

Effect of psychological interventions on depressive symptoms in patients with schizophrenia - a systematic review and meta-analysis

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Publications related to this work

- Irene Bighelli et al. “Psychological Interventions to Reduce Positive Symptoms in Schizophrenia: Systematic Review and Network Meta-Analysis”[1]
- Irene Bighelli et al. “Response Rates in Patients with Schizophrenia and Positive Symptoms Receiving Cognitive Behavioural Therapy: A Systematic Review and Single-Group Meta-Analysis”[2]
- Irene Bighelli et al. “Psychological Interventions for Positive Symptoms in Schizophrenia: Protocol for a Network Meta-Analysis of Randomised Controlled Trials” [3]
- Irene Bighelli et al. "Are Randomized Controlled Trials on Pharmacotherapy and Psychotherapy for Positive Symptoms of Schizophrenia Comparable? A Systematic Review of Patient and Study Characteristics." [4]

Chapter 1

Introduction

1.1 Schizophrenia

Schizophrenia is a serious illness, which has far-reaching consequences for the person affected, their relatives and society.

1.1.1 Epidemiology

The frequency of schizophrenia is reported in the systematic review of Saha with a median point prevalence 4.6 per 1000 population in an international comparison [5] and is therefore not a rare disease. (The median values per 1,000 persons (10%-90% quantiles) for the distributions for point, period, lifetime, and lifetime morbid risk were 4.6 (1.9-10.0), 3.3 (1.3-8.2), 4.0 (1.6-12.1), and 7.2 (3.1-27.1), respectively). The distribution of the disease between women and men shows a slightly higher incidence in men compared to women [6]. The first occurrence of the disease has its peak in young adulthood, mainly between the 15th and the 35th year of life [7].

1.1.2 Etiology

A single disease-causing factor that is causative for the development of schizophrenia has not yet been found. Various studies indicate that the occurrence of schizophrenia is influenced by multiple factors. Thus, it is the combination of a certain existing vulnerability and on it accumulating disease-causing factors. If these factors accumulate above a certain threshold, the first manifestation of schizophrenia occurs. This hypothesis is referred to as the multiple-hit theory [7, 8]. Davis cites several vulnerability factors in his study, including lowered prenatal vitamin D exposure, viral infections, smoking, intelligence quotient, social cognition, cannabis use, social defeat, nutri-

tion and childhood trauma. It is likely that these genetic risks, environmental risks and vulnerability factors are cumulative and interactive with each other and with critical periods of neurodevelopmental vulnerability [8]. Neurobiologically, multiple changes are also evident. Thus, post-mortem examinations of CNS tissue of diseased persons showed changes in the dopaminergic, serotonergic, cholinergic, glutamatergic and also the GABAergic system. It is assumed that this leads to an imbalance of the neurotransmitter systems [9], such as an "overactivity of the mesolimbic dopaminergic system" [7].

1.1.3 Symptoms Clinic

The clinical picture of schizophrenia is characteristic and manifests itself in the impairment of mental functionalities, such as concentration, attention, content-related and formal thinking, ego functions (differentiation from the environment), perception, intentionality, drive, affectivity and psychomotor functions [7]. A division into negative symptoms, including flattening of affect, social withdrawal or lack of drive, and positive symptoms, including auditory hallucinations, delusions, disturbances of ego functions, is generally applied. While positive symptoms usually occur during an acute episode, negative symptoms are usually long-lasting and a major factor in the suffering/severity of illness [7]. In addition to a chronification of the symptoms, those affected often develop other illnesses, both somatic and psychiatric. The most common psychiatric comorbidities include substance abuse and dependence (especially tobacco, alcohol, and cannabis), depression and suicidality, obsessive-compulsive disorder, post-traumatic stress disorder, anxiety disorders, agitation and agitation states, and sleep disorders [7]. Depressive symptoms, often of substantial severity, are found in 50% of newly diagnosed people with schizophrenia and 33% of people with chronic schizophrenia who have relapsed [10]. The lifetime prevalence of an additional depressive episode or depression is high in people with schizophrenia [11, 12]. The occurrence of depression negatively influences the course of schizophrenia. There is an increase in substance abuse [13], psychotic episodes, and suicide [10]. In connection with this and other factors, people with schizophrenia have a two- to threefold increased risk of dying [14].

1.1.4 Socioeconomic impact

Since the onset of this disease is usually early and the subsequent course is usually chronic, the overall impairment of the affected persons is very high and severe [15]. This is also reflected in the WHO burden of disease report, in which schizophrenia ranks 20th among the reasons for Years Lived

with Disability (YLD) [16]. The length and severity of the illness are also a burden on society. First, the direct costs per patient per year in Germany are estimated at 14,000-18,000 €[17]. Hospitalization accounts for one of the largest shares of health care costs [18]. However, indirect costs are estimated to be many times higher. One factor here is loss of productivity with declining functioning or employment difficulties [18–20]. Another burden hits the closer environment of the affected person, the caregivers, who suffer from a financial burden and a loss of productivity [15, 18, 20].

1.2 Therapy

The goal of therapy in the acute phase of schizophrenia is a reduction to, in the optimal case, the disappearance of symptoms. In the course of the disease the stabilization and prevention or prophylaxis is important. In addition to focusing on the acute symptoms of schizophrenia, reintegration into society and therapy of other complaints of the patient, somatic or other psychiatric comorbidities are important. A therapy concept based on evidence-based medicine should therefore be developed according to the guidelines of the National Institute for Health and Care Excellence (NICE) and the "Deutsche Gesellschaft für Psychiatrie und Psychotherapie, Psychosomatik und Nervenheilkunde" [7, 21], and antipsychotic medication should be accompanied by psychotherapeutic and psychosocial therapy.

1.2.1 Antipsychotics

Antipsychotics act via antagonism at central dopamine receptors. The various antipsychotics have different affinities for the different dopamine receptors/systems, which means that they differ in their effects. What they all have in common is an effect on the mesolimbic system, which is thought to be responsible for positive symptomatology [7]. A general classification is first-generation and second-generation antipsychotics. The first generation includes haloperidol or melperone. Haloperidol shows good efficacy especially in cases of severe positive symptoms. An undesirable side effect of these antipsychotics are extrapyramidal-motor side effects, which can be seen e.g. in Parkinson syndromes [7]. As the first antipsychotic of the second generation, clozapine showed this side effect less frequently or not at all [7]. In addition, clozapine still showed efficacy in negative symptoms or cognitive deficits. The second generation of antipsychotics also includes olanzapine, quetiapine, and others. Although these antipsychotics hardly show extrapyramidal motor side effects, clozapine has agranulocytosis as a dangerous side effect, and

QTc time prolongation, sedation or metabolic syndromes also occur more frequently as adverse effects. A recent network-meta-analysis by Huhn et al. showed that especially the newer antipsychotics produce more weight gain and sedation, whereas older antipsychotics are associated with more extrapyramidal motor side-effects and prolactin elevation [22].

