It] is through such practices that the differential boundaries between humans and nonhumans, culture and nature, science and the social, are constituted. (Barad, 2007, p. 140)

Barad's agential realism provides a framework for analysing how scientific practices might foreground certain aspects while other aspects or ideas remain not easily accessible or even indiscernible. To return to my example above, the long-known connection between early-life trauma and later life disease is – through specific apparatuses of knowledge production and agential cuts – staged as a predominantly molecular, epigenetic phenomenon. At the same time, only some, not all, existing environmental factors are rendered as elements of the apparatus; my analysis reveals how *unintended environments* are often excluded from the apparatus and hence remain unattended and ultimately unacknowledged and undiscussed.

In that vein, environmental epigenetic research so far predominantly focuses on stressful and adverse experiences due to methodological reasons. Researchers widely assume that they can produce biological knowledge on mental health only in the "activated" system; that they can learn only from stressed organisms (see Ch. 4.1). Such a research perspective systematically excludes the power of careful social relationships, of pleasure and joy. Why do epigeneticists assume to be able to measure the effects of neglect but not the effects of friendship? Associating epigenetic changes continuously to violence and illness crucially omits the "kinds of pleasures and possibilities" (Kenney, 2019, p. 11) of what epigenetic changes could *also* mean for human life.

Against this background, I would like to emphasise all the more strongly that there are already individual efforts in the field to research the preventive or even curative effects of positive environments (so far only in the mouse model with so-called "enriched environments" in which mice are provided with diversified environmental stimuli such as toys). How can epigenetic marks as a consequence of earlier negative life experiences be reversed? In this sense, environmental epigenetics has the potential to discuss not only stress as a disease-causing factor, but also well-being as a health-promoting aspect. Biological stress researchers have started to critically reflect on their own methodologies and, for instance, started to test mice in groups, with their "family and friends" (Noam, pos. 35) rather than isolating them to investigate the effects of social behaviour. Maybe not only the restrainer leaves its epigenetic marks in the mice but also the scientists' careful handling when they gently pet their laboratory animals and reassure them. Based on these initial research endeavours, researchers anticipate ultimately producing knowledge on how social relationships could prevent or reverse epigenetic changes, serving as a "social buffer" (Cunliffe, 2016) and emphasising the plasticity of the epigenome and human body throughout life. Such research is one way to responsibly tell the *whole* story, without

running into the danger of discriminating groups of people as eternally epigenetically impaired due to their biographies.

As research practices are practices based on agency, being accountable to the worlds the scientists study is an important duty (Kenney, 2015). As I have shown, within this scientific responsibility, epigenetics re-emphasises questions of the indeterminacy of scientific knowledge and the indeterminacy of a certain scientific objectivity. In this context, Mol (2002) suggests shifting the question of *how can we be sure*? to the question of *how to live with doubt?*, foregrounding the fact that producing knowledge always also means managing the unknown. For the environmental epigenetic context, it would be reasonable to be more concrete: how can we live with indeterminacy, with shades of *grey*? And how can we live with all of the *unintended environments* that are part of the experiment, though "uninvited"? One way could be to tell "better scientific stories" (Kenney, 2015, p. 749) by explicitly narrating relations between the objects and subjects involved in scientific inquiry. This would include tracing back the material as well as the historical, economic, social, political, and other relations that are part of producing knowledge (Barad, 2007) – even if, or perhaps just because these often are not considered as "facts" but as side stages of scientific claims-making. This would also include re-assembling the deconstructed epistemic objects after scientific scrutiny, all the while being attentive to their manifold entanglements to environment. Such an inventory of the scientific apparatus can contribute to a critical attention to what is included and what is excluded within the agential cuts. It can cast light on the notion that different research practices, different material-discursive apparatuses, "materialize ... a different agential reality" (Barad, 1999, p. 8). In this vein, "responsibility to the past and the future entails an opening-up of possibilities of different kinds of responses – responses that may transform the 'edge' in the making of scientific cuts" (Schrader, 2010, p. 299).

We as STS scholars constantly dwell in technoscientific worlds. Therefore, it is equally important to raise the question of how *we*, as social scientists, can contribute to telling better technoscientific stories, to responsibly responding to the life scientists' accounts. How *we*, through our own empirical inquiry, can be accountable to the worlds we study and what our stories teach (Kenney, 2019). We can accomplish this by reflecting on and discussing the politics of our own research methods and by acknowledging our own entanglements within the worlds we study. Sometimes, I was an "extra" *unintended environment*. I for instance posed a threat to an ongoing mouse experiment when I accidentally entered a room that was in the "blue", the clean area. Occasionally, I also turned into an *unwanted environment*, when my informants for example expressed that they would need a break from my shadowing. As I also discuss in my methods chapter, I am aware that my participation in the institute led to a very specific technoscientific story that would have unfolded differently without my presence. Thus, I regard myself as a participant-storyteller rather than a participant-observer (Kenney, 2015).

More so, I applied my very own practices of reductionism in order to be able to tell this story. First, regarding my research perspective, I focused on the *practices* by which researchers apply and perform approaches from environmental epigenetics in three different experimental arrangements. I am aware that there would have been other ways of approaching this topic. One of these ways would have been, for example, to probe the scientists' notion of environment, to investigate alternative ontologies of environment, organisms, objects, and *Umwelt* that social anthropology and philosophy offer us. Against this background it remains open how a different conception of the environment would lead to other ways of intra-acting stress. How, for instance, would a theory of environment as a process or as a *fluid space* where there are no well-defined objects or entities might offer ways into different *cuts* ()?[76] And how would these *cuts* then produce significantly different results? Following my work, future research projects in this direction could provide valuable insights into how a theory of environment is related to epigenetic practice by leaving behind the topographic view of environment.

Second, I reduced my research design to a specific time and to a specific space. Therefore, my story reveals very situated, partly site-specific arguments that are bound to the time of my observation. These arguments are non-relativising and non-universalising descriptions (Winthereik & Verran, 2012). My reductionism leads to my ethnographic story being a *whole-part* in a *here-now*, emphasising its character as an emergent entity instead of an element contributing to the evidence base of a more general statement. Therefore, my ethnographic story is a "situating moment" (Winthereik & Verran, 2012, p. 38) and only one of a plethora of possible stories of how and with what effects environmental epigenetics is enacted within psychiatric research. Relating to these ideas, I hope that my ethnographic story can contribute to a profound understanding of the character of research practices by adding an interesting and inspiring vantage point: revealing productive tensions and delineating epigenetic research practices as thought styles in-the-making is my anticipated way of carrying out an accountable participatory practice. Following Kenney (2015), writing a book can be understood as such. Thus, I wish to suggest that with this dissertation, I have taken the first step towards being held accountable to my own scientific story.

[76] See Dupré, 2012; Ingold, 2000; Nicholson & Dupré, 2018; Oyama et al., 2001 for processual theories on environments and organisms

8 References

Abbott, A. (2016). US mental-health chief: psychiatry must get serious about mathematics. *Nature*, *539*(7627).

Alhamwe, B. A., Khalaila, R., Wolf, J., von Bülow, V., Harb, H., Alhamdan, F., Hii, Ch. S., Prescott, S. L., Ferrante, A., Renz, H. (2018). Histone modifications and their role in epigenetics of atopy and allergic diseases. *Allergy, Asthma & Clinical Immunology, 14*(1), 1-16. https://doi.org/10.1186/s13223-018-0259-4

Allen, A. P., Kennedy, P. J., Dockray, S., Cryan, J. F., Dinan, T. G., & Clarke, G. (2017). The trier social stress test: principles and practice. *Neurobiology of Stress*, *6*, 113-126. Allen, A. P., Kennedy, P. J., Dockray, S., Cryan, J. F., Dinan, T. G., & Clarke, G. (2016). The Trier Social Stress Test: Principles and practice. *Neurobiology of stress*, *6*, 113–126. https://doi.org/10.1016/j.ynstr.2016.11.001

Allis, C. D., & Jenuwein, T. (2016). The molecular hallmarks of epigenetic control. *Nature Reviews Genetics, 17*(8), 487-500. https://doi.org/10.1038/nrg.2016.59

Angelova, M. T., Dimitrova, D. G., Dinges, N., Lence, T., Worpenberg, L., Carré, C., & Roignant, J.-Y. (2018). The emerging field of epitranscriptomics in neurodevelopmental and neuronal disorders. *Frontiers in bioengineering and biotechnology, 6*, 1-15. https://doi.org/10.3389/fbioe.2018.00046

Anway, M. D., Cupp, A. S., Uzumcu, M., & Skinner, M. K. (2005). Epigenetic transgenerational actions of endocrine disruptors and male fertility. *Science*, *308*(5727), 1466–1469. https://doi.org/10.1126/science.1108190

American Psychiatric Association (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). https://doi.org/10.1176/appi.books.9780890425596

Bali, A., & Jaggi, A. S. (2015). Clinical experimental stress studies: Methods and assessment. *Reviews in the neurosciences*, *26*(5), 555–579. https://doi.org/10.1515/revneuro-2015-0004

Barad, K. (1999). Agential realism: Feminist interventions in understanding scientific practices. In M. Biagiol (Ed.) *The science studies reader* (pp. 1-11).

Barad, K. (2007). *Meeting the universe halfway: Quantum physics and the entanglement of matter and meaning*. Duke University Press.

