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Magnetic Resonance Imaging and the Prediction of Outcome in First-Episode Schizophrenia: A Review of Current Evidence and Directions for Future Research

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Magnetic Resonance Imaging (MRI) measures are promising outcome markers for schizophrenia, since regional frontal and temporal grey matter volumes reductions, and enlargement of the ventricles, have been associated with outcome in this disorder. However, a number of methodological issues have limited the potential clinical utility of these findings. This article reviewed studies that examined brain structure at illness onset as a predictor of outcome, discusses the limitations of the findings, and highlights the challenges that would need to be addressed if structural data are to inform the management of an individual patient. ***Methods:*** **Using a set of a priori criteria, we systematically searched Medline and EMBASE databases for articles evaluating brain structure at the time of the first psychotic episode and assessed response to treatment, symptomatic outcome, or functional outcome at any point in the first 12 months of illness.** ***Results:*** **The 11 studies identified suggest that alterations in medial temporal and prefrontal cortical areas, and in the networks that connect them with subcortical structures, are promising neuroanatomical markers of poor symptomatic and functional outcomes.** ***Conclusion:*** **Neuroimaging data, possibly in combination with other biomarkers of disease, could help stratifying patients with psychoses to generate patient clusters clinically meaningful, and useful to detect true therapeutic effects in clinical trials. Optimization of Treatment and Management of Schizophrenia in Europe (OPTiMiSE), a large multicenter study funded by the FP7 European Commission, could generate these much-needed findings.**

Key words: psychosis/MRI/brain structure/treatment response/OPTiMiSE

Introduction

The first and most pressing challenge in individuals experiencing the first episode of schizophrenia is how to predict who will respond to an antipsychotic with a specific pharmacological profile, so that symptom remission is achieved quickly. However, our current treatment algorithms do not allow for individual differences, and treatments are still chosen by "trial and error," without reference to, or guidance from, the biological background of the individual. This is because we lack knowledge on reliable predictive (biological) markers. Given that schizophrenia is associated with robust reductions in regional frontal and temporal grey matter volumes, and enlargement of the ventricles, and that these have been associated with symptom profiles as well as outcome, Magnetic Resonance Imaging (MRI) measures are promising biological markers for treatment outcome.[1] Since structural measures are often easier to ascertain across imaging platforms and are relatively independent on patient cognitive condition and cooperation, they will form the focus of the present review. MRI as a tool can be used to identify these neuroanatomical

markers in vivo, and play an important role: it is non-invasive, quick, and inexpensive compared with other neuroimaging approaches such as Positron Emission Tomography (PET).

Neuroanatomical Markers in Schizophrenia

Some of these neuroanatomical abnormalities, including volume reductions of prefrontal, temporal, cingulate cortices, are already evident before the first psychotic symptoms emerge, and even at illness onset before antipsychotic treatment starts.[2–4] Among other brain areas, recent meta-analytic evidence incorporating findings from both structural and functional neuroimaging studies[5] suggests a predominant role for perigenual cingulate and insular cortices.

The fact that these volumetric abnormalities are not generally visible to the naked eye in a radiological examination, as they reflect quantitative changes distributed across several brain regions, has affected their clinical utility in psychosis. Nevertheless, several computerized tomography (CT) and MRI studies have reported that their severity is related to subsequent clinical outcome, with more marked reductions in total and in regional grey matter volume, and greater enlargement of the ventricles associated with a relatively poor response to treatment.[6–12] However, other studies have been inconclusive.[13,14] This may reflect the use of small samples, heterogeneous with respect to the stage of the disorder and previous exposure to treatment, both of which can affect neuroimaging measures in schizophrenia. Moreover, treatment in these studies has generally been naturalistic, with patients receiving a variety of different drugs at varying doses and durations, and with therapeutic response defined retrospectively in an unblinded fashion, on the basis of clinical records. At least some of these issues can be addressed by studying patients at the initial stages of the illness, when they are still drug naïve or have only been exposed to short-term treatment, and response assessed in a more standardized way.