1.2.2 Psychological interventions

The goal of psychological interventions, in addition to reducing symptoms, is primarily to integrate the patient into society by strengthening social skills and social functioning. Various forms are used in the therapy of schizophrenia. The current DGPPN guideline recommends the following therapies: Psychoeducation, Cognitive-behavioral therapy (CBT), Metacognitive training (MCT), Family interventions (FI). Psychoeducation attempts to educate and inform patients about the disease and the associated therapy. To enhance this effect, family members and the patient's environment are also involved. The Cochrane meta-analysis by Xia et al. 2011 showed that psychoeducation has positive effects on relapse, readmission and medication compliance [23]. According to NICE [21], CBT should aim to help patients recognize the links between their thoughts, feelings, or actions and their current or past symptoms and/or functioning. Second, they should be enabled to re-evaluate their perceptions, beliefs, or thinking in relation to their symptoms. To do this, CBT should include the following therapy points, according to NICE[21]: Patients observing their own thoughts, feelings, or behaviors in relation to their symptoms or the reoccurrence of symptoms, teaching patients further coping techniques to deal with their symptoms, reducing distress, and increasing functioning. NICE recommends the use of at least 16 sessions of CBT in the acute phase of the disease in their 2014 guideline.[21] Several meta-analyses show efficacy of CBT for symptoms of schizophrenia [1, 24, 25], whereas Jones et al. noted that CBT had no advantage compared to other psychological or social interventions [26].

Metacognitive Training is a further development of CBT. The aim of this training is to show affected persons wrong thinking patterns/thinking distortions/biases, which have a role in the development of delusions up to positive symptoms [27]. The effectiveness of metacognitive training has been investigated in several meta-analyses. A moderate effect on delusions [28], improved insight [29], moderate effects on insight, positive symptomatology, and cognitive biases [30], and small effects on positive symptomatology and delusions [31] were found.

Family interventions are a broad field of interventions. According to one definition from NICE, a family intervention should include the following: There

is a specific supportive, educational, or therapeutic function and includes work on problem-solving skills or crisis intervention skills. In addition it should take the relationship between the main carer and the person with schizophrenia into account. It can be conducted as single family-therapy or in groups of families [21]. This definition creates intersections with psychoeducation, in which the involvement of the environment is an important pillar. A meta-analysis by Pharoah et al. 2010 showed a reduction of frequency of relapse, a possible reduction of hospital admission and increased medication compliance [32]. Positive results in preventing relapse were also found in a meta-analysis on family therapy in persons with schizophrenia by Rodolico et al. [33].

Furthermore, the DGPPN guideline recommends the use of Social Skills Training for persistent negative symptoms and Cognitive Remediation for cognitive impairment. NICE further recommends the provision of art therapy for negative symptomatology.

1.3 Depression in Schizophrenia

Depressive symptoms are common over the course of schizophrenia. In fact, Upthegrove et al. 2017 stated that up to 80% of all people with schizophrenia exhibited depressive symptoms over time [34]. The effects or consequences of this comorbidity include increased suicidality, substance abuse and psychotic episodes. Current therapy recommendation according to DGPPN are in addition to the optimization of antipsychotic medication, the use of antidepressants and CBT [7]. Studies show that even the optimal use of antipsychotics has the effect of improving depressive symptoms; Leucht et al. found that both haloperidol and SGA have a positive effect on depressive symptoms [35]. An additional use of antidepressants had a better effect on depressive symptomatology than monotherapy with antipsychotics [36]. In terms of psychotherapeutic interventions, CBT in particular has been investigated, with Wykes et al. 2008 showing a positive effect on mood [25]. Jones et al. 2012 examined in their meta-analysis the effect of CBT in comparison to other psychosocial interventions, whereby only a few studies reported depression as an outcome, so that only a few comparisons were possible, which saw a small advantage for CBT (on the Beck's Depression Inventory (BDI)) or no advantage for CBT (on the Montgomery-Åsberg Depression Rating Scale)[26]. In an update of this work Jones et al. [37] still found that there is small effect for CBT plus standard care in comparison to standard care, but the quality of evidence is very low. In comparison to standard care plus other psychological treatments Jones et al. showed that there is only inconsistent

evidence for the advantage of CBT for depressive symptoms [38].

1.4 Aim of this work

Patients with schizophrenia often suffer not only from positive symptoms, but also from other comorbidities, including depression. This has a negative influence on the course of the disease as well as on the quality of life, so that treating these depressive symptoms is of high importance. Currently, it is recommended by the DGPPN, that for patients with schizophrenia suffering from depressive symptoms CBT is to be used in addition to medications (for example adjust antipsychotic or add an antidepressive medication) [7]. Since both antipsychotics and antidepressants have serious undesirable side effects, it is important to know the effect of psychological interventions on depressive symptoms. The current literature deals mainly with the effectiveness of psychological interventions on general symptomatology in patients with schizophrenia [24, 32, 39]. In addition, the effectiveness of different forms of psychotherapy on depressive symptomatology has hardly been studied so far. Thus, the aim of this work is to investigate to what extent psychological interventions can alleviate depressive symptomatology in patients suffering from schizophrenia.

Chapter 2

Methods

2.1 Inclusion criteria

This work was conducted in cooperation with the research group of Leucht et al. and in the context of a greater network-meta-analysis for patients with schizophrenia receiving psychotherapy[1, 2]. The present work is focusing on how psychological interventions have an impact on the depressive symptomatic in patients with schizophrenia. In order to investigate this question, a systematic review and meta-analysis was conducted. Doctoral dissertations focusing on other aspects use a similar methodology, that is a standard in the research field of meta-analysis and in the working group.

2.1.1 Characteristics of studies

For this thesis randomized controlled studies were included, if participants with a diagnosis of schizophrenia received some kind of psychological intervention (which we will define more precisely in the following part). Studies were excluded if they were cluster-randomized or quasi-randomized. If there was a high risk of bias in sequence generation (see section below) the study was also excluded. Both open and RCTs were included. This is especially important in psychological trials, because the blinding of participants and therapist is hardly possible and only the assessor of outcome can be masked. In a sensitivity analysis studies in which the assessor is not blinded have been excluded. RCTs that compared any psychological intervention to a control condition as well as to any other intervention were included.

2.1.2 Characteristics of participants

We included RCTs that enrolled adult participants as defined by each study author, with a diagnosis of schizophrenia or schizophrenia related disorder. There were no restrictions in setting, ethnicity or gender. In line with the recommendations of the Cochrane Schizophrenia Group [40] we accepted all diagnostic criteria, including the International Classification of Diseases, 10th revision [41] or the Diagnostic and Statistical Manual of Mental Disorders [42–44] to achieve a more general and broader selection of studies. RCTs were only included, if the percentage of participants with schizophrenia, schizophreniform or schizoaffective disorder was higher than 80%. Additional exclusion criteria were the following subgroups of participants:

- patients with psychiatric comorbidities (including substance abuse)
- patients with concomitant medical illness
- patients with a first episode of psychosis
- patients with prodromal signs of psychosis, also defined as 'At high risk'

Studies focused on patients with predominantly negative symptoms are eligible for inclusion. In order to ascertain the effects of psychological interventions on this special subgroup of patients, these studies were also analysed separately in a subgroup analysis (see below).