Bard, J. (2007). Systems developmental biology: the use of ontologies in annotating models and in identifying gene function within and across species. *Mammalian Genome*, *18*(6-7), 402-411. https://doi.org/10.1007/s00335-007-9027-3

Beaulieu, A. (2010). Research Note: From co-location to co-presence: Shifts in the use of ethnography for the study of knowledge. *Social Studies of Science*, *40*(3), 453–470. https://doi.org/10.1177/0306312709359219

Beck, S., & Niewöhner, J. (2006). Somatographic Investigations Across Levels of Complexity. *BioSocieties, 1*(2), 219-227. https://doi.org/10.1017/S1745855206050113

Beck, S., Niewöhner, J., & Sörensen, E. (Eds.). (2014). *Science and technology studies: Eine sozial-anthropologische Einführung*. Transcript Verlag.

Beskow L. M. (2016). Lessons from HeLa Cells: The Ethics and Policy of Biospecimens. *Annual review of genomics and human genetics*, *17*, 395–417. https://doi.org/10.1146/annurev-genom-083115-022536

Beurton, P., Falk, R., & Rheinberger, H. (Eds.). (2000). *The Concept of the Gene in Development and Evolution: Historical and Epistemological Perspectives* (Cambridge Studies in Philosophy and Biology). Cambridge: Cambridge University Press. https://doi.org/10.1017/CBO9780511527296

Birck, A. (2002). Echte und vorgetäuschte posttraumatische Belastungsstörungen. *Psychotraumatologie*, *3*(1), 26. Doi:10.1055/s-2001-20177

Birkett M. A. (2011). The Trier Social Stress Test protocol for inducing psychological stress. *Journal of visualized experiments*, (56), 3238. https://doi.org/10.3791/3238

Birney, E., Soranzo, N. The end of the start for population sequencing. *Nature* 526, 52–53 (2015). https://doi.org/10.1038/526052a

Blaze, J., Asok, A., & Roth, T. L. (2015). The long-term impact of adverse caregiving environments on epigenetic modifications and telomeres. *Frontiers in behavioral neuroscience*, *9*, 79. https://doi.org/10.3389/fnbeh.2015.00079

Böhme, G. & Stehr, N. (1986) The growing impact of scientific knowledge on social relations. In G. Böhme G. & N. Stehr (Eds). *The knowledge society: Sociology of the sciences*. Springer. https://doi.org/10.1007/978-94-009-4724-5_2

Boring, E. (1954). The nature and history of experimental control. *The American Journal of Psychology, 67*(4), 573-589. https://doi.org/10.2307/1418483

Boucsein, W. (2012). *Electrodermal activity*. Springer. Doi:10.1007/978-1-4614-1126-

Brückl, T. M., & Binder, E. B. (2017). Folgen früher Traumatisierung aus neurobiologischer Sicht. *Forensische Psychiatrie, Psychologie, Kriminologie, 11*(2), 118-132. https://doi.org/10.1007/s11757-017-0412-9

Burri, R. V., & Dumit, J. (2007). *Biomedicine as culture: Instrumental practices, technoscientific knowledge, and new modes of life*. Routledge.

Canguilhem, G. (2012). *On the normal and the pathological*. Springer.

Cannon, W. B. (1929). Organization for physiological homeostasis. *Physiological Reviews*, *9*(3), 399-431. https://doi.org/10.1152/physrev.1929.9.3.399

Charmaz, K. (2006). *Constructing grounded theory: A practical guide through qualitative analysis*. Sage.

Charmaz, K. & Belgrave, L. (2012). Qualitative interviewing and grounded theory analysis. In J. F. Gubrium, J. A. Holstein, A. B. Marvasti, K. D. & McKinney. *The SAGE handbook of interview research: The complexity of the craft* (chapter 24, pp. 347-366). Sage. https://dx.doi.org/10.4135/9781452218403.n25

Chiapperino, L. (2019). Environmental enrichment: an experiment in biosocial intervention. *BioSocieties*, 1-29. https://doi.org/10.1057/s41292-019-00181-5

Clancy, S. (2008). RNA functions. *Nature Education, 1*(1), 102.

Clarke, A. E. (2003). Situational analysis: Grounded theory mapping after the postmodern turn. *Symbolic Interaction*, *26*(4), 553-576. https://www.jstor.org/stable/10.1525/si.2003.26.4.553

Clarke, A. E., Shim, J. K., Mamo, L., Fosket, J. R., & Fishman, J. R. (2003). Biomedicalization: Technoscientific transformations of health, illness, and US biomedicine. *American Sociological Review*, *68*(2), 161-194. https://doi.org/10.2307/1519765

Clevers, H. (2016). Modeling development and disease with organoids. *Cell, 165*(7), 1586-1597. https://doi.org/10.1016/j.cell.2016.05.082

Conrad, P. (1992). Medicalization and social control. *Annual Review of Sociology, 18*(1), 209-232. https://doi.org/10.1146/annurev.so.18.080192.001233

Conrad, P., & Schneider, J. W. (1980). *Deviance and medicalization: From badness to sickness*. Temple University Press.

Corbin, J. M., & Strauss, A. (1990). Grounded theory research: Procedures, canons, and evaluative criteria. *Qualitative sociology, 13*(1), 3-21. https://doi.org/10.1007/BF00988593

Cunliffe, V. T. (2016). The epigenetic impacts of social stress: how does social adversity become biologically embedded? *Epigenomics, 8*(12), 1653-1669. https://doi.org/10.2217/epi-2016-0075

Darling, K. W., Ackerman, S. L., Hiatt, R. H., Lee, S. S.-J., & Shim, J. K. (2016). Enacting the molecular imperative: How gene-environment interaction research links bodies and environments in the post-genomic age. *Social Science & Medicine, 155,* 51-60. https://doi.org/10.1016/j.socscimed.2016.03.007

Daston, L. (2002). I The morality of natural orders: the power of medea & II. Nature's customs versus nature's laws. Tanner Lectures on Human Values delivered at Harvard University. https://tannerlectures.utah.edu/_documents/a-to-z/d/daston_2002.pdf

De Quervain, D., Schwabe, L., & Roozendaal, B. (2017). Stress, glucocorticoids and memory: implications for treating fear-related disorders. *Nature reviews. Neuroscience*, *18*(1), 7–19. https://doi.org/10.1038/nrn.2016.155

De Souza, Y. G., & Greenspan, J. S. (2013). Biobanking past, present and future: responsibilities and benefits. *AIDS (London, England)*, *27*(3), 303–312. https://doi.org/10.1097/QAD.0b013e32835c1244

Deichmann, U. (2016). Epigenetics: the origins and evolution of a fashionable topic. *Developmental Biology, 416*(1), 249-254. https://doi.org/10.1016/j.ydbio.2016.06.005

Delpu, Y., Larrieu, D., Gayral, M., Arvanitis, D., Dufresne, M., Cordelier, P., & Torrisani, J. (2016). Noncoding RNAs: clinical and therapeutic applications. In G. Egger, P. Arimondo (Eds.), *Drug Discovery in Cancer Epigenetics* (pp. 305-326). Elsevier. https://doi.org/10.1016/B978-0-12-802208-5.00012-6

Delves, P. J., Martin, S. J., Burton, D. R., & Roitt, I. M. (2017). *Roitt's essential immunology*. John Wiley & Sons.

Despret, V. (2004). The Body We Care for: Figures of Anthropo-zoo-genesis. *Body & Society*, *10*(2–3), 111–134. https://doi.org/10.1177/1357034X04042938

Dewey, J. (1938/2018). *Logic: The theory of inquiry*. Saerchinger Press.

Dewey, J. (1958). *Experience and nature*. Dover Publications.

Dickerson, S. S., & Kemeny, M. E. (2004). Acute Stressors and Cortisol Responses: A Theoretical Integration and Synthesis of Laboratory Research. *Psychological Bulletin, 130*(3), 355–391. https://doi.org/10.1037/0033-2909.130.3.355

Doherty, T. S., Chajes, J. R., Reich, L., Duffy, H. B., & Roth, T. L. (2019). Preventing epigenetic traces of caregiver maltreatment: A role for HDAC inhibition. International Journal of *Developmental Neuroscience, 78*, 178-184. https://doi.org/10.1016/j.ijdevneu.2019.05.002

Doing, P. (2008). Give me a laboratory and I will raise a discipline: The past, present, and future politics of laboratory studies in STS. In E. J. Hackett (Ed.). *The handbook of science and technology studies* (pp. 279-295). MIT Press.

Dolinoy D. C. (2008). The agouti mouse model: an epigenetic biosensor for nutritional and environmental alterations on the fetal epigenome. *Nutrition reviews*, *66 Suppl 1*(Suppl 1), S7–S11. https://doi.org/10.1111/j.1753-4887.2008.00056.x

Douglas, M. (2003). *Purity and danger: An analysis of concepts of pollution and taboo*. Routledge.

Dumit, J. (2004). *Picturing Personhood: Brain scans and biomedical identity*. Princeton University Press.

Dupras, C., & Ravitsky, V. (2016). The ambiguous nature of epigenetic responsibility. *Journal of Medical Ethics, 42*(8), 534-541. http://dx.doi.org/10.1136/medethics-2015-103295

Dupré, J. (2011). Emerging sciences and new conceptions of disease; or, beyond the monogenomic differentiated cell lineage. *European Journal for Philosophy of Science, 1*(1), 119-131. https://doi.org/10.1007/s13194-010-0008-0

Dupré, J. (2012). *Processes of life: Essays in the philosophy of biology*. Oxford University Press. Doi:10.1093/acprof:oso/9780199691982.001.0001

Eisenstein, M. (2018). Organoids: The body builders. *Nature Methods, 15*, 19-22. https://doi.org/10.1038/nmeth.4538

Emerson, R. M., Fretz, R. I., & Shaw, L. L. (2011). *Writing ethnographic fieldnotes*. University of Chicago Press.