Brain Structure at the First Psychotic Episode as a Predictor of Outcome and Response to Treatment

We know that in fact there is large variability in response to the first antipsychotic prescribed. For example, in the large European First Episode Schizophrenia Trial (EUFEST) trial only ~55% of first-episode psychosis patients responded to antipsychotics in the first 12 months. Here response was defined as ≥50% response according to the Positive and Negative Syndrome Scale (PANSS) scores.[15] Two other important first episode studies found higher remission rates of about 80%, even though they also used stringent criteria for remission.[16,17] Although symptomatic response is thought to be one of the strongest predictors of subsequent functional and clinical outcome in psychosis,[18,19] the relationship between response within the first 12 month of illness and brain structure at onset has not been extensively investigated.

We therefore searched Medline and EMBASE databases using the terms: ["schizophrenia" OR "psychosis" OR "schizo$"] AND ["response" OR "outcome" OR "antipsychotic" AND ["MRI NOT functional]. Abstracts were reviewed to assess the relevance of the articles identified and any duplicates were removed. Further, references were also examined for relevance and included if appropriate. The criterion of adherence to the keywords was defined as the presence of a significant number of keywords in either the text or the abstract. Since we did not follow a published prespecified protocol during our systematic review, the inclusion/exclusion criteria and search strategy were defined a priori. The inclusion criteria were: (1) publication between January 1976 and December 2015; (2) diagnosis of any functional psychotic illness; (3) age of patients between 16 and 80 years; (4) evaluation of brain structure with morphometric techniques that measured volume, shape, thickness, or surface area of gray matter structures or volume of white matter; (5) assessment of response to treatment, symptomatic outcome, or functional outcome conducted at any point in the first 12 months from onset; and (6) analysis of longitudinal data explicitly evaluating the relationship between structural brain measures at the time of first onset, and outcomes measured in the first 12 months. Exclusion criteria were as follows: (1) inclusion of high-risk subjects with no diagnosis of psychosis; (2) use of MRI sequences other that T1, T2, or dual spin echo, such as Diffusion Tensor Imaging; (3) absence of a longitudinal evaluation of outcome or evaluation conducted more than 12 months after illness onset; and (4) publication in the form of short reports or brief communications.

The articles included in this review are listed in table 1.

Brain Structure and Prediction of Outcome at 1 Year

We identified 5 articles that evaluated brain structure at illness onset and remission at 1 year. Fung and colleagues[20] used voxel-based morphometry to study brain structure in 39 patients naïve to antipsychotics. They found that in female patients a larger striatothalamic volume was correlated with response to antipsychotic medications at the 1-year follow up (defined according to threshold score equal to 60 in the General Assessment of Function (GAF) scale).[21] This is important as striatal volume has been previously linked to antipsychotic use, confirming a susceptibility of these structures to treatment.[22] In this study however this correlation was not present in males, who were also less likely to be remitted at the follow-up evaluation. The authors suggest

Table 1. List of Articles Identified in the Review: Details of Methods and Findings