2.1.3 Characteristics of interventions

All interactions between a therapist and a patient were considered as a psychological treatment, conducted both in group or in individual sessions. After extraction of all eligible studies a classification of intervention took place. Therefore the recommendations of the Cochrane Collaboration were followed [45]. Interventions were analyzed for their main intervention strategy and grouped for the meta-analysis. For the meta-analysis we included studies, which compared psychological interventions either to:

- other psychological interventions
- inactive psychological interventions, in which the patient spends time with a professional, but without receiving the specific elements of a therapy
- standard care (or "treatment as usual"), usually including pharmacological treatment

- waiting list (patients first receive standard care, but know that afterwards they will receive the intervention)

For a detailed description see section 3.2. A subgroup analysis was conducted to investigate the role of these different control conditions (see section 3.5. If the treatment as usual consisted only of a pharmacological therapy, the study was not excluded.

2.1.4 Characteristic of outcome

For this work studies were included in the analysis, if they provided data for depression or depressive symptoms. The outcome parameter depression can be measured with different rating scales. The results of a rating scale were used for this work only if the instrument has been published in a peer-reviewed journal. This is a conservative approach, since non-published rating scales have been found to exaggerate differences [46].

2.2 Search strategy

2.2.1 Electronic search

The following databases were used for a electronic search for reports published up to January 2018: Embase, MEDLINE, PsycINFO and PubMed, WHO International Clinical Trials Registry Platform, BIOSIS, Cochrane Collaboration Controlled Trials Register and ClinicalTrials.gov. There were no restrictions on language or publication period. The complete search can be found in the Appendix, chapter 7.2.

2.2.2 Reference lists and other sources

We checked already conducted reviews on similar topics for further potentially eligible studies.

2.3 Identification and selection of studies

All records that were found via the search strategy were listed in Citavi with title and abstracts. We excluded duplicates. Two independent reviewers inspected the records' titles and abstracts to check if they were eligible according to our inclusion criteria. In case of disagreement they were resolved by discussion and if still no agreement was found, the fulltext was retrieved

for further information.

After retrieving all full text articles of the potentially eligible records in the next step, two researcher checked them again independently for eligibility. Any disagreements were first discussed and in doubt a senior researcher was consulted. Another action taken for deciding if a study could be eligible for our analysis was contacting the study authors for further information.

2.4 Measurement of treatment effects

Since depression as a continuous outcome can be measured with different rating scales, for data analysis the standardized mean difference was used. The standardized mean difference is used to express the size of the intervention effect in each study relative to the variability observed in that study [47]. When available, data for all randomised participants was extracted (Intention-to-treat analysis). For missing outcome data mixed-effect models were preferred over last-observation-carried-forward-data.

Published standard deviations (SDs) were primarily extracted for the analysis. When only the standard errors (SEs) were given, the SD was calculated out of it. If neither SD or SE were given, we estimated the SD from the 95% CI or p-value with a method described in the Cochrane Handbook [47]. If no data was given the study author was contacted. If none of the options above were possible the SD was calculated via a imputation method published by Furukawa et al. [48].

2.5 Data extraction

The next step in our research was the extraction of data in a Microsoft-Access database, that was specifically created for this project. According to Cochrane standards, also the data extraction was performed by two reviewers independently. Data was searched in main reports, supplementary material and secondary publications of each study. The inconsistencies between the extractions for the two reviewers, automatically recognised by our Access database, were resolved by discussion and if no agreement could be found we involved a third reviewer. In addition, the authors of included studies published less than 30 years ago were contacted for missing data or further information. Following data was extracted:

- Basic information on the trial:
Citation, trial registration number, year of publication, duration of

study, location, setting, number of sites, sample size, diagnostic criteria, funding/sponsorin

- Methods of the study:
randomisation, allocation concealment, blinding of participants, therapists and assessors, outcome reporting, data analysis and number of arms
- Characteristics of participants:
gender, mean age, details on diagnosis, duration of illness, sociodemographic data(e.g ethnicity, level of education, living situation...)
- Characteristics of interventions:
detailed description of each intervention, number and frequency, therapist experience, group or individual therapy, researcher allegiance
- Outcome measures
change or endpoint data (where both were provided, change was preferred to endpoint data), Intention-to-treat analysis or completer analysis, also taking care of the direction of the scale (higher or lower score mean better outcome)

2.6 Risk of bias assessment

The risk of bias was assessed for every study using the Cochrane Collaboration 'risk of bias' tool [49]. The tool evaluates the risk of bias in seven domains, providing a judgment that can be:

- low risk of bias: the reported methods and outcomes secure a low risk
- unclear risk of bias: There was not enough information to rate this bias
- high risk of bias: there were no correct/secure methods used for a low risk of bias

see at Higgins [47]. Therefore we rated the included studies in the following domains of risk of bias:

1. Selection bias

Selection bias refers to systematic differences between baseline characteristics of the groups that are compared (as defined in the Cochrane Handbook Chapter 8.4) [47]. It further consist of

- Sequence generation
There is a low risk of bias, if the distribution of study participants is based on randomisation/a process by chance.
- Allocation concealment
In this domain it is rated whether the allocation of a participant cannot be foreseen and is concealed for persons taking part in the study.

2. Performance bias

The bias that leads to a systematic difference between the groups due to unequal treatment or other external factors that influence the outcome other than the intervention itself [47]. Therefore we looked at the blinding of participants and therapists/personnel. In the case of studies on psychological interventions, blinding of therapist and participants is not possible.

3. Detection bias

This bias describes the presence of a systematic difference in assessing the outcome [47]. In other words the assessor should be blinded, so the outcome is not falsified, because the assessor is influenced by his knowledge about the trials arm.

4. Attrition bias

Attrition bias refers to systematic differences between groups in withdrawals from the study [47]. For this bias we checked if complete data is published or if data of drop-outs is not reported. Only analyzing data on participants that completed the study can distort the results.

5. Reporting bias

Reporting bias refers to systematic differences between reported and unreported findings [47]. Often results for outcomes that do not find significant differences between the intervention and the control condition remain unpublished. That leads to an imbalance of reported data. To detect this kind of bias, we compared for example planned analysis in the protocol with the actual reported results.

6. Other biases

We reported possible other biases, that were none of the above.