Engel, M., Eggert, C., Kaplick, P. M., Eder, M., Röh, S., Tietze, L., Namendorf, C., Arloth, J., Weber, P., Rex-Haffner, M., Geula, S., Jakovcevski, M., Hanna, J. H., Leshkowitz, D., Uhr, M., Wotjak, C. T., Schmidt, M. V., Deussing, J. M., Binder, E. B., & Chen, A. (2018). The Role of m^6A/m-RNA Methylation in Stress Response Regulation. *Neuron*, *99*(2), 389–403.e9. https://doi.org/10.1016/j.neuron.2018.07.009

Evans, K. L., Porteous, D. J., Muir, W. J., & Blackwood, D. H. (2001). Nuts and bolts of psychiatric genetics: building on the Human Genome Project. *TRENDS in Genetics, 17*(1), 35-40. https://doi.org/10.1016/S0168-9525(00)02170-3

Fedoroff, N. V. (2012). Transposable elements, epigenetics, and genome evolution. *Science, 338*(6108), 758-767. https://doi.org/10.1126/science.338.6108.758

Feil, R., & Fraga, M. F. (2012). Epigenetics and the environment: emerging patterns and implications. *Nature Reviews Genetics, 13*(2), 97-109. https://doi.org/10.1038/nrg3142

Felsenfeld G. (2014). A brief history of epigenetics. *Cold Spring Harbor perspectives in biology*, *6*(1), a018200. https://doi.org/10.1101/cshperspect.a018200

Felt, U., & Müller, R. (2011). Tentative (id)entities: On technopolitical cultures and the experiencing of genetic testing. *BioSocieties, 6*(3), 342-363. https://doi.org/10.1057/biosoc.2011.5

Fife-Schaw, C. E. (2006). Quasi-experimental designs. In G. M. Breakwell, S. E. Hammond, C. E. Fife-Schaw, & J. A. Smith (Eds.), *Research methods in psychology* (pp. 88-103). Sage.

Fleck, L. (1979). *Genesis and development of a scientific fact*. University of Chicago Press.

Flick, U. (1991). Stationen des qualitativen Forschungsprozesses. In U. Flick, E. v. Kardoff, H. Keupp, L. v. Rosenstiel, & S. Wolff (Eds.), *Handbuch qualitative Sozialforschung: Grundlagen, Konzepte, Methoden und Anwendungen* (pp.147-173). Beltz – Psychologie Verl. Union. https://nbn-resolving.org/urn:nbn:de:0168-ssoar-37305

Folkers, A., & Rödel, M. (2015). Biopolitik/Biomacht. In *Gender Glossar / Gender Glossary*. https://nbn-resolving.org/urn:nbn:de:bsz:15-qucosa-219523

Fosket, J. (2004). Constructing "High-Risk Women": The Development and Standardization of a Breast Cancer Risk Assessment Tool. *Science, Technology, & Human Values*, *29*(3), 291–313. https://doi.org/10.1177/0162243904264960

Foucault, M. (1980). *Power/knowledge: Selected interviews and other writings*, 1972-1977. Vintage.

Foucault, M. (1988). *Madness and civilization: A history of insanity in the age of reason*. Vintage.

Foucault, M. (1973). *The birth of the clinic: An archaeology of medical perception*. Routledge.

Fox Keller, E. (2005). The century beyond the gene. *Journal of Biosciences*, *30*(1), 3-10. https://doi.org/10.1007/BF02705144

Fox Keller, E. (2009). *The century of the gene*. Harvard University Press.

Franklin, T. B., Russig, H., Weiss, I. C., Gräff, J., Linder, N., Michalon, A., Vizi, S., Mansuy, I. M. (2010). Epigenetic transmission of the impact of early stress across generations. *Biological Psychiatry, 68*(5), 408-415. https://doi.org/10.1016/j.biopsych.2010.05.036

Fryers, T., Melzer, D., Jenkins, R., & Brugha, T. (2005). The distribution of the common mental disorders: social inequalities in Europe. *Clinical practice and epidemiology in mental health : CP & EMH*, *1*, 14. https://doi.org/10.1186/1745-0179-1-14

Garcia-Diaz, M., & Kunkel, T. A. (2006). Mechanism of a genetic glissando: structural biology of indel mutations. *Trends in biochemical sciences*, *31*(4), 206–214. https://doi.org/10.1016/j.tibs.2006.02.004

Garforth, L. (2012). In/visibilities of research: Seeing and knowing in STS. *Science, Technology, & Human Values, 37*(2), 264-285. https://doi.org/10.1177/0162243911409248

Garrison, L. (2013). The anthropology of biopolitics. *A blog about knowledge, power, and the individual in society today*. [Retrieved from https://anthrobiopolitics.wordpress.com/2013/04/22/knowledge-resistance-and-labor/ on 1.9.20

Geertz, C. (1989). *Works and lives: The anthropologist as author*. Stanford University Press.

Goffman, E. (1961). *Asylums: Essays on the Condition of the Social Situation of Mental Patients and Other Inmates*. Anchor.

Goffman, E. (1963). *Stigma: Notes on the management of spoiled identity*. Simon and Schuster.

Greenberg, M., & Bourc'his, D. (2019). The diverse roles of DNA methylation in mammalian development and disease. *Nature reviews. Molecular cell biology*, *20*(10), 590–607. https://doi.org/10.1038/s41580-019-0159-6

Grealley, J. M. (2015). Over-interpreted epigenetics study of the week. In *EpgntEinstein*. Available at http://epgntxeinstein.tumblr.com/post/127416455028/over-interpreted-epigenetics-study-of-the-week

Greer, E. L., & Shi, Y. (2012). Histone methylation: a dynamic mark in health, disease and inheritance. *Nature reviews. Genetics*, *13*(5), 343–357. https://doi.org/10.1038/nrg3173

Griffith, J. S., & Mahler, H. R. (1969). DNA ticketing theory of memory. *Nature*, *223*(5206), 580–582. https://doi.org/10.1038/223580a0

Gubrium, J. F., & Holstein, J. A. (2003). From the individual interview to the interview society. In J. F. H. Gubrium & A. James (Eds.), *Postmodern interviewing* (pp. 21-49). Sage.

Hackett, E. J., Amsterdamska, O., Lynch, M., & Wajcman, J. (2008). *The handbook of science and technology studies*. MIT Press.

Hacking, I. (1986). Making up people. In M. Biagioli (Ed.). *The science studies reader* (pp. 161–171). Routledge

Hacking I. (1994). Styles of scientific thinking or reasoning: A new analytical tool for historians and philosophers of the sciences. In K. Gavroglu, J. Christianidis, E. Nicolaidis (Eds.), *Trends in the historiography of science*: *Vol. 151. Boston studies in the philosophy of science* (pp. 31-48). Springer, Dordrecht. https://doi.org/10.1007/978-94-017-3596-4_3

Haig D. (2004). The (dual) origin of epigenetics. *Cold Spring Harbor symposia on quantitative biology*, *69*, 67–70. https://doi.org/10.1101/sqb.2004.69.67

Hanson, M. A., & Skinner, M. K. (2016). Developmental origins of epigenetic transgenerational inheritance. *Environmental epigenetics*, *2*(1), dvw002. https://doi.org/10.1093/eep/dvw002

Haraway, D. (1988). Situated knowledges: The science question in feminism and the privilege of partial perspective. *Feminist studies, 14*(3), 575-599. https://www.jstor.org/stable/i359114

Haraway, D. (1992). The promises of monsters: a regenerative politics for inappropriate/d others. In L. Grossberg, C. Nelson, & P. Treichler (Eds.), *Cultural studies* (pp. 295-337). Routledge. https://doi.org/10.4324/9780203699140

Haraway, D. J. (2016). *Staying with the trouble: Making kin in the Chthulucene*. Duke University Press.

Heard, E., & Martienssen, R. A. (2014). Transgenerational epigenetic inheritance: myths and mechanisms. *Cell, 157*(1), 95-109. http://dx.doi.org/10.1016/j.cell.2014.02.045

Hedgecoe, A. (2001). Schizophrenia and the narrative of enlightened geneticization. *Social Studies of Science, 31*(6), 875-911. https://doi.org/10.1177/030631201031006004

Hedlund, M. (2012). Epigenetic responsibility. *Medicine Studies, 3*(3), 171-183. https://doi.org/10.1007/s12376-011-0072-6

Heijmans, B. T., Tobi, E. W., Stein, A. D., Putter, H., Blauw, G. J., Susser, E. S., Slagboom, P. E., & Lumey, L. H. (2008). Persistent epigenetic differences associated with prenatal exposure to famine in humans. *Proceedings of the National Academy of Sciences of the United States of America*, *105*(44), 17046–17049. https://doi.org/10.1073/pnas.0806560105

Hirschauer, S. (2006). Putting things into words. Ethnographic description and the silence of the social. *Human Studies, 29*(4), 413. https://doi.org/10.1007/s10746-007-9041-1

Ho, S. M., Johnson, A., Tarapore, P., Janakiram, V., Zhang, X., & Leung, Y. K. (2012). Environmental epigenetics and its implication on disease risk and health outcomes. *ILAR journal*, *53*(3-4), 289–305. https://doi.org/10.1093/ilar.53.3-4.289

Hoffmann, A., Sportelli, V., Ziller, M., & Spengler, D. (2017). Epigenomics of Major Depressive Disorders and Schizophrenia: Early Life Decides. *International journal of molecular sciences*, *18*(8), 1711. https://doi.org/10.3390/ijms18081711

Holliday R. (2006). Epigenetics: a historical overview. *Epigenetics*, *1*(2), 76–80. https://doi.org/10.4161/epi.1.2.2762

Holliday, R., & Pugh, J. E. (1975). DNA modification mechanisms and gene activity during development. *Science*, *187*(4173), 226–232.