	Reference	Clinical Sample	Time of Outcome Assessment	Outcome Definition	Neuroimaging Details	Main Results
1	Fung et al[20]	1. 39 patients 2. DSM-IV Schizophrenia 3. Drug-naïve	1 y	Remission: score ≥ 60 at GAF[21] scale	1. 1.5-T General Electric scanner 2. Fast spoiled gradient echo 3D sequence; Dual echo/fast spin echo (PD/T2) sequence 3. VBM	1. 29 remitters 2. In females, larger striatothalamic volume correlated with early remission
2	Lieberman et al[23]	1. 70 patients 2. Research Diagnostic Criteria Schizophrenia or Schizoaffective disorder 3. Less than 12 wk of antipsychotic treatment at entry	1 y	Remission: no rating greater than 3 on any of SADS-CPD scale[24] positive psychotic symptom items (suspiciousness, severity of delusions, severity of hallucinations, impaired understandability, bizarre behavior); CGI[25] severity items rating of 3 or less and improvement rating of 2 or 1, for at least 8 wk	1. 1-T Siemens 2. 3D gradient echo pulse sequence (fast low angle shot) 3. Qualitative ratings and automated quantitative measurements	1. 58 remitters 2. Lateral and third ventricles abnormalities predicted longer time to remission 3. Cortical or medial temporal lobe volumes did not predict time to remission
3	Wobrock et al[26]	1. 45 patients (32 included in MRI analyses) 2. DSM-IV schizophrenia	1 y	Outcome defined as stable (an increase of PANSS[15] scores below 10% of the baseline score) or poor (increase of PANSS score above 40% of baseline score)	1. 1.5-T Siemens and Phillips 2. T1-weighted 3D data (MPRAGE) 3. Region of interest and SPM99	1. 12 good outcome 2. Lateral ventricular or hippocampal volumes did not differ between outcome group 3. Poor outcome patients had smaller left anterior limb of the internal capsule
4	Bodnar et al[27]	1. 59 patients 2. Schizophrenia 3. Less than 1 mo of antipsychotic treatment at entry	1 y	Remission defined according to Schizophrenia Working Group criteria[38] (reduction in 8 core PANSS[15] symptoms to 3 (mild) or less, which has to be sustained for at least 6 mo over the first year of illness).	1. 1.5-T Siemens 2. 3D gradient echo pulse sequence 3. VBM and manual segmentation	1. 17 remitters 2. Remitters had larger volume of the parahippocampal cortex, but not of the entorhinal or perirhinal cortices.
5	Prasad et al[29]	1. 27 patients (25 completed follow up) 2. DSM-IV schizophrenia or Schizoaffective disorder 3. Drug-naïve	1 y	Score at Strauss-Carpenter Scale[30] used as continuous measure of functional outcome (0–4 scale, with lower scores representing worse outcome)	1 1.5-T General Electric 2. T1-weighted 3D spoiled-gradient recalled acquisition 3. Manual tracings and histogram-based segmentation	Dorsolateral prefrontal cortex volume, but not intracranial volume, predicted functional outcome at 1 y
6	Kasparek et al[31]	1. 32 male patients 2. ICD-10 schizophrenia	1 y	Good functioning defined as score >60 at GAF[21] scale	1. 1.5-T Siemens 2. T1-weighted images 3D acquisition 3. VBM	1. 21 good functioning 2. Left prefrontal regional volume (extending to inferior, middle and superior frontal gyri) was smaller in those with poor functioning