For classifying the overall bias at study level we followed the system used by Furukawa and colleagues [50]. Therefore we classified the studies in having a overall low risk of bias, if none of the above points were rated at high risk and

only three or less were rated as unclear, in having a moderate risk of bias, if one was rated at high risk or more than three were rated at unclear risk. In all other cases the studies were classified as overall at high risk. For this process the "blinding of participants and therapist" was not considered, because in this kind of studies therapists and participants cannot be blinded. In addition to the domains of the Cochrane risk of bias tool, we reported information on "Researcher Allegiance" because it was found as another important source of bias in RCTs on psychological interventions [51–53]. Under this point we evaluated if the study conductor has some kind of interest that the study has positive results, e.g. because they developed the treatment manual.

2.7 Data analysis

2.7.1 Preparation

A descriptive table of all included studies that offered usable data was created. The first section reports about the study itself, providing information on the blinding, allocation method, diagnostic criteria, outcome scale, trial duration and site, the clinical setting and the overall risk of bias.

The next section mainly focuses on the participants that were included, giving information on number of participants, diagnosis, mean age and duration of illness in each study arm if available and gender distribution. The last section mainly focuses on the interventions. It contains data on number of participants in each arm and number of sessions (see Chapter 3.1, Table 3.1). For a better overview and transparency on how studies were grouped for the meta-analysis and subgroup analysis a detailed table with a description of interventions was created. It follows the suggestion of the Cochrane collaboration [47] and contains information on the main intervention strategy according to which the study was grouped and analysed. (see Chapter 3.2, Table 3.2)[45].

2.7.2 Type of data

For the outcome of this thesis continuous data was extracted. Depression is measured on mostly linear scales, where each step has the same difference/means a equal quantitative of change in depressive symptoms. There are also some scales, that work with categories, and are not completely with a linear scope. But for this thesis all were analysed as continuous outcome data. If change data (change in scores from baseline to end of study) was

available, it was preferred to endpoint data.

Depressive symptoms can be measured with different rating scales, therefore we used the standardised mean difference (SMD) as effect size. If the decrease in the intervention group was higher than in the control group (benefit for the intervention), the SMD will have a negative value. To interpret if the difference between the groups is significant, the 95% confidence interval must be observed. If it includes the 0, it means that we cannot exclude the possibility that there was no difference between the interventions, with a 5% probability of error.

2.7.3 Analysis

Random effects pairwise meta-analyses were done with Review Manager 5.4 from the Cochrane Collaboration [54].

To be able to compare the continuous outcome data of different scales the standardized mean difference (SMD) was calculated. The formula used is described in the Cochrane Handbook [47]:

$$SMD = \frac{\text{Difference in mean between groups}}{\text{Standard deviation of outcome among participants}}$$

This formula assumes that standard deviations mainly derive from the different outcome scales and not from the study population.

Heterogeneity

Therefore in a next step the study population was checked for heterogeneity. Heterogeneity I^2 is a value for quantifying inconsistencies between the studies that are not caused by chance [47]. As suggested by the Cochrane Collaboration, the values of I^2 were interpreted as follows [47]:

- 0-40%: might not be important
- 30-60%: may represent moderate heterogeneity
- 50-90%: may represent substantial heterogeneity
- 75-100%: considerable heterogeneity

To explore possible causes of heterogeneity subgroup analyses (dichotomous variables) and meta-regressions (continuous variables) were performed.

Investigation of potential moderators: subgroup analyses and metaregressions

The following items were a-priori identified as possible moderators. Subgroup-analysis:

- The intensity of control conditions:
 - TAU or waitlist control (no control condition)
 - Inactive control condition (no therapy, but an intervention was given): Supportive Counselling and Befriending
 - Active control (another therapeutic intervention was given): Cognitive Remediation, Supportive Therapy, Family Intervention, Psychoeducation, PMR
- Therapy setting
- Blinding of outcome assessors
- Treatment resistant participants
- Participants with predominantly negative symptoms
- Different risk of bias in Researcher Allegiance
- Different overall risk of bias

Meta-regression:

- Number of sessions
- Study duration
- Baseline severity of schizophrenic symptoms (PANSS)

A subgroup-analysis and meta-regression was only performed, if the comparison involved 10 or more studies as suggested by the Cochrane Collaboration [47].

Meta-regression was performed with R and R-Studio using the metafor package [55].

Exclusion of "problematic" studies: sensitivity analyses

Sensitivity analyses were performed to check if decision made in any stage of the systematic review did not influence the result.

- studies with imputed SD
- studies with only completer analysis

Investigation of publication bias

A possible publication bias was researched for comparison with ten or more studies via a funnel plot done by Cochrane Review Manager 5.4 [54]. In addition to the creation of a funnel plot to investigate a possible publication bias, an Egger's test for funnel plot asymmetry [56] was performed. The standard error was examined as a possible predictor.

Chapter 3

Results

3.1 Characteristics of included studies

The last search update took place in January 2018 after which 21,772 potential records were identified. After screening of title and abstracts, 2754 fulltext articles were retrieved. After checking the fulltexts, 192 RCTs met the inclusion criteria, of which 40 studies with overall 3039 participants had usable outcome data for this meta-analysis. More details can be found in the PRISMA-Flowchart (Figure 3.1).

The publication period of the studies ranged from 2000 to 2018. The minimum of study duration was from 1 day to a maximum of 52 weeks. None of the included studies had blinded participants or therapists and they were thus not double blind. Furthermore 5 RCTs of the 40 included studies did not sufficiently blind the outcome assessor and were thus classified as open label studies. In 31 studies one of the authors designed the manual or developed the intervention, they were therefore rated as having a high risk of bias for researcher allegiance. 17 studies used diagnostic criteria based on the DSM-IV [42], one study used the DSM-IV and the ICD-10 [41, 42], four studies used the DSM-IV-TR [44], one study used the DSM-V [43], five studies used the ICD-10 [41], one study used the ICD-10 [41] or PANSS [57], one study used the ICD-10 research [58] and DSM-IV [42], four studies used the ICD-10 research [58] and one study used the Operational Criteria Checklist (OPCRIT) [59]. Two Studies used a clinical diagnosis as diagnostic criteria and three did not provide data on which diagnostic criteria were used.