Hollis, F., & Kabbaj, M. (2014). Social defeat as an animal model for depression. *ILAR journal*, *55*(2), 221–232. https://doi.org/10.1093/ilar/ilu002

Holmberg, T. (2011). Mortal love: Care practices in animal experimentation. *Feminist Theory*, *12*(2), 147-163. https://doi.org/10.1177/1464700111404206

Holsboer, F. (2000). The corticosteroid receptor hypothesis of depression. *Neuropsychopharmacology*, 23(5), 477-501. https://doi.org/10.1016/S0893-133X(00)00159-7

Holstein, J. A., & Gubrium, J. F. (2008). Constructionist impulses in ethnographic fieldwork. In J. A. Holstein & J. F. Gubrium (Eds.), *Handbook of constructionist research* (pp. 373-395).

Huhman K. L. (2006). Social conflict models: can they inform us about human psychopathology?. *Hormones and behavior*, *50*(4), 640–646. https://doi.org/10.1016/j.yhbeh.2006.06.022

Hütten, F. (2016, May 25). *Armut hinterlässt Spuren im Erbgut von Kindern*. Süddeutsche Zeitung. https://www.sueddeutsche.de/gesundheit/epigenetik-armut-hinterlaesst-spuren-im-erbgut-von-kindern-1.3006578

Ingold, T. (2000). *The perception of the environment: essays on livelihood, dwelling and skill*. Psychology Press.

Jasanoff, S. (2004). *States of knowledge: the co-production of science and the social order*. Routledge.

Jenkins, J. H., Jenkins, J. D., & Barrett, R. J. (Eds.). (2004). *Schizophrenia, culture, and subjectivity: The edge of experience*: *Vol. 11. Cambridge studies in medical anthropology. Cambridge*. University Press.

Jin, B., Li, Y., & Robertson, K. D. (2011). DNA methylation: superior or subordinate in the epigenetic hierarchy?. *Genes & cancer*, *2*(6), 607–617. https://doi.org/10.1177/1947601910393957

Kahn, J. (2012). *Race in a bottle: The story of BiDil and racialized medicine in a post-genomic age*. Columbia University Press.

Kay, L. E. (1992). *The molecular vision of life: Caltech, the Rockefeller Foundation, and the rise of the new biology*. Oxford University Press.

Kay, L. E. (2000). *Who wrote the book of life? A history of the genetic code*. Stanford University Press.

Kehl, C. (2014). *Zwischen Geist und Gehirn: Das Gedächtnis als Objekt der Lebenswissenschaften: Vol. 18. VerKörperungen/MatteRealities - Perspektiven empirischer Wissenschaftsforschung*. transcript Verlag. https://doi.org/10.14361/transcript.9783839421130

Keiger, D. (2010). Immortal Cells, Enduring Issues. *Johns Hopkins Magazine*, *62*(2), 1-2. Available at https://magazine.jhu.edu/2010/06/02/immortal-cells-enduring-issues/

Kellermann N. P. (2013). Epigenetic transmission of Holocaust trauma: can nightmares be inherited?. *The Israel journal of psychiatry and related sciences*, *50*(1), 33–39. Available at http://doctorsonly.co.il/wp-content/uploads/2013/07/08_Epigenetic-Transmission.pdf

Kenney M. (2015). Counting, accounting, and accountability: Helen Verran's relational empiricism. *Social studies of science*, *45*(5), 749–771. https://doi.org/10.1177/0306312715607413

Kenney, M. (2019). Fables of Response-ability: Feminist Science Studies as Didactic Literature. *Catalyst: Feminism, Theory, Technoscience, 5*(1), 1-39. https://doi.org/10.28968/cftt.v5i1.29582

Kenney, M., & Müller, R. (2017). Of rats and women: narratives of motherhood in environmental epigenetics. *BioSocieties*, 12(1), 23-46. https://doi.org/10.1057/s41292-016-0002-7

Kino, T. (2015). Stress, glucocorticoid hormones, and hippocampal neural progenitor cells: implications to mood disorders. *Frontiers in Physiology*, *6*(230), 1-9. https://doi.org/10.3389/fphys.2015.00230

Kirschbaum, C., Pirke, K. M., & Hellhammer, D. H. (1993). The 'Trier Social Stress Test'--a tool for investigating psychobiological stress responses in a laboratory setting. *Neuropsychobiology*, *28*(1-2), 76–81. https://doi.org/10.1159/000119004

Knorr Cetina, K. (1981). *The manufacture of knowledge: An essay on the constructivist and contextual nature of science*. Pergamon.

Knorr Cetina, K. (1988). Das naturwissenschaftliche Labor als Ort der „Verdichtung “von Gesellschaft. *Zeitschrift für Soziologie, 17*(2), 85-101. https://doi.org/10.1515/zfsoz-1988-0201

Knorr Cetina, K. (1999). *Epistemic cultures: How the sciences make knowledge*. Harvard University Press.

Koolhaas, J. M., Coppens, C. M., de Boer, S. F., Buwalda, B., Meerlo, P., & Timmermans, P. J. (2013). The resident-intruder paradigm: a standardized test for aggression, violence and social stress. *Journal of Visualized Experiments,* (77), e4367. https://doi.org/10.3791/4367

Krishnan, V., & Nestler, E. J. (2008). The molecular neurobiology of depression. *Nature*, *455*(7215), 894–902. https://doi.org/10.1038/nature07455

Kundakovic, M., & Champagne, F. A. (2015). Early-life experience, epigenetics, and the developing brain. *Neuropsychopharmacology*, *40*(1), 141. https://doi.org/10.1038/npp.2014.140

Lancaster, M. A., Renner, M., Martin, C. A., Wenzel, D., Bicknell, L. S., Hurles, M. E., Homfray, T., Penninger, J. M., Jackson, A. P., & Knoblich, J. A. (2013). Cerebral organoids model human brain development and microcephaly. *Nature, 501*(7467), 373-379. https://doi.org/10.1038/nature12517

Landecker, H. (2009). *Culturing life. How cells became technologies*. Harvard University Press.

Landecker, H. (2011). Food as exposure: Nutritional epigenetics and the new metabolism. *BioSocieties*, 6(2), 167-194. https://doi.org/10.1057/biosoc.2011.1

Landecker, H. (2013). When the control becomes the experiment. *Limn*, 3, 6-8. Available at https://limn.it/articles/when-the-control-becomes-the-experiment/

Landecker, H. (2016). The social as signal in the body of chromatin. *The Sociological Review*, 64(1_suppl), 79-99. https://doi.org/10.1111/2059-7932.12014

Landecker, H., & Panofsky, A. (2013). From social structure to gene regulation, and back: A critical introduction to environmental epigenetics for sociology. *Annual Review of Sociology*, 39, 333-357. https://doi.org/10.1146/annurev-soc-071312-145707

Langlitz, N. (2011). Cultural brains and neural histories. *BioSocieties*, *6*(2), 262-275. https://doi.org/10.1057/biosoc.2011.7

Lappé, M. (2018). The paradox of care in behavioral epigenetics: Constructing early-life adversity in the lab. *BioSocieties*, 13(4), 698-714. Lappé M. (2018). The paradox of care in behavioral epigenetics: Constructing early-life adversity in the lab. *BioSocieties*, *13*(4), 698–714. https://doi.org/10.1057/s41292-017-0090-z

Lappé, M., & Landecker, H. (2015). How the genome got a life span. *New Genetics and Society*, *34*(2), 152-176. Lappé, M., & Landecker, H. (2015). How The Genome Got a Life Span. *New genetics and society*, *34*(2), 152–176. https://doi.org/10.1080/14636778.2015.1034851

Latour, B. (1999). Pandora's hope: essays on the reality of science studies. Harvard University Press.

Latour, B. (2005). Reassembling the social: an introduction to actor-network-theory. Oxford University Press.

Latour, B., & Woolgar, S. (1979/2013). Laboratory life: The construction of scientific facts. Princeton University Press.

Law, J. (2011). Collateral realities. In P. Baert & F. D. Rubio (Eds.), *The politics of knowledge* (pp. 157-178). Routledge.

Law, J., & Mol, A. (1995). Notes on Materiality and Sociality. *The Sociological Review*, *43*(2), 274–294. https://doi.org/10.1111/j.1467-954X.1995.tb00604.x

Lemke, T. (2002). Mutationen des Gendiskurses: der genetische Determinismus nach dem Humangenomprojekt. *Leviathan*, 30(3), 400-425. https://doi.org/10.1007/s11578-002-0029-y

Liburkina, R., & Niewöhner, J. (2017). Laborstudien. Einführung. In S. Bauer, T. Heinemann, T. Lemke (Eds.), *Science and Technology Studies. Klassische Positionen und aktuelle Perspektiven* (pp. 173-197). Suhrkamp.

Licinio, J., & Wong, M. (2014). Launching the 'war on mental illness'. *Molecular Psychiatry*, *19*(1), 1-5. https://doi.org/10.1038/mp.2013.180

Lim, D. H., & Maher, E. R. (2010). DNA methylation: a form of epigenetic control of gene expression. *The Obstetrician & Gynaecologist, 12*(1), 37-42.

https://doi.org/10.1576/toag.12.1.037.27556

Lippman, A. (1992). Led (astray) by genetic maps: The cartography of the human genome and health care. *Social Science & Medicine*, 35(12), 1469-1476. https://doi.org/10.1016/0277-9536(92)90049-v

Lloyd, S., & Müller, R. (2018). Situating the biosocial: Empirical engagements with environmental epigenetics from the lab to the clinic. *BioSocieties, 13*, 675–680. https://doi.org/10.1057/s41292-017-0094-8

Lloyd, S., & Raikhel, E. (2018a). Epigenetics and the suicidal brain: Reconsidering context in an emergent style of reasoning. In M. Meloni, J. Cromby, D. Fitzgerald, S. Lloyd (Eds.), *The Palgrave Handbook of Biology and Society* (pp. 491-515). Springer.