Table 1. ***Continued***

	Reference	Clinical Sample	Time of Outcome Assessment	Outcome Definition	Neuroimaging Details	Main Results
7	Bodnar et al[32]	1. 68 patients 2. Schizophrenia	6 mo	Symptom remission defined according to Schizophrenia Working Group criteria[38] (reduction in 8 core PANSS[15] symptoms to 3 (mild) or less).	1. 1.5-T Siemens 2. 3D gradient echo pulse sequence 3. VBM	1. 28 remitters 2. Parahippocampal volume was larger in remitters 3. Classification model correctly classified remission status 79% of the time
8	Molina et al[10]	1. 19 patients 2. DSM-IV schizophrenia	6 mo	Response defined as percentage of change in PANSS[15] scores over 6 mo across positive, negative, and disorganization dimension	1. 1.5-T Philips Gyroscan 2. T1-weighted 3D gradient echo sequence 3. VBM	No association between response and brain measures (cerebro spinal fluid and grey matter volume of dorsolateral prefrontal cortex, temporal lobe, hippocampus)
9	Palaniyappan et al[33]	1. 80 patients 2. DSM-IV functional psychoses	12 wk	Treatment response defined according to Schizophrenia Working Group criteria for symptom remission[38] (reduction in 8 core PANSS[15] symptoms to 3 (mild) or less)	1. 3T General Electric 2. 3D MPRAGE 3. Automated surface extraction	1. 40 responders 2. Reduced cortical folding (hypogyria) of frontotemporal regions and insula in nonresponders
10	Szeszko et al[37]	1. 39 patients 2. DSM-IV Schizophrenia, Schizoaffective disorder, Schizophreniform disorder	Up to 16 wk	Treatment response defined as having, at least in 2 consecutive visits, a rating ≤ 3 in the psychosis and disorganization items of the SADS-CPD scale[24] (delusions, hallucinations, understandability, derailment, illogical thinking, bizarre behavior) and a rating of "much" or "very much" improved on the CGI[25]	1. 1.5-T GE 2. T1-weighted, 3D fast SPGR sequence 3. Automated classification and manual delineation of sulcal and gyral landmarks 4. Surface rendering	1. 25 responders 2. Greater frontal cortical asymmetry and greater occipital cortical thickness in responders. 3. Greater temporal cortical thickness was associated with shorter time in the response to antipsychotics
11	Zipursky et al[12]	26 patients 1. DSM-IIIR Schizophrenia, Schizophreniform, Delusional disorder and Psychotic disorder not otherwise specified 2. 21 antipsychotic naïve	1 wk	Response was defined as a reduction of at least 15% in PANSS SADS-CPD scale[15] baseline scores	1. 1.5T General Electric 2. Dual Echo spin sequence 3. Manual segmentation	1. 12 patients improved 2. Greater cortical grey matter volume was associated with improvement in positive and negative symptoms 3. Sulcal and total cerebrospinal fluid volume, and total grey matter volume were associated with symptom improvement at trend level association

Notes: CGI, Clinical Global Impression; DSM, Diagnostic and Statistical Manual; GAF, General Assessment of Function; ICD, International Classification of Diseases; MPRAGE, Magnetization Prepared Rapid Acquisition Gradient Echo; PANSS, Positive and Negative Syndrome Scale; SADS-CPD, Schedule for Affective Disorders - Change and Psychosis and Disorganization; SPGR, Spoiled Gradient Recalled Acquisition; T, Tesla; VBM, Voxel-based morphometry; 3D, Three dimensional.

that gender effect may contribute to the potential for brain structural alterations to predict outcome.[20] Males were less likely to have remitted from a first episode of illness also in an older study,[23] mirroring clinical experience about the course of schizophrenia. In this study 70 patients were examined at their first psychotic episode,

all treated according to a standardized pharmacological protocol with first generation antipsychotics. Patients were classified as remitted according to the positive psychotic symptom items (ie, suspiciousness, severity of delusions, severity of hallucinations, impaired understandability, bizarre behavior) of the Schedule for Affective Disorders (SADS) Change and Psychosis and Disorganization Scale[24] and to Clinical Global Impression (CGI) severity scores.[25] These authors, however, did not report a gender effect, and found that lateral and third ventricles abnormalities predicted longer time to remission. These data suggest that even in males the presence of brain alterations at onset seems associated with more resistant symptoms. In contrast, cortical or medial temporal lobe volumes were not predictive of time to remission. These findings were taken to suggest that medial temporal structures (hippocampus, amygdala) may be particularly involved in mediating the response to positive, rather than the more resistant negative, symptoms; in contrast, alterations in structures that may affect ventricular volumes may be particularly associated with poor outcome. However, the evidence from these studies remains largely correlative and cannot claim to have demonstrated causal effects. Furthermore, the hypothesis from this article was not confirmed by another study, which examined lateral ventricles and the hippocampus in patients with schizophrenia.[26] Here, 45 patients at their first episode were classified at 1 year as having either stable psychopathology (defined as having an increase of PANSS scores below 10% of the baseline score, ~5 points) or bad outcome (increase of PANSS total score above 40% of baseline score, ~20 points) outcome. There were no differences between the 2 groups in lateral ventricular or hippocampal volumes. However, those patients with a poor outcome showed a smaller left anterior limb of the internal capsule. This tract contains fibres linking the frontal cortex with subcortical areas, and the authors interpreted this finding as reflecting a disturbance of frontothalamic connectivity.