Five RCTs included inpatients, 16 outpatients and six in- and outpatients. 13 studies did not give information on the clinical setting. Two studies included patients with predominantly negative symptoms and four included treatment resistant participants. Number of intervention sessions ranges from 1 to 40

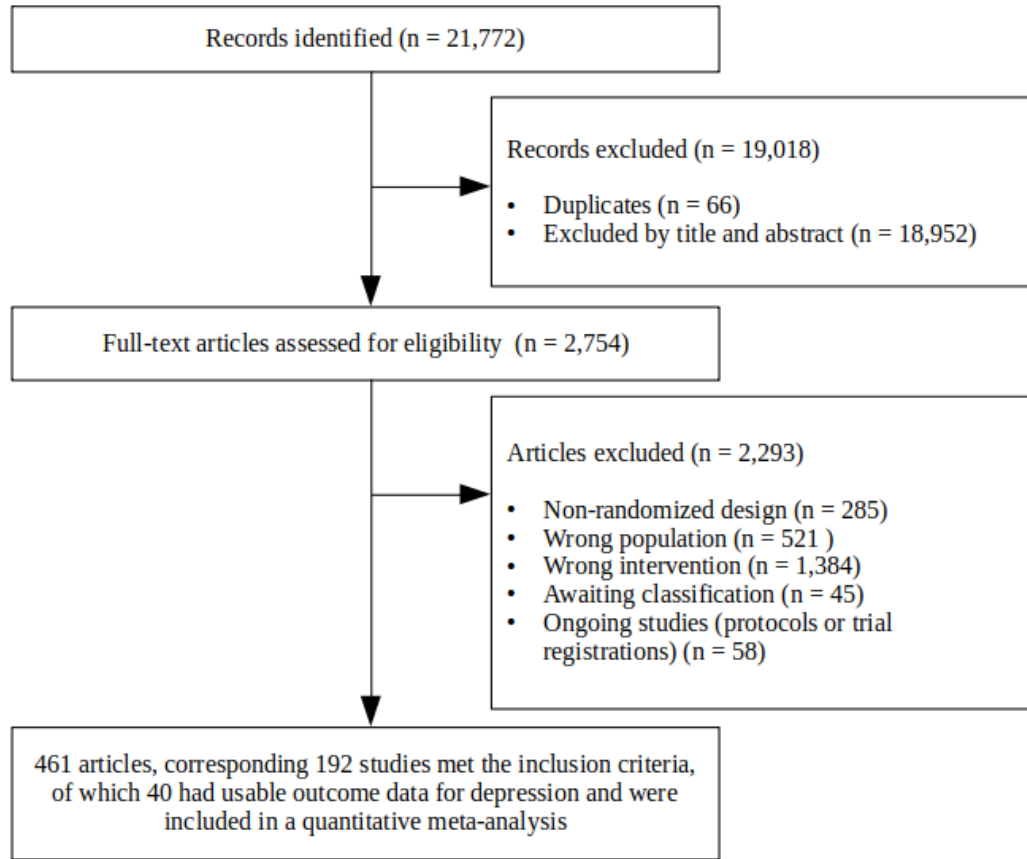


Figure 3.1: PRISMA Flowchart [60, 61]

with a median of 12. The baseline severity measured in PANSS varies from 49,57 to 78,58 with a median of 64,48 (for the studies, that provided data for this item). In 27 studies the psychological intervention was conducted in an individual setting, in two studies in a family setting and in 13 studies in a group setting. More information on the included studies with usable data can be found in Table 3.1.

Table 3.1: Table of Studies

Study	Methods	Participants	Intervention
ACTRN12616000976482 [67]	Country: Australia Allocation: randomized Blinding: SB Diagnostic criteria: DSM-V Outcome scale: DASS (Depression subscale) Trial duration (weeks): 4 Setting: NA Overall Risk of bias: Moderate	Participants (n): 54 Diagnosis: schizophrenia spectrum disorder Gender distribution: - women (n): NA - men (n): NA Mean age (years): - Metacognitive Training: NA - Cognitive Remediation: NA	Metacognitive Training: - Participants (n): 27 - Number of sessions: 4 Cognitive Remediation: - Participants (n): 27 - Number of sessions: 4
Andreou 2017 [68]	Country: Germany Allocation: randomized Blinding: SB Diagnostic criteria: DSM-IV Outcome scale: PANSS depression factor Trial duration (weeks): 6 Setting: In- and outpatient Overall Risk of bias: Low	Participants (n): 92 Diagnosis: Schizophrenia spectrum disorder Gender distribution: - women (n): 41 - men (n): 51 Mean age (years): - Metacognitive Training: 36,9 - Cognitive remediation: 35,6	Metacognitive Training: - Participants (n): 46 - Number of sessions: 8,28 Cognitive Remediation: - Participants (n): 46 - Number of sessions: 5,59
Barrowclough 2006 [69]	Country: UK Allocation: randomized Blinding: SB Diagnostic criteria: DSM-IV Outcome scale: Hospital Anxiety and depression scale Trial duration (weeks): 26 Setting: NA Overall Risk of bias: Moderate	Participants (n): 113 Diagnosis: schizophrenia or schizoaffective disorder Gender distribution: - women (n): 82 - men (n): 31 Mean age duration of illness (years): - Cognitive behavioral therapy: 38,8 13,7 - Treatment as usual: 38,8 13,7	Cognitive Behavioral Therapy: - Participants (n): 57 - Number of sessions: 10,4 Treatment as usual: - Participants (n): 56
Birchwood 2014 [70]	Country: UK Allocation: randomized Blinding: SB Diagnostic criteria: ICD-10 Outcome scale: Calgary Depression Scale Trial duration (weeks): 39 Setting: NA Overall Risk of bias: Moderate	Participants (n): 197 Diagnosis: Schizophrenia or schizoaffective disorder Gender distribution: - women (n): 113 - men (n): 84 Mean age duration of illness (years): - Cognitive Behavioral Therapy: 38,8 17 - Treatment as Usual: 35,9 13,4	Cognitive Behavioral Therapy: - Participants (n): 98 - Number of sessions: 19 Treatment as usual - Participants (n): 99

NA = not available; SB = single blind; OL = open label; DASS = Depression Anxiety Stress Scales [62]; PANSS = Positive and Negative Syndrome Scale[57]; BDI (-II) = Becks Depression Inventory [63] (II)[64]; SCL-27 plus = The symptom checklist-27-plus [65]; MADRS = Montgomery-Åsberg Depression Rating Scale [66]; DSM-IV(-TR)= Diagnostic and Statistical Manual of Mental Disorders [42] (-text revised) [44]; ICD-10 = International statistical Classification of Diseases and related health problems : tenth revision [41]