Lloyd, S., & Raikhel, E. (2018b). "It was there all along": Situated uncertainty and the politics of publication in environmental epigenetics. *BioSocieties*, *13*(4), 737-760. https://doi.org/10.1057/s41292-017-0092-x

Lock, M. (1993). *Encounters with aging: Mythologies of menopause in Japan and North America*. University of California Press.

Lopez, A. D., & Murray, C. C. (1998). The global burden of disease, 1990–2020. *Nature Medicine*, *4*(11), 1241-1243. https://doi.org/10.1038/3218

Lowy, M. T., Reder, A., Antel, J., & Meltzer, H. (1984). Glucocorticoid resistance in depression: the dexamethasone suppression test and lymphocyte sensitivity to dexamethasone. *The American Journal of Psychiatry*, *141*(11), 1365. https://doi.org/10.1176/ajp.141.11.1365

Lucey, B. P., Nelson-Rees, W. A., & Hutchins, G. M. (2009). Henrietta Lacks, HeLa cells, and cell culture contamination. *Archives of Pathology & Laboratory Medicine*, *133*(9), 1463-1467. https://doi.org/10.1043/1543-2165-133.9.1463

Lux, V. (2012). Epigenetik als Molekulare Bio-Graphie. *Gen-ethischer Informationsdienst, 213,* 33-35. Available at https://www.gen-ethisches-netzwerk.de/wissenschaftskritik/gentests-und-genomsequenzierung/epigenetik-als-molekulare-bio-graphie

Maccari, S., Polese, D., Reynaert, M.-L., Amici, T., Morley-Fletcher, S., & Fagioli, F. (2017). Early-life experiences and the development of adult diseases with a focus on mental illness: the human birth theory. *Neuroscience, 342*, 232-251. https://doi.org/10.1016/j.neuroscience.2016.05.042

Macvarish, J., Lee, E., & Lowe, P. (2014). The 'first three years' movement and the infant brain: A review of critiques. *Sociology Compass*, *8*(6), 792-804. https://doi.org/10.1111/soc4.12183

Malabou, C. (2008). *What should we do with our brain?* Fordham University Press.

Mansfield, B. (2012). Race and the new epigenetic biopolitics of environmental health. *BioSocieties*, *7*(4), 352-372. https://doi.org/10.1057/biosoc.2012.22

Mansfield, B. (2017). Folded futurity: Epigenetic plasticity, temporality, and new thresholds of fetal life. *Science as Culture, 26*(3), 355-379. https://doi.org/10.1080/09505431.2017.1294575

Marmot, M. (2017). The health gap: the challenge of an unequal world: the argument. *International Journal of Epidemiology*, *46*(4), 1312-1318. https://doi.org/10.1093/ije/dyx163

Maselko, J., Bates, L., Bhalotra, S., Gallis, J. A., O'Donnell, K., Sikander, S., & Turner, E. L. (2018). Socioeconomic status indicators and common mental disorders: Evidence from a study of prenatal depression in Pakistan. *SSM-population Health*, 4, 1-9. https://doi.org/10.1016/j.ssmph.2017.10.004

Max-Planck-Gesellschaft (2003-2020). Modellorganismus Maus [webpage]. Retrieved from https://www.mpg.de/10888337/maus on 25.7.2020.

Max-Planck-Gesellschaft (2003-2020). Modellorganismus Maus [webpage]. Retrieved from https://www.mpg.de/10888547/warum-erforschen-wissenschaftler-maeuse on 25.7.2020

McCrae, R. R., & Costa Jr, P. T. (2008). The five-factor theory of personality. In O. P. John, R. W. Robins, & L. A. Pervin (Eds.), *Handbook of personality: Theory and research* (pp. 159–181). The Guilford Press.

McEwen, B. S. (1998). Stress, adaptation, and disease: Allostasis and allostatic load. *Annals of the New York Academy of Sciences, 840(*1), 33-44. https://doi.org/10.1111/j.1749-6632.1998.tb09546.x

McEwen, B. S., & Bulloch, K. (2019). Epigenetic impact of the social and physical environment on brain and body. *Metabolism, 100*, 153941. https://doi.org/10.1016/j.metabol.2019.07.005

McEwen, B. S., & Stellar, E. (1993). Stress and the individual: mechanisms leading to disease. *Archives of Internal Medicine*, *153*(18), 2093-2101. doi:10.1001/archinte.1993.00410180039004

McEwen, B. S., & Wingfield, J. C. (2003). The concept of allostasis in biology and biomedicine. *Hormones and Behavior*, *43*(1), 2-15. https://doi.org/10.1016/s0018-506x(02)00024-7

Meloni, M. (2014). Biology without biologism: social theory in a postgenomic age. *Sociology*, *48*(4), 731-746. https://doi.org/10.1177/0038038513501944

Meloni, M. (2015). Heredity 2.0: the epigenetics effect. *New Genetics and Society, 34*(2), 117-124. https://doi.org/10.1080/14636778.2015.1036156

Meloni, M. (2016). *Political biology: Science and social values in human heredity from eugenics to epigenetics*. Springer.

Meloni, M. (2019). *Impressionable biologies: from the archaeology of plasticity to the sociology of epigenetics*. Routledge.

Meloni, M., & Müller, R. (2018). Transgenerational epigenetic inheritance and social responsibility: perspectives from the social sciences. *Environmental Epigenetics*, *4*(2), dvy019. https://doi.org/10.1093/eep/dvy019

Meloni, M., & Testa, G. (2014). Scrutinizing the epigenetics revolution. *BioSocieties*, *9*(4), 431-456. https://doi.org/10.1057/biosoc.2014.22

Meloni, M., Williams, S., & Martin, P. (2016). The Biosocial: Sociological Themes and Issues. *The Sociological Review*, *64*(1_suppl), 7–25. https://doi.org/10.1111/2059-7932.12010

Meskus, M. (2018). *Craft in Biomedical Research: The iPS Cell Technology and the Future of Stem Cell Science*. Springer.

Metzler, I. (2010). Biomarkers and their consequences for the biomedical profession: a social science perspective. *Personalized Medicine*, *7*(4), 407-420. https://doi.org/10.2217/pme.10.41

Miller, P., & Rose, N. (1986). *The power of psychiatry*. Polity Press.

Mol, A. (1999). Ontological politics. A word and some questions. *The Sociological Review*, *47*(1_suppl), 74-89. https://doi.org/10.1111/j.1467-954X.1999.tb03483.x

Mol, A. (2002). *The body multiple: Ontology in medical practice*. Duke University Press.

Molinie, B., Wang, J., Lim, K. S., Hillebrand, R., Lu, Z.-x., Van Wittenberghe, N., Howard, B. D., Daneshvar, K., Mullen, A. C., Dedon, P. (2016). m^6A-LAIC-seq reveals the census and complexity of the m^6A epitranscriptome. *Nature Methods*, *13*(8), 692-698. https://doi.org/10.1038/nmeth.3898

Moore, L. D., Le, T., & Fan, G. (2013). DNA methylation and its basic function. *Neuropsychopharmacology*, *38*(1), 23-38. https://doi.org/10.1038/npp.2012.112

Moorheard, J. (2010). Henrietta Lacks: The mother of modern medicine. *The Guardian*. Retrieved from https://www.theguardian.com/science/2010/jun/23/henrietta-lacks-cells-medical-advances

Müller, R. (2017). Der epigenetische Körper. Zwischen biosozialer Komplexität und Umweltdeterminismus. *Open Gender Journal*, *1*. https://doi.org/10.17169/ogj.2017.17

Müller R. (2020). A task that remains before us: Reconsidering inheritance as a biosocial phenomenon. *Seminars in cell & developmental biology*, *97*, 189–194. https://doi.org/10.1016/j.semcdb.2019.07.008

Müller, R., Hanson, C., Hanson, M., Penkler, M., Samaras, G., Chiapperino, L., Dupré, J., Kenney, M., Kuzawa C., Latimer, J., Lloyd, S., Lunkes, A., Macdonald, M., Meloni, M., Nerlich, B., Panese, F., Pickersgill, M., Richardson, S., Rüegg, J., Schmitz, S., Stelmach, A., Villa, P.-.I. (2017). The biosocial genome? *EMBO reports*, 18(10), 1677-1682. https://doi.org/10.15252/embr.201744953

Müller, R., & Samaras, G. (2018). Epigenetics and aging research: Between adult malleability and early life programming. *BioSocieties*, *13*(4), 715-736. https://doi.org/10.1057/s41292-017-0091-y

Murgatroyd, C. (2010). *The power of the gene*. Nova Science Publishers.

Murgatroyd, C., & Spengler, D. (2011). Epigenetics of early child development. *Frontiers in Psychiatry*, *2*(16). 1-15. https://doi.org/10.3389/fpsyt.2011.00016

Murgatroyd, C., Wu, Y., Bockmühl, Y., & Spengler, D. (2010). Genes learn from stress: how infantile trauma programs us for depression. *Epigenetics*, *5*(3), 194-199. https://doi.org/10.4161/epi.5.3.11375

Murphy, M. (2006). *Sick building syndrome and the problem of uncertainty: Environmental politics, technoscience, and women workers*. Duke University Press.