Interestingly, in a recent study, Bodnar and colleagues[27] specifically examined another medial temporal area, the parahippocampal gyrus. They studied 3 subregions of this gyrus (entorhinal, perirhinal, parahippocampal), together with verbal memory, in 42 nonremitted and 17 remitted first-episode schizophrenia patients, classified according to the Remission criteria of the Schizophrenia Working Group (based on a reduction in 8 core PANSS symptoms to 3 (mild) or less, which has to be sustained for at least 6 months over the first year of illness).[28] Using a manual segmentation method, the authors found that patients who did not remit showed a smaller volume of the parahippocampal cortex, but not of the entorhinal or perirhinal cortices. Furthermore, this reduction was associated with social withdrawal and severe memory deficits, suggestive of abnormalities in a posterior memory network involving both medial temporal areas and their connections to the prefrontal cortex.

The presence of functional deficits in relation to altered brain structure was also investigated in 2 studies that specifically measured functional rather than symptomatic outcome. Prasad and colleagues[29] used the Strauss–Carpenter Scale[30] to assess functional outcome (which includes frequency of social contacts, employment duration, symptomatology, and duration of re-hospitalization) in 27 antipsychotic-naïve patients with schizophrenia or schizoaffective disorder. They found the dorsolateral prefrontal (DLPF) cortex volume, but not intracranial volume, was a significant predictor of functional outcome at 1 year. A second study[31] conducted in a sample of 32 male only patients with a first-episode schizophrenia evaluated functional outcome with the GAF: patients with scores below or equal to 60 were classified as having poor functioning, and those with GAF score above 60 as good functioning. Using voxel-based morphometry, this study found that patients with poor functioning had smaller volumes than those with good functioning in the left prefrontal region and extending to the inferior, middle, and superior frontal gyri. Again, alterations in these frontal areas may be reflected in emotional and cognitive dysfunctions that affect the individual's ability to carry out everyday activities and experience pleasure.

Brain Structure and Prediction of Outcome Earlier Than 1 Year

Only 2 studies have evaluated the relationship between brain structure and treatment response in the first 6 months of illness.[10,32] One study was conducted by Bodner and colleagues in the same clinical group evaluated also at 1 year and discussed in the previous section.[27,32] These authors evaluated symptomatic response at 6 months in 68 never-treated patients with schizophrenia, using the Remission in Schizophrenia Working Group consensus criteria, and conducted a brain-wide analysis using voxel-based morphometry (VBM). This showed that parahippocampal volume was significantly smaller in those 40 patients who had not remitted, compared with the 28 who had achieved remission after 6 months of treatment. The authors also built a classification model using parahippocampal grey matter concentration, and found that this model could correctly classify remission status 79% of the time. In contrast, Molina and colleagues[10] evaluated 19 patients, examining the relationship between percentage of change in PANSS scores over 6 months across 3 dimensions (positive, negative and disorganization), and volumes of the cerebrospinal fluid, dorsolateral-prefrontal and temporal regions and hippocampus.[10] They found that none of these measures predicted response at 6 months, although Cerebro Spinal Fluid (CSF) volume of the dorsolateral-prefrontal and temporal regions were associated with baseline symptom severity.