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Study	Methods	Participants	Intervention
Briki 2014 [71]	Country: France Allocation: randomized Blinding: SB Diagnostic criteria: DSM-IV-TR Outcome scale: Calgary Depression Scale for Schizophrenia Trial duration (weeks): 8 Setting: In- and outpatient Overall risk of bias: High	Participants (n): 68 Diagnosis: Schizophrenia or schizoaffective disorders Gender distribution: - women (n): 17 - men (n): 33 Mean age duration of illness (years): - Metacognitive Training: 41,1 14,6 - Supportive Therapy: 41,1 17,8	Metacognitive Training - Participants (n): 35 - Number of sessions: 14,6 Supportive Therapy: - Participants (n): 33 - Number of sessions: 14,2
Chadwick 2016 [72]	Country: UK Allocation: randomized Blinding: SB Diagnostic criteria: ICD-research Outcome scale: Hospital Anxiety and Depression Scale - Depression Trial duration (weeks): 16 Setting: NA Overall risk of bias: Low	Participants (n): 108 Diagnosis: Schizophrenia or schizoaffective disorder Gender distribution: - women (n): 53 - men (n): 54 Mean age (years): - Mindfulness: 42 - Treatment as Usual: 42	Mindfulness: - Participants (n): 54 - Number of sessions: 12 Treatment as usual: - Participants (n): 54
Craig 2018 [73]	Country:UK Allocation: randomized Blinding: SB Diagnostic criteria:ICD-10 Outcome scale: Calgary Depression Scale Trial duration (weeks): 12 Setting: Outpatient Overall risk of bias: Low	Participants (n): 150 Diagnosis: Schizophrenia spectrum disorder, affective disorder with psychotic symptoms Gender distribution: - women (n): 48 - men (n): 102 Mean age duration of illness (years): - AVATAR therapy: 42,5 20,5 - Supportive counseling: 42,9 19,8	AVATAR therapy: - Participants (n): 75 - Number of sessions(n): 5,6 Supportive counseling: - Participants (n): 75 - Number of sessions(n): 5,1
Farhall 2009 [74]	Country: Australia Allocation: randomized Blinding: OL Diagnostic criteria:DSM-IV Outcome scale: Hospital Anxiety and Depression Scale - Depression Trial duration (weeks): 52 Setting: Outpatient Overall risk of bias: High	Participants (n): 94 Diagnosis: Schizophrenia, schizoaffective disorder, delusional disorder, or mood disorder with psychotic features Gender distribution: - women (n): 38 - men (n): 54 Mean age (years): - Cognitive Behavioral Therapy: 32,1 - Treatment as Usual: 33,6	Cognitive Behavioral Therapy: - Participants (n): 45 - Number of sessions: 17,5 Treatment as usual: - Participants (n): 49

NA = not available; SB = single blind; OL = open label; DASS = Depression Anxiety Stress Scales [62]; PANSS = Positive and Negative Syndrome Scale[57]; BDI (-II) = Becks Depression Inventory [63] (II)[64]; SCL-27 plus = The symptom checklist-27-plus [65]; MADRS = Montgomery-Åsberg Depression Rating Scale [66]; DSM-IV(-TR)= Diagnostic and Statistical Manual of Mental Disorders [42] (-text revised) [44]; ICD-10 = International statistical Classification of Diseases and related health problems : tenth revision [41]

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Study	Methods	Participants	Intervention
Freeman 2014 [75]	Country: UK Allocation: randomized Blinding: SB Diagnostic criteria: Clinical Diagnosis Outcome scale: BDI-II Trial duration (weeks): 8 Setting: Outpatients Overall risk of bias: Low	Participants (n): 30 Diagnosis: Schizophrenia, schizoaffective disorder or delusional disorder (i.e. a diagnosis of non-affective psychosis) Gender distribution: - women (n): 10 - men (n): 20 Mean age (years): - Cognitive Behavioral Therapy: 41,9 - Treatment as Usual: 41,5	Cognitive Behavioral Therapy: - Participants (n): 15 - Number of sessions: 6 Treatment as usual: - Participants (n): 15
Garety 2008 [76]	Country: UK Allocation: randomized Blinding: SB Diagnostic criteria: DSM-IV and ICD-10 Outcome scale: BDI-II Trial duration (weeks):39 Setting:In- and Outpatient Overall risk of bias: Moderate	Overall Participants (n): 301 Diagnosis: non-affective psychosis Overall Gender distribution: - women (n): 90 - men (n): 211 Overall Mean age duration of illness (years): - Cognitive Behavioral Therapy: 38,9 10,9 - Family Intervention: 35 13,3 - Treatment as Usual: 36,8 10,2 Gartey 2008a Participants (n): 83 Gender distribution: - women (n): 23 - men (n): 60 Mean age duration of illness (years): - Cognitive Behavioral Therapy: 38,6 10,9 - Family Intervention: 35 13,3 - Treatment as Usual: 35,6 10,5 Gartey 2008b Participants (n): 218 Gender distribution: - women (n): 67 - men (n): 151 Mean age duration of illness (years): - Cognitive Behavioral Therapy: 39,1 10,9 - Treatment as Usual: 37,1 9,9	Two pathways one with carer and 3 arms (Garety 2008a) and one with no carer and 2 arms (Garety 2008b) Garety 2008a - Cognitive Behavioral Therapy Participants (n): 27 Number of sessions: 13,9 - Family Intervention Participants (n): 28 Number of sessions: 13,9 - Treatment as Usual Participants (n): 28 Garety 2008b - Cognitive Behavioral Therapy Participants (n): 106 Number of sessions: 14,3 - Treatment as Usual Participants (n): 112
Garety 2008 [76]			

NA = not available; SB = single blind; OL = open label; DASS = Depression Anxiety Stress Scales [62]; PANSS = Positive and Negative Syndrome Scale[57]; BDI (-II) = Becks Depression Inventory [63] (II)[64]; SCL-27 plus = The symptom checklist-27-plus [65]; MADRS = Montgomery-Åsberg Depression Rating Scale [66]; DSM-IV(-TR)= Diagnostic and Statistical Manual of Mental Disorders [42] (-text revised) [44]; ICD-10 = International statistical Classification of Diseases and related health problems : tenth revision [41]

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Study	Methods	Participants	Intervention
Gottlieb 2017 [77]	Country: USA Allocation: randomized Blinding: SB Diagnostic criteria: NA Outcome scale: BDI-II Trial duration (weeks): 24 Setting: Outpatient Overall risk of bias: Moderate	Participants (n): 37 Diagnosis: Schizophrenia, schizoaffective disorder, or psychosis not otherwise specified diagnosis Gender distribution: - women (n): 14 - men (n): 23 Mean age (years): - Cognitive Behavioral Therapy: 43,8 - Treatment as Usual: 40,3	Cognitive Behavioral Therapy - Participants (n): 19 - Number of sessions: 10 Treatment as Usual - Participants (n): 18
Granholm 2005 [78]	Country: USA Allocation: randomized Blinding: SB Diagnostic criteria: DSM-IV Outcome scale: Hamilton Trial duration (weeks): 24 Setting: Outpatient Overall risk of bias: Moderate	Participants (n): 76 Diagnosis: schizophrenia or schizoaffective disorder Gender distribution: - women (n): 20 - men (n): 56 Mean age duration of illness (years): - Cognitive behavioral social skills training: 54,5 30,1 - Treatment as Usual: 53,1 28,4	Cognitive behavioral social skills training: - Participants (n): 37 - Number of sessions: 24 Treatment as Usual - Participants (n): 39
Granholm 2013 [79]	Country: USA Allocation: randomized Blinding: SB Diagnostic criteria: DSM-IV Outcome scale: BDI-II Trial duration (weeks): 36 Setting: Outpatient Overall risk of bias: High	Participants (n): 79 Diagnosis: Schizophrenia or schizoaffective disorder Gender distribution: - women (n): 35 - men (n): 44 Mean age (years): - Cognitive behavioral social skills training: 55 - Supportive contact: 55	Cognitive behavioral social skills training: - Participants (n): 41 - Number of sessions: 30,3 Supportive contact: - Participants (n): 38 - Number of sessions: 29,6
Granholm 2014 [80]	Country: USA Allocation: randomized Blinding: SB Diagnostic criteria: DSM-IV Outcome scale: BDI-II Trial duration (weeks): 36 Setting: Outpatient Overall risk of bias: High	Participants (n): 149 Diagnosis: schizophrenia or schizoaffective disorder Gender distribution: - women (n): 50 - men (n): 99 Mean age duration of illness (years): - Cognitive behavioral social skills training: 41,1 21,3 - Supportive contact: 41,6 21,4	Cognitive behavioral social skills training: - Participants (n): 73 - Number of sessions: 12,2 Supportive contact: - Participants (n): 76 - Number of sessions: 15,6