N.N. (2018). Method of the Year 2017: Organoids. *Nature Methods*, 15(1), 1-1. https://doi.org/10.1038/nmeth.4575

Nagy, C., & Turecki, G. (2012). Sensitive periods in epigenetics: bringing us closer to complex behavioral phenotypes. *Epigenomics*, *4*(4), 445–457. https://doi.org/10.2217/epi.12.37

Nelkin, D. (1994). *Selling science: How the press covers science and technology* (revised ed.). W. H. Freeman Co.

Nelkin, D. (2001). Molecular metaphors: the gene in popular discourse. *Nature Reviews Genetics, 2*(7), 555-559. https://doi.org/10.1038/35080583

Nelkin, D., & Lindee, M. S. (2010). *The DNA mystique: The gene as a cultural icon*. University of Michigan Press.

Nelson, N. C. (2013). Modeling mouse, human, and discipline: Epistemic scaffolds in animal behavior genetics. *Social Studies of Science*, *43*(1), 3-29. https://doi.org/10.1177/0306312712463815

Nelson, N. C. (2018). *Model behavior: Animal experiments, complexity, and the genetics of psychiatric disorders*. University of Chicago Press.

Nevin, C., & Carroll, M. (2015). Sperm DNA methylation, infertility and transgenerational epigenetics. *Journal of Human Genetics and Clinical Embryology*, *1*(004), 1-9. http://doi.org/10.24966/GGS-2485/100004

Nicholson, D. J., & Dupré, J. (2018). *Everything flows: Towards a processual philosophy of biology*. Oxford University Press.

Niewöhner, J. (2011). Epigenetics: Embedded bodies and the molecularisation of biography and milieu. *BioSocieties*, *6*(3), 279-298. https://doi.org/10.18452/19376

Niewöhner, J. (2015). Epigenetics: localizing biology through co-laboration. *New Genetics and Society*, *34*(2), 219-242. https://doi.org/10.1080/14636778.2015.1036154

Niewöhner, J., & Lock, M. (2018). Situating local biologies: Anthropological perspectives on envi-

ronment/human entanglements. *BioSocieties*, *13*(4), 681-697. https://doi.org/10.1057/s41292-017-0089-5

Nowotny, H. (2015). *The cunning of uncertainty*. John Wiley & Sons.

Ohnuki, M., & Takahashi, K. (2015). Present and future challenges of induced pluripotent stem cells. Philosophical Transactions of the Royal Society B: *Biological Sciences*, *370*(20140367), 1-8. https://doi.org/10.1098/rstb.2014.0367

Orlikowski, W. J., & Scott, S. V. (2008). 10 sociomateriality: challenging the separation of technology, work and organization. *Academy of Management Annals, 2*(1), 433-474.

Oyama, S., Griffiths, P. E., & Gray, R. D. (2003). *Cycles of contingency: Developmental systems and evolution*. MIT Press.

Park, M., & Kobor, M. S. (2015). The potential of social epigenetics for child health policy. *Canadian Public Policy*, *41*(Supplement 2), 89-96. https://doi.org/10.3138/cpp.2014-081

Peedicayil, J. (2014). Epigenetics and the war on mental illness. *Molecular Psychiatry*, *19*(9), 960-960. https://doi.org/10.1038/mp.2014.16

Peña, C. J., & Nestler, E. J. (2018). Progress in Epigenetics of Depression. *Progress in molecular biology and translational science*, *157*, 41–66. https://doi.org/10.1016/bs.pmbts.2017.12.011

Penkler, M., & Müller, R. (2018). Von ‚Fehlanpassungen ‘und ‚metabolischen Ghettos ‘: Zur Konzeptualisierung globaler Gesundheitsunterschiede im Feld der Developmental Origins of Health and Disease. *Berichte zur Wissenschaftsgeschichte*, *41*(3), 258-278. https://doi.org/10.1002/bewi.201801902

Pentecost, M., & Meloni, M. (2020). “It's Never Too Early”: Preconception Care and Postgenomic Models of Life. *Frontiers in Sociology*, *5*(21). 1-13. https://doi.org/10.3389/fsoc.2020.00021

Phillips, T. (2008). The role of methylation in gene expression. *Nature Education*, *1*(1), 116. Available at https://www.nature.com/scitable/topicpage/the-role-of-methylation-in-gene-expression-1070/

Pickersgill, M. (2009). Between soma and society: Neuroscience and the ontology of psychopathy. *BioSocieties*, *4*(1), 45-60. https://doi.org/10.1017/S1745855209006425

Pickersgill, M. (2011). Ordering disorder: Knowledge production and uncertainty in neuroscience research. *Science as Culture*, *20*(1), 71-87. https://doi.org/10.1080/09505431.2010.508086

Pickersgill, M. (2012). What is psychiatry? Co-producing complexity in mental health. *Social Theory & Health*, *10*(4), 328-347. https://dx.doi.org/10.1057%2Fsth.2012.9

Pickersgill, M. (2013). The social life of the brain: Neuroscience in society. *Current Sociology*, *61*(3), 322-340. https://doi.org/10.1177%2F0011392113476464

Pickersgill, M. (2014). The endurance of uncertainty: antisociality and ontological anarchy in British psychiatry, 1950–2010. *Science in Context*, *27*(1), 143-175. https://dx.doi.org/10.1017%2FS0269889713000410

Pickersgill, M. (2016). Epistemic modesty, ostentatiousness and the uncertainties of epigenetics: on the knowledge machinery of (social) science. *The Sociological Review*, *64*, 186-202. https://doi.org/10.1002/2059-7932.12020

Pickersgill, M., Niewöhner, J., Müller, R., Martin, P., & Cunningham-Burley, S. (2013). Mapping the new molecular landscape: social dimensions of epigenetics. *New Genetics and Society*, *32*(4), 429-447. https://doi.org/10.1080/14636778.2013.861739

Pinel, C., Prainsack, B., & McKevitt, C. (2018). Markers as mediators: A review and synthesis of epigenetics literature. *BioSocieties*, *13*(1), 276-303. https://doi.org/10.1057/s41292-017-0068-x

Popper, K. (1959/2005). *The logic of scientific discovery*. Routledge.

Prainsack, B. (2017). *Personalized medicine: empowered patients in the 21st century?* NYU Press.

Qureshi, I. A., & Mehler, M. F. (2018). Epigenetic mechanisms underlying nervous system diseases. *Handbook of clinical neurology*, *147*, 43–58. https://doi.org/10.1016/B978-0-444-63233-3.00005-1

Raabe, F. J., & Spengler, D. (2013). Epigenetic Risk Factors in PTSD and Depression. *Frontiers in Psychiatry*, *4*, 80. https://doi.org/10.3389/fpsyt.2013.00080

Rabinow, P., & Rose, N. (2006). Biopower today. *BioSocieties*, *1*(2), 195-217. https://doi.org/10.1017/S1745855206040014

Rees, T. (2016). *Plastic reason: An anthropology of brain science in embryogenetic terms*. University of California Press.

Rheinberger, H.-J. (1997). *Toward a history of epistemic things: Synthesizing proteins in the test tube*. Stanford University Press Stanford, CA.

Rheinberger, H.-J. (2000). Gene Concepts: Fragments from the Perspective of Molecular Biology. In P. Beurton, R. Falk, & H.-J. Rheinberger (Eds.), *The Concept of the Gene in Development and Evolution: Historical and Epistemological Perspectives* (Cambridge Studies in Philosophy and Biology, pp. 219-239). Cambridge University Press. https://doi.org/10.1017/CBO9780511527296.012

Rheinberger, H.-J. (2008). What happened to molecular biology? *BioSocieties*, *3(*3), 303-310. https://doi.org/10.1017/S1745855208006212

Richardson, S. (2015). Maternal bodies in the postgenomic order. In S. Richardson, H. Stevens (Eds.), *Postgenomics*: *Perspectives on biology after the genome* (pp. 210-231). Duke University Press. https://doi.org/10.1215/9780822375449-011

Richardson, S. S. (2017). Plasticity and programming: Feminism and the epigenetic imaginary. *Signs: Journal of women in culture and society*, *43*(1), 29-52. Available at https://j.mp/2o67aGv

Richardson, S. S., & Stevens, H. (Eds.). (2015*). Postgenomics: Perspectives on biology after the genome*. Duke University Press.

Riggs, A. D. (1975). X inactivation, differentiation, and DNA methylation. Cytogenetic and *Genome Research*, *14*(1), 9-25. https://doi.org/10.1159/000071569

Roepstorff, A. (2001). Thinking with animals. *Σημειωτκή-Sign Systems Studies*, 29(1), 203-218. https://philpapers.org/go.pl?id=ROETWA&proxyId=&u=http%3A%2F%2Fdx.doi.org%2F10.5840%2Fsignsystems200129158

Rose, N. (2007). *The politics of life itself: biomedicine, power and subjectivity in the twenty-first century*. Princeton University Press.

Rose, N. (2019). *Our psychiatric future*. Polity Press.