Studies that have looked at outcomes shorter than 6 months are only few (n = 3). One study from our group evaluated a different neuroanatomical measure, cortical gyrification, as a predictor of treatment response at 12 weeks in patients at their first episode of any psychosis.[33] Cortical gyrification is a marker that suggests early neurodevelopmental disturbances,[34,35] and it has been associated with psychotic symptoms resistant to treatment.[36] We defined response to treatment according to the symptomatic criteria of the Schizophrenia Working Group.[28] Our data showed that, already at illness onset, the 40 patients who subsequently did not respond to treatment had significant cortical folding defects (hypogyria) of several frontotemporal regions and the insula when compared with the 40 patients who did respond. The nonresponders also had more widespread deficits in gyrification extending to the precuneus, angular gyrus, and lingual gyrus when compared with healthy controls. Another study looked at cortical pattern (asymmetry) and cortical thickness measures, in 39 patients with first episode schizophrenia.[37] The study found greater frontal cortical asymmetry in patients who showed symptomatic improvement, which occurred on average following 7.8 weeks of treatment. This finding was also taken to suggest the presence of a neurodevelopmental disruption of the normal brain asymmetry. Patients with symptomatic improvement also showed greater occipital cortical thickness, a finding consistent with evidence of increased metabolism and activity in this area in relation to treatment response.[37] Interestingly, a greater thickness in temporal regions was associated with shorter time in the response to antipsychotics in another study, consistently with findings from patients with treatment resistant schizophrenia.[10] Finally, one study looked at very early response to treatment.[12] In this study, 26 patients with first episode of schizophrenia, schizophreniform, delusional disorder, and psychotic disorder not otherwise specified were treated with haloperidol 2 mg per day for 1 week. At this point, response was defined as a reduction of at least 15% in PANSS baseline scores. Brain measures were collected at baseline for total CSF volume, ventricular volume, sulcal volume, total grey matter volume, cortical grey matter volume, and white matter volume. An improvement in positive and negative symptoms at the end of the first week was significantly associated only with greater cortical grey matter volume. In contrast, there was only a trend level association with sulcal and total CSF volume, and total grey matter volume. The authors again suggest that the magnitude of these global abnormalities may indeed represent a stable deficit, possibly reflected in a poorer ability to respond to treatment with antipsychotics.

It is immediately evident from this literature that there are relatively few studies that have assessed this topic and most have been relatively underpowered. These studies show large variability in findings, and are often inconsistent. Also, it is difficult to establish to what extent the treatment effects predicted from MRI are actually carried-forward severity differences from before treatment, unless baseline scores of the outcome of interest is controlled for in the analyses. Nevertheless, alterations in medial temporal and prefrontal cortical areas, and in the networks that connect them with other subcortical structures, seem to show promise as potential neuroanatomical markers of poor response to treatment. This is supported by studies in individuals at chronic illness stages, which have also reported hippocampal and frontal volume reductions in patients with poor response to antipsychotics.[38,39] Furthermore, there is evidence that partially responsive patients with larger frontal brain volumes may be more likely to benefit from clozapine treatment.[6] It is also possible that prefrontal and temporal pathology affects the ability to learn novel situations and impair those behaviors that rely on pre-existing cognitive strategies, and memory, which when affected could eventually lead to poor functional outcomes.[29,31] The next section will discuss the limitations of this evidence, and the aspects that would need to be addressed before neuroanatomical alterations at illness onset could be used as predictors of response to treatment in clinical practice.

Translating Research Findings into Clinical Practice

Limitations of Existing Studies

An important limitation of this literature is that it mainly comprises single-centre studies. Even at major clinical academic sites, it is difficult to enroll very large numbers of patients in a single centre, especially if the study involves a lengthy period of assessment, the use of a standardized treatment protocol, and strict patient inclusion criteria, such as being medication-naïve. These logistical constraints on sample size have limited the statistical power of some of these studies, especially when the sample is subdivided into smaller subgroups according to therapeutic response, with variable criteria as seen above. Furthermore, the use of a single-scanner platform, while advantageous in removing potential methodological confounds, may limit the generalizability of these studies to a realistic clinical environment.