NA = not available; SB = single blind; OL = open label; DASS = Depression Anxiety Stress Scales [62]; PANSS = Positive and Negative Syndrome Scale [57]; BDI (-II) = Becks Depression Inventory [63] (II) [64]; SCL-27 plus = The symptom checklist-27-plus [65]; MADRS = Montgomery-Åsberg Depression Rating Scale [66]; DSM-IV(-TR) = Diagnostic and Statistical Manual of Mental Disorders [42] (-text revised) [44]; ICD-10 = International statistical Classification of Diseases and related health problems : tenth revision [41]

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Study	Methods	Participants	Intervention
Hazell 2016 [81]	Country: England Allocation: randomized Blinding: SB Diagnostic criteria: NA Outcome scale: Hospital Anxiety and Depression Scale - Depression Trial duration (weeks): 12 Setting: NA Overall risk of bias: Moderate	Participants (n): 30 Diagnosis: NA Gender distribution: - women (n): NA - men (n): NA Mean age duration of illness: - Cognitive Behavioral Therapy: NA - Waitlist: NA	Cognitive Behavioral Therapy: - Participants (n): 15 - Number of sessions: 8 Waitlist: - Participants (n): 15
Jenner 2004 [82]	Country: The Netherlands Allocation: randomized Blinding: OL Diagnostic criteria: DSM-IV Outcome scale: PANSS depression Trial duration (weeks): 39 Setting: Outpatients Overall risk of bias: High	Participants (n): 78 Diagnosis: Non-affective psychosis, including schizophrenia, schizoaffective, or psychotic disorder not otherwise specified (NOS) Gender Distribution: - women (n): 35 - men (n): 41 Mean age (years): - Hallucination Focused Integrative Treatment: 36,7 - Treatment as Usual: 36	Hallucination Focused Integrative Treatment - Participants (n): 39 - Number of sessions: 11 Treatment as Usual - Participants (n): 39
Kim 2010 [83]	Country: South Korea Allocation: randomized Blinding: SB Diagnostic criteria: DSM-IV Outcome scale: Hamilton Trial duration (weeks): 4 Setting: Inpatients Overall risk of bias: Moderate	Participants (n): 45 Diagnosis: schizophrenia Gender distribution: - women (n): 33 - men (n): 12 Mean age duration of illness (years): - Eye movement desensitization and reprocessing therapy: 29,9 2,81 - Progressive muscle relaxation: 36 1,76 - Treatment as Usual: 31,8 2,3	Eye movement desensitization and reprocessing therapy: - Participants (n): 15 - Number of sessions: 3 Progressive muscle relaxation: - Participants (n): 15 - Number of sessions: 3 Treatment as Usual - Participants (n): 15
Klingberg 2011 [84]	Country: Germany Allocation: randomized Blinding: SB Diagnostic criteria: DSM-IV Outcome scale: DSM-IV Trial duration (weeks): 36 Setting: Outpatient Overall risk of bias: Moderate	Participants (n): 198 Diagnosis: Schizophrenia Gender distribution: - women (n): 87 - men (n): 111 Mean age duration of illness (years): - Cognitive behavioral therapy: 37,6 13,1 - Cognitive remediation: 36,2 11,9	Cognitive behavioral therapy - Participants (n): 99 - Number of sessions: 16,6 Cognitive Remediation - Participants (n): 99 - Number of sessions: 13,7

NA = not available; SB = single blind; OL = open label; DASS = Depression Anxiety Stress Scales [62]; PANSS = Positive and Negative Syndrome Scale [57]; BDI (-II) = Becks Depression Inventory [63] (II) [64]; SCL-27 plus = The symptom checklist-27-plus [65]; MADRS = Montgomery-Åsberg Depression Rating Scale [66]; DSM-IV(-TR) = Diagnostic and Statistical Manual of Mental Disorders [42] (-text revised) [44]; ICD-10 = International statistical Classification of Diseases and related health problems : tenth revision [41]

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Study	Methods	Participants	Intervention
Kowalski 2017 [85]	Country: Poland Allocation: randomized Blinding: SB Diagnostic criteria: ICD-10 Outcome scale: SCL-27 plus depression subscale Trial duration (weeks): 1 Setting: Inpatients Overall risk of bias: High	Participants (n): 38 Diagnosis: Schizophrenia and acute polymorphic psychotic disorder with schizophrenia symptoms Gender distribution: - women (n):9 - men (n): 22 Mean age duration of illness (years): - Metacognitive training - jumping to conclusions: 28 6,42 - Metacognitive training - theory of mind: 29,1 4,4 - Control: 31,7 8,3	Metacognitive training - jumping to conclusions: - Participants (n): 13 - Number of sessions: 1 Metacognitive training - theory of mind: - Participants (n): 12 - Number of sessions: 1 Control: - Participants (n): 13
Kuipers 2004 [86]	Country: UK Allocation: randomized Blinding: SB Diagnostic criteria: Operational Criteria Checklist (OPCRIT) Outcome scale: BDI Trial duration (weeks): 39 Setting: Outpatients Overall risk of bias: Moderate	Participants (n): 59 Diagnosis: any functional psychosis Gender distribution: - women (n): 14 - men (n): 45 Mean age (years): - Cognitive behavioral therapy + family intervention COAST: 27,7 - Treatment as Usual: 27,9	Cognitive behavioral therapy + family intervention COAST - Participants (n): 32 - Number of sessions: NA Treatment as Usual - Participants (n): 27
Lee 2012 [87]	Country: South Korea Allocation: randomized Blinding: SB Diagnostic criteria: DSM-IV-TR Outcome scale: Hamilton Trial duration (weeks): 7 Setting: Inpatients Overall risk of bias: Moderate	Participants (n): 25 Diagnosis: Schizophrenia Gender distribution: - women (n): 1 - men (n): 8 Mean age duration of illness (years): - Cognitive behavioral social skills training: 51,8 15,4 - Treatment as Usual: 52,7 23	Cognitive behavioral social skills training: - Participants (n) 12 - Number of sessions: 12 Treatment as Usual - Participants (n): 13
Lincoln 2012 [88]	Country: Germany Allocation: randomized Blinding: OL Diagnostic criteria: DSM-IV Outcome scale: Calgary Depression Scale Trial duration (weeks): 38 Setting: Outpatients Overall risk of bias: High	Participants (n): 80 Diagnosis: Schizophrenia, schizoaffective disorder, delusional disorder, or brief psychotic disorder Gender distribution: - women (n): 35 - men (n): 45 Mean age duration of illness (years): - Cognitive Behavioral Therapy: 33,2 11,1 - Treatment as Usual: 33,1 9,7	Cognitive Behavioral Therapy: - Participants (n): 40 - Number of sessions: 28,9 Treatment as Usual: - Participants (n): 40