Rose, N. R., & Klose, R. J. (2014). Understanding the relationship between DNA methylation and histone lysine methylation. *Biochimica et Biophysica Acta*, *1839*(12), 1362-1372. http://dx.doi.org/10.1016/j.bbagrm.2014.02.007

Roseboom, T. J., Van Der Meulen, J. H., Ravelli, A. C., Osmond, C., Barker, D. J., & Bleker, O. P. (2001). Effects of prenatal exposure to the Dutch famine on adult disease in later life: an overview. *Twin Research and Human Genetics*, *4*(5), 293-298. https://doi.org/10.1375/twin.4.5.293

Rüppel, J. (2019). "Now Is a Time for Optimism": The Politics of Personalized Medicine in Mental Health Research. *Science, Technology, & Human Values*, *44*(4), 581-611. https://doi.org/10.1177%2F0162243919845049

Rüppel, J., Schnieder, L., & Lemke, T. (2018). *Die Personalisierung der Depression*. Gen-ethischer Informationsdienst. Available at https://www.gen-ethisches-netzwerk.de/oktober-2018/die-personalisierung-der-depression

Rüppel, J., & Voigt, T. H. (2019). The Death of the Clinic? Emerging Biotechnologies and the Reconfiguration of Mental Health. *Science, Technology, & Human Values*, *44*(4), 567–580. https://doi.org/10.1177/0162243919853619

Ryan, J., Chaudieu, I., Ancelin, M. L., & Saffery, R. (2016). Biological underpinnings of trauma and post-traumatic stress disorder: focusing on genetics and epigenetics. *Epigenomics*, *8*(11), 1553–1569. https://doi.org/10.2217/epi-2016-0083

Saha, K., & Jaenisch, R. (2009). Technical challenges in using human induced pluripotent stem cells to model disease. *Cell Stem Cell*, *5*(6), 584–595. https://doi.org/10.1016/j.stem.2009.11.009

Samaras, G. (2019). Care Revisited. Behandeln und Begutachten als Spannungsfeld in der psychiatrischen Praxis mit Flüchtlingen. In S. Hess., C. Bischoff, C. Endter, S. Kienitz, S. Bergmann, & B. Binder (Eds.), *Care: Praktiken und Politiken der Fürsorge: Ethnographische und geschlechtertheoretische Perspektiven*. Verlag Barbara Budrich

Schatzki, T. R. (1996). *Social practices: A Wittgensteinian approach to human activity and the social*. Cambridge University Press.

Scheff, T. J. (1974). The labelling theory of mental illness. *American Sociological Review, 39*(3), 444–452. https://doi.org/10.2307/2094300

Schmuckler, M. A. (2001). What is ecological validity? A dimensional analysis. *Infancy, 2*(4), 419–436. https://doi.org/10.1207/S15327078IN0204_02

Schrader A. (2010). Responding to Pfiesteria piscicida (the fish killer): phantomatic ontologies, indeterminacy, and responsibility in toxic microbiology. *Social studies of science*, *40*(2), 275–306. https://doi.org/10.1177/0306312709344902

Scudellari M. (2016). How iPS cells changed the world. *Nature*, *534*(7607), 310–312. https://doi.org/10.1038/534310a

Seaberg, R. M., & van der Kooy, D. (2003). Stem and progenitor cells: the premature desertion of rigorous definitions. *Trends in Neurosciences*, *26*(3), 125-131. https://doi.org/10.1016/S0166-2236(03)00031-6

Selye, H. (1956). *The stress of life*. McGraw Hill.

Shostak, S., & Moinester, M. (2015). Beyond Geneticization. In S. E. Bell & A. E. Figert (Eds.), *Reimagining (Bio) medicalization, pharmaceuticals and genetics: Old critiques and new engagements* (pp. 216-238). Routledge.

Silverman, D. (2013). *Doing qualitative research: A practical handbook*. Sage.

Skinner M. K. (2015). Environmental Epigenetics and a Unified Theory of the Molecular Aspects of Evolution: A Neo-Lamarckian Concept that Facilitates Neo-Darwinian Evolution. *Genome biology and evolution*, *7*(5), 1296–1302. https://doi.org/10.1093/gbe/evv073

Skloot, R. (2017). *The immortal life of Henrietta Lacks*. Broadway Paperbacks.

Slack, J. M. (2012). *Essential developmental biology*. John Wiley & Sons.

Sörensen, E. (2014). Akteur-Netzwerk Theorie überdacht. In S. Beck, J. Niewöhner, & E. Sörensen (Eds.), *Science and Technology Studies: eine sozialanthropologische Einführung* (Vol. 17, pp. 327-344): transcript Verlag.

Speer, S. A. (2002). 'Natural' and 'Contrived' Data: a Sustainable Distinction? Discourse studies, *4(*4), 511-525. https://doi.org/10.1177%2F1461445602004004060 1

Spradley, J. P. (1980). *Participant observation*. Waveland Press.

Stelmach, A., & Nerlich, B. (2015). Metaphors in search of a target: the curious case of epigenetics. *New genetics and society*, *34*(2), 196–218. https://doi.org/10.1080/14636778.2015.1034849

Sterling, P., & Eyer, J. (1988). Allostasis: A new paradigm to explain arousal pathology. In S. Fisher & J. Reason (Eds.), *Handbook of life stress, cognition and health* (pp. 629–649). John Wiley & Sons.

Strauss, A., & Corbin, J. (1998). *Basics of qualitative research techniques*. Sage.

Strauß, B., & Schumacher, J. (2004). *Klinische Interviews und Ratingskalen*. Hogrefe Verlag.

Ströhle, A., & Holsboer, F. (2003). Stress responsive neurohormones in depression and anxiety. *Pharmacopsychiatry*, *36 Suppl 3*, S207–S214. https://doi.org/10.1055/s-2003-45132

Szasz, T. (1974). *The myth of mental illness: Foundations of a theory of personal conduct*. Harper & Row.

Szyf, M., & Pluess, M. (2015). Epigenetics and well-being: Optimal adaptation to the environment. In M. Pluess (Ed.), *Genetics of Psychological Well-being: The role of heritability and genetics in positive psychology* (pp. 211-230). Oxford University Press.

Tolstoy, L. (1878/2003). *Anna Karenina*. Penguin Books.

Tolwinski, K. (2013). A new genetics or an epiphenomenon? Variations in the discourse of epigenetics researchers. *New Genetics and Society*, *32*(4), 366-384. https://doi.org/10.1080/14636778.2013.849928

Van Speybroeck, L. (2000). The organism: a crucial genomic context in molecular epigenetics? *Theory in Biosciences*, *119*(3-4), 187-208. https://doi.org/10.1078/1431-7613-00016

Verran, H. (2001). *Science and an African logic*. University of Chicago Press.

Vidal, F., & Ortega, F. (2017). *Being brains: Making the cerebral subject*. Fordham University Press.

Vigo, D., Thornicroft, G., & Atun, R. (2016). Estimating the true global burden of mental illness. *The Lancet Psychiatry*, *3*(2), 171-178. https://doi.org/10.1016/S2215-0366(15)00505-2

Von Uexküll, J. (1940/1982). The theory of meaning. *Semiotica*, *42*(1), 25-82. https://doi.org/10.1515/semi.1982.42.1.25

Waddington, C. H. (1942). Canalization of development and the inheritance of acquired characters. *Nature*, *150*(3811), 563-565. https://doi.org/10.1038/150563a0

Waggoner, M. R., & Uller, T. (2015). Epigenetic determinism in science and society. *New Genetics and Society*, *34*(2), 177-195. https://doi.org/10.1080/14636778.2015.1033052

Walf, A. A., & Frye, C. A. (2007). The use of the elevated plus maze as an assay of anxiety-related behavior in rodents. *Nature Protocols*, *2(*2), 322-328. https://doi.org/10.1038/nprot.2007.44

Walker, L. E. (1979). *The battered woman*. Harper & Row.

Walsh, R. N., & Cummins, R. A. (1976). The open-field test: A critical review. *Psychological Bulletin, 83*(3), 482–504. https://doi.org/10.1037/0033-2909.83.3.482

Warneken, B. J., & Wittel, A. (1997). Die neue Angst vor dem Feld. Ethnographisches research up am Beispiel der Unternehmensforschung. *Zeitschrift für Volkskunde*, *93*, 1-16.

Waterland, R. A., & Jirtle, R. L. (2003). Transposable elements: targets for early nutritional effects on epigenetic gene regulation. *Molecular and cellular biology*, *23*(15), 5293–5300. https://doi.org/10.1128/mcb.23.15.5293-5300.2003

Weaver, I. C., Cervoni, N., Champagne, F. A., D'Alessio, A. C., Sharma, S., Seckl, J. R., Dymov, S., Szyf, M., Meaney, M. J. (2004). Epigenetic programming by maternal behavior. *Nature Neuroscience*, *7*(8), 847-854. https://doi.org/10.1038/nn1276

Weber, M. (1904). Die "Objektivität" sozialwissenschaftlicher und sozialpolitischer Erkenntnis. *Archiv für Sozialwissenschaft und Sozialpolitik*, *19*(1), 22-87. https://nbn-resolving.org/urn:nbn:de:0168-ssoar-50770-8

Wehling, P., Viehöver, W., Keller, R., & Lau, C. (2007). Zwischen Biologisierung des Sozialen und neuer Biosozialität: Dynamiken der biopolitischen Grenzüberschreitung. *Berliner Journal für Soziologie*, *17*(4), 547-567. https://doi.org/10.1007/s11609-007-0045-5

Wells, J. C. (2010). Maternal capital and the metabolic ghetto: an evolutionary perspective on the transgenerational basis of health inequalities. *American Journal of Human Biology: The Official Journal of the Human Biology Association*, *22*(1), 1-17. https://doi.org/10.1002/ajhb.20994

Wilkie, R. (2015). Multispecies scholarship and encounters: Changing assumptions at the human-animal nexus. *Sociology*, *49*(2), 323-339. https://doi.org/10.1177%2F0038038513490356

Winthereik, B. R., & Verran, H. (2012). Ethnographic Stories as Generalizations that Intervene. *Science & Technology Studies*, *28*(1). Available at https://sciencetechnologystudies.journal.fi/article/view/55280

World Health Organization (2013). *Mental health action plan* 2013-2020.