One potential solution is to conduct multicentre studies, which can permit the recruitment of patient samples that are an order of magnitude larger than that in a typical single centre study. The OPTiMiSE study (http://www.optimisetrial.eu), provides a good example of the potential benefits of adopting this approach. Funded by Framework 7 of the European Commission, the project is designed to identify predictors of the response to treatment in a sample of n = 500 medication-naïve patients with a first episode of schizophreniform psychosis who will be randomized to a standardized treatment protocol. Participants are being assessed using a range of clinical, neuroimaging and peripheral blood measures at baseline,

and then treated with a standardized protocol involving amisulpride for at least 4 weeks. Follow-up assessments are used to classify participants into "responders" and "nonresponders" according to the symptom remission criteria of the Schizophrenia Working Group.[28] To date, on average, each centre in the OPTiMiSE consortium has recruited 20 patients. However, when the data from the 7 centres will be combined, we expect to have neuroimaging data on $n = 200$ patients (comprising both responders and nonresponders) out of the total sample of 500 patients randomized to the treatment protocol. For the analysis of neuroimaging data, subgroups of these sizes are more than adequate to permit the detection of significant differences, but this would not be the case if the sample was derived from a single site.

Multicentre studies can thus provide the necessary scale to examine the utility of neuroimaging as a predictor of treatment response. However, such studies are logistically more difficult to run than single centre projects, and require larger levels of grant support, which only a limited number of agencies can provide. There are also important methodological considerations. Ideally, the neuroimaging data should be collected using identical protocols at each site, using similar scanners. Even if the machines and protocols are identical, site effects can be sources of variance and bias.[40] This issue can be addressed by using standardized imaging phantoms, and by scanning the same group of volunteers at each of the sites in the consortium.[41] Multicentre studies will typically involve centres in a variety of different countries, where the local clinical environment, research culture, and requirements of ethical committees may be quite different. Nevertheless, the potential benefits of multisite studies probably outweigh the associated difficulties, and the number of such studies in this area is clearly increasing.

Baseline and Longitudinal Data

The bulk of the existing literature contains studies that have sought to use a single cross-sectional neuroimaging measure to predict the subsequent therapeutic response. However, it is likely that the longitudinal change in serial neuroimaging measurements made in the same patient over time may provide important information that can facilitate response prediction. For example, studies involving serial scanning of patients after presentation suggest that measuring the longitudinal progression of volumetric findings may also predict clinical outcome.[42–44] Also, assessing a patient before and after a given treatment may reveal the extent to which that intervention has altered a neuroimaging measure, and within a patient sample this effect may correspond to the effect of the drug at a clinical level. For example, Goff and colleagues[45] reported that the effect of olanzapine on brain glutamate levels differed in those that did and did not respond to the drug. In the OPTiMiSE study, a subgroup of the sample are being scanned using Magnetic Resonance Spectroscopy (MRS) before treatment with amisulpride, and then rescanned after 4 weeks of treatment. In this case, the hypothesis being tested is that the initial effect of treatment on regional glutamate levels will correspond to the initial clinical response. However, it will also be possible to assess whether the initial neurochemical effect of treatment predicts the clinical response in the longer term. This is a critical issue for this approach, as longitudinal scanning is more likely to be clinically useful in this context if it can aid prediction about symptomatic and functional responses subsequent to collection of the neuroimaging data.