Wu, C. T., & Morris, J. R. (2001). Genes, genetics, and epigenetics: a correspondence. *Science, 293*(5532), 1103–1105. https://doi.org/10.1126/science.293.5532.1103

Yehuda, R., & Bierer, L. M. (2009). The relevance of epigenetics to PTSD: implications for the DSM-V. *Journal of traumatic stress*, *22*(5), 427–434. https://doi.org/10.1002/jts.20448

Yehuda, R., Daskalakis, N. P., Bierer, L. M., Bader, H. N., Klengel, T., Holsboer, F., & Binder, E. B. (2016). Holocaust exposure induced intergenerational effects on FKBP5 methylation. *Biological Psychiatry*, *80*(5), 372-380. http://dx.doi.org/10.1016/j.biopsych.2015.08.005

Yue, Y., Liu, J., & He, C. (2015). RNA N6-methyladenosine methylation in post-transcriptional gene expression regulation. *Genes & development*, *29*(13), 1343–1355. https://doi.org/10.1101/gad.262766.115

Zannas, A. S., Arloth, J., Carrillo-Roa, T., Iurato, S., Röh, S., Ressler, K. J., Nemeroff, C. B., Smith, A. K., Bradley, B., Heim, C., Menke, A., Lange, J. F., Brückl, T., Ising, M., Wray, N. R., Erhardt, A., Binder, E. B., & Mehta, D. (2015). Lifetime stress accelerates epigenetic aging in an urban, African American cohort: relevance of glucocorticoid signaling. *Genome Biology*, 16(1), 1-12. https://doi.org/10.1186/s13059-015-0828-5

Zhang, T.-Y., Keown, C. L., Wen, X., Li, J., Vousden, D. A., Anacker, C., Bhattacharyya, U., Ryan, R., Diorio, J., O'Toole, N., Lerch, J. P., Mukamel, E. A., & Meaney, M. J. (2018). Environmental enrichment increases transcriptional and epigenetic differentiation between mouse dorsal and ventral dentate gyrus. *Nature Communications*, *9*(1), 1-11. https://doi.org/10.1038/s41467-017-02748-x

Zola, I. K. (1972). Medicine as an institution of social control. *The Sociological Review*, *20*(4), 487-504. https://doi.org/10.1111%2Fj.1467-954X.1972.tb00220.x

9 Annex

9.1 List of abbreviations

APA	American Psychological Association
Dex	Dexamethasone
DNA	Deoxyribonucleic acid
DSM	Diagnostic and Statistical Manual of Mental Disorders
ECG	Electrocardiogram
fMRI	Functional magnetic resonance imaging
HPA axis	Hypothalamic–pituitary–adrenal axis
ICD	International Statistical Classification of Diseases and Related Health Problems
ID	Identity domain
iPS cells	Induced pluripotent stem cells
GR	Glucocorticoid receptor
GT	Grounded Theory
MDD	Major Depressive Disorder
m^{6}A	N^6-methyladenosine
mRNA	Messenger RNA
NGS	Next-generation-sequencing
PCR	Polymerase chain reaction
PET	Positron emission tomography
PTSD	Post-traumatic stress disorder
RNA	Ribonucleic acid
SES	Socio-economic status
SNPs	Single nucleotide polymorphisms
TRBP	Trauma-Related Binding Protein
TSST	Trier Social Stress Test
WHO	World Health Organization

9.2 List of figures

10 Abstracts

10.1 English abstract

During the last two decades, we can observe a change in how the life sciences conceptualise life: no longer mainly based on an unchangeable genome, but increasingly as affected by the way we live. Environmental epigenetics is an emerging research approach within this perspective and proposes that human bodies and minds are malleable, able to adapt to socio-material environments, among them toxins, nutrition, and stressful experiences. These adaptations, researchers suggest, take place via molecular processes, altering the way our genes are transcribed and therefore the way our bodies and health develop. While environmental epigenetics offers important novel insights for understanding human life as a *biosocial* phenomenon, it also extends the biological gaze from the laboratory towards suitable objects of study out in the *real* world – an extension that possibly implies social and political consequences for individual and community live, as well as for scientific research practices.

This thesis therefore studies how a psychiatric research institute uses approaches from environmental epigenetics to better understand the causes for and development of mental health conditions. Within epigenetic research in psychiatry, stressful experiences are described as a crucial epigenetic environment which gives rise to research strategies attempting to re-enact stress in the laboratory setting. In my thesis, I provide in-depth insights into these everyday research practices based on ethnographic fieldwork, qualitative interviews, and literature analysis. I specifically investigate re-enactments of stress in three different experimental arrangements: cell models, animal models, and research with human material. Given this context, I argue that these different experimental arrangements enable equally different epigenetic accounts of mental health with diverse social implications.

In addition to the analysis of how researchers operate with environment/stress in their experiments, the work also looks at the *environment* of these research practices and the biological laboratory. Given this perspective, I demonstrate a divergence between the scientists' ideal imaginations about conducting neat stress research and the actual research conditions. That is to say, that environment in epigenetics not only matters as a stimulus in stress experiments, but also as *a real-world* phenomenon that influences research practices, such as a noisy construction site, that might have effects on behavioural experiments with mice.

Given the central hypothesis of environmental epigenetic research – namely that environmental experiences are reflected in our biology, even down to the cell nucleus – my work provides important insights into how epigenetic perspectives are not only integrated into psychiatric research, but also how environmental epigenetics itself might change biological research. In other words, this thesis

shows how epigenetics holds the potential to change the epistemology of the life sciences and our social science understanding of the biological laboratory.

10.2 Zusammenfassung

In den letzten zwei Jahrzehnten können wir einen Wandel in der Art und Weise beobachten, wie die Biologie das menschliche Leben konzeptualisiert: nicht mehr hauptsächlich basierend auf einem unveränderlichen Genom, sondern zunehmend dadurch beeinflusst, wie wir leben. Innerhalb dieser Perspektive ist die Umweltepigenetik ein neuer wichtiger Forschungsansatz. Sie geht davon aus, dass unser Körper und Geist formbar sind und durch sozio-materielle Umweltaspekte, darunter Toxine, Ernährung und Stresserfahrungen, verändert werden können. Diese Anpassungen, so die Forscher*innen, erfolgen über molekulare Mechanismen, die die Art und Weise beeinflusst, wie unsere Gene abgeschrieben werden und damit, wie sich unser Körper und unsere Gesundheit entwickeln. Während die Umweltepigenetik wichtige neue Einsichten zum Verständnis des menschlichen Lebens als *biosoziales* Phänomen bietet, erweitert sie auch den biologischen Blick aus dem Labor auf geeignete Studienobjekte in der *realen* Welt – eine Erweiterung, die möglicherweise soziale und politische Konsequenzen für das Leben des Einzelnen und der Gemeinschaft sowie für die wissenschaftliche Forschungspraxis mit sich bringt.

In dieser Arbeit wird daher untersucht, wie ein psychiatrisches Forschungsinstitut Ansätze aus der Umweltepigenetik integriert, um die Ursachen für und die Entwicklung von psychischen Gesundheitszuständen besser zu verstehen. Im Rahmen der epigenetischen Forschung in der Psychiatrie werden Stresserfahrungen als eine entscheidende epigenetische Umwelt beschrieben. Diese Konzeptualisierung führt zu Forschungsstrategien, Stress in der Laborsituation nachzustellen. In meiner Dissertation gebe ich vertiefte Einblicke in diese alltäglichen Forschungspraktiken auf Grundlage ethnographischer Feldforschung, qualitativer Interviews und Literaturanalyse. Ich untersuche insbesondere die Inszenierung von Stress in drei verschiedenen experimentellen Versuchsanordnungen: Zellmodelle, Tiermodelle und Forschung mit menschlichem Material. Vor diesem Hintergrund argumentiere ich, dass diese unterschiedlichen Versuchsanordnungen ebenso unterschiedliche epigenetische Konfigurationen psychischer Gesundheit mit spezifischen sozialen Auswirkungen realisieren.

Neben der Analyse, wie Forscher*innen in ihren Experimenten mit Umwelt/Stress umgehen, befasst sich die Arbeit auch mit der *Umwelt* dieser Forschungspraktiken und dem biologischen Labor. Aus dieser Perspektive zeige ich eine Diskrepanz zwischen den Idealvorstellungen der Wissenschaftler*innen über die Durchführung sauberer Stressforschung und den tatsächlichen Forschungsbedingungen. Das heißt, dass die Umwelt in der Epigenetik nicht nur als Stimulus in Stressexperimenten wirksam wird. Sie tritt auch auch als reales Phänomen in Erscheinung, das die Forschungspraktiken beeinflusst, wie z.B. eine laute Baustelle, die potentiell Auswirkungen auf Verhaltensexperimente mit Mäusen haben kann.

Angesichts der zentralen Hypothese der epigenetischen Umweltforschung – nämlich, dass sich Umwelterfahrungen in unserer Biologie bis hinunter zum Zellkern widerspiegeln – liefert meine Arbeit wichtige Erkenntnisse darüber, wie epigenetische Perspektiven nicht nur in die psychiatrische Forschung integriert werden, sondern auch darüber, wie die Umweltepigenetik möglicherweise die biologische Forschung selbst verändern kann. Mit anderen Worten: Diese Arbeit zeigt, wie die Epigenetik das Potenzial hat, die Epistemologie der Lebenswissenschaften und unser sozialwissenschaftliches Verständnis des biologischen Labors zu verändern.