Making Predictions in an Individual

The research findings that we have described constitute mean differences between *groups* of patients who differ in terms of their antipsychotic response. However, in clinical practice, management decisions need to be made on the basis of neuroimaging data from *an individual*. This presents a key challenge to translating these research findings into tools that could allow clinicians to stratify patients according to their likely future therapeutic response. The application of complex statistical approaches that have previously been employed in other research fields, such as machine learning methods, may provide a solution to this problem, and is central to current neuroimaging research in this area. In fact, the evaluation of volumetric alterations in schizophrenia is more suited to approaches that can take account of spatially distributed information in imaging data, which can provide a more powerful mean of classifying patients according to treatment response. These approaches have shown good promise in predicting the onset and subsequent severity of psychosis in individuals at ultra-high risk on the basis of MRI data.[46,47] Relevant to illness outcome prediction, 1 group recently showed evidence that structural brain scans at the first episode could be used to predict, with significant accuracy, outcome at 6 years. This group found that the MRI scan obtained when patients first presented to services predicted which patients developed a continuous nonremitting illness course, and could distinguish them with significant accuracy from both healthy controls (sensitivity = 71; specificity = 61) and from those patients who had an episodic, more benign course (sensitivity = 71; specificity = 68).[48] While encouraging, these approaches need replication in larger samples of patients at the same illness stages and treated with the same pharmacological intervention, and also need validation for scans obtained across different scanners. Furthermore, using categorical measures of outcome may be less useful than dimensional measures, which are increasingly seen as useful in the assessment and classification of psychotic disorders.[49] OPTiMiSE will give us the opportunity to study a large, clinical sample of individuals homogenous in terms of

illness stage and treatment. We will employ state-of-the-art machine learning approaches, to complement the well-established method of voxel-based morphometry. In fact, OPTiMiSE will go beyond categorical classification used in SVM studies to date, and will additionally use methods such as those based on Gaussian Processes (GP) that allow to also make probabilistic rather than categorical predictions of class membership, and to operate in a regression rather than classification setting. Furthermore, we will use methods naturally suited to analyzing more than 2 classes of data, such as Sparse Multinomial Logistic Regression (SMLR). This will increase the translational potential of the findings, since clinicians often have to make decisions between several different options, rather than just 2.

Integration with Non imaging Data

In other areas of medicine, prediction of therapeutic response relies on many different kinds of data, rather than one type alone. It is thus likely that the prediction of therapeutic response in psychosis using neuroimaging data may be enhanced if demographic, clinical, cognitive, genetic, and other peripheral blood measures were incorporated into the assessment. To date, very few studies have examined this issue in relation to treatment response in psychosis. More generally, there is some evidence that the integration of data from different neuroimaging modalities may enhance the predictive power in studies using machine learning,[50] although adding an additional neuroimaging measure does not necessarily improve prediction.[51] The OPTiMiSE study aims to investigate this issue, by assessing the impact of including psychopathological, genetic, proteomic, metabolomic, autoimmune, and inflammatory measures on the prediction of response using neuroimaging data. It will also examine the impact of integrating MRI and Magnetic Resonance Spectroscopy (MRS)-glutamate data. More specifically, OPTiMiSE will systematically compare alternative approaches for the optimal integration of imaging and non imaging measures, including unweighted sum of kernels, weight vector averaging, majority voting and multikernel learning, to test whether this enhances the accuracy of patient classification in psychosis.

Developing Clinical Tools

If researchers in this field succeed in identifying predictors of therapeutic responses, the next step would be to incorporate the relevant measures into tools that could be used in a real-world clinical setting. Academics generally have little or no experience of developing or disseminating such tools, whereas there are a number of companies that specialize in this area. For example, there are commercially available tools for predicting the onset of dementia in people at high risk that use cognitive data (http://www.cambridgecognition.com/healthcare/cantabmobile) or neuroimaging data (http://www.ixico.com/products/assessa). Collaborating with industry may therefore help facilitating the translation of research findings in the area of therapeutic response prediction in psychosis, and recently funded multicentre studies in this area have directly involved companies with specialist expertise in tool development (http://ec.europa.eu/research/health/medical-research/brainresearch/projects/psyscan_en.html).

Conclusion

Accumulating evidence points to schizophrenia and psychoses as pathophysiologically heterogeneous disorders with variable outcomes. This has hampered our ability to identify biomarkers for early diagnosis, stratification and measurement of disease progression. Neuroimaging data, possibly in combination with other biomarkers of disease, represent promising tools for stratifying patients with psychoses in an objective, quantitative way, according to clinical and functional outcomes, to eventually generate patient clusters that are more clinically meaningful, and useful to detect true therapeutic effects in clinical trials.

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