NA = not available; SB = single blind; OL = open label; DASS = Depression Anxiety Stress Scales [62]; PANSS = Positive and Negative Syndrome Scale[57]; BDI (-II) = Becks Depression Inventory [63] (II)[64]; SCL-27 plus = The symptom checklist-27-plus [65]; MADRS = Montgomery-Åsberg Depression Rating Scale [66]; DSM-IV(-TR)= Diagnostic and Statistical Manual of Mental Disorders [42] (-text revised) [44]; ICD-10 = International statistical Classification of Diseases and related health problems : tenth revision [41]

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Study	Methods	Participants	Intervention
Lu 2013 [89]	Country: Taiwan Allocation: randomized Blinding: SB Diagnostic criteria: DSM-IV-TR Outcome scale: Calgary Depression Scale Trial duration (weeks): 5 Setting: Inpatients Overall risk of bias: Moderate	Participants (n): 80 Diagnosis: Schizophrenia Gender distribution: - women (n): 21 - men (n): 59 Mean age duration of illness (years): - Music therapy: 51,7 26,1 - Treatment as Usual: 52,4 27,9	Music therapy: - Participants (n): 38 - Number of sessions: 8,4 Treatment as Usual: - Participants (n): 42
Montag 2014 [90]	Country: Germany Allocation: randomized Blinding: SB Diagnostic criteria: DSM-IV Outcome scale: Calgary Depression Scale Trial duration (weeks): 6 Setting: Inpatients Overall risk of bias: High	Participants (n): 58 Diagnosis: schizophrenia Gender distribution: - women (n): 15 - men (n): 38 Mean age duration of illness (years): - Psychodynamic art therapy: 37,4 11,3 - Treatment as Usual: 38,8 13,9	Psychodynamic art therapy: - Participants (n): 29 - Number of sessions: 12 Treatment as Usual: - Participants (n): 29
Morrison 2014 [91]	Country: UK Allocation: randomized Blinding: SB Diagnostic criteria: ICD-10 or PANSS Outcome scale: BDI Trial duration (weeks): 39 Setting: NA Overall risk of bias: Moderate	Participants (n): 74 Diagnosis: Schizophrenia, schizoaffective disorder, or delusional disorder Gender distribution: - women (n): 35 - men (n): 39 Mean age (years): - Cognitive Therapy: 33,0 - Treatment as Usual: 29,7	Cognitive Therapy: - Participants (n): 37 - Number of sessions: 13,3 Treatment as Usual: - Participants (n): 37
Ochoa 2017 [92]	Country: Spain Allocation: randomized Blinding: SB Diagnostic criteria: DSM-IV-TR Outcome scale: BDI Trial duration (weeks): 8 Setting: Outpatients Overall risk of bias: High	Participants (n): 122 Diagnosis: Schizophrenia, psychotic disorder not otherwise specified, delusional disorder, schizoaffective disorder, brief psychotic disorder, or schizophreniform disorder Gender distribution: - women (n): 37 - men (n): 85 Mean age duration of illness (years): - Metacognitive group training: 27,1 2,2 - Psychoeducation: 28,2 2,5	Metacognitive group training: - Participants (n): 65 - Number of sessions: 5,5 Psychoeducation: - Participants (n): 57 - Number of sessions: 5,0

NA = not available; SB = single blind; OL = open label; DASS = Depression Anxiety Stress Scales [62]; PANSS = Positive and Negative Syndrome Scale[57]; BDI (-II) = Becks Depression Inventory [63] (II)[64]; SCL-27 plus = The symptom checklist-27-plus [65]; MADRS = Montgomery-Åsberg Depression Rating Scale [66]; DSM-IV(-TR)= Diagnostic and Statistical Manual of Mental Disorders [42] (-text revised) [44]; ICD-10 = International statistical Classification of Diseases and related health problems : tenth revision [41]

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Study	Methods	Participants	Intervention
Penades 2006 [93]	Country: Spain Allocation: randomized Blinding: SB Diagnostic criteria: DSM-IV Outcome scale: Calgary Depression Scale Trial duration (weeks): 16 Setting: Outpatient Overall risk of bias: Moderate	Participants (n): 40 Diagnosis: Schizophrenia Gender distribution: - women (n): 17 - men (n): 23 Mean age duration of illness: - Cognitive Behavioral Therapy: 35,8 14,3 - Cognitive Remediation: 34,4 13,3	Cognitive Behavioral Therapy: - Participants (n): 20 - Number of sessions: 40 Cognitive remediation: - Participants (n): 20 - Number of sessions: 40
Penn 2009 [94]	Country: USA Allocation: randomized Blinding: SB Diagnostic criteria: DSM-IV Outcome scale: BDI-II Trial duration (weeks): 12 Setting: Outpatients Overall risk of bias: Low	Participants (n): 65 Diagnosis: Schizophrenia or schizoaffective disorder Gender distribution: - women (n): 32 - men (n): 33 Mean age duration of illness: - Cognitive Behavioral Therapy: 41,7 14 - Supportive Therapy: 39,6 16,8	Cognitive Behavioral Therapy: - Participants (n): 32 - Number of sessions: 8,3 Supportive Therapy: - Participants (n): 33 - Number of sessions: 7,9
Pinninti 2010 [95]	Country: USA Allocation: randomized Blinding: SB Diagnostic criteria: DSM-IV Outcome scale: Hamilton Trial duration (weeks): 12 Setting: Outpatients Overall risk of bias: Moderate	Participants (n): 33 Diagnosis: Schizophrenia or schizoaffective disorder Gender distribution: - women (n): 14 - men (n): 11 Mean age duration of illness (years): - Cognitive Behavioral Therapy: 38,7 18,7 - Treatment as Usual: 42,27 24,1	Cognitive Behavioral Therapy: - Participants (n): 18 - Number of sessions: 11,9 Treatment as Usual: - Participants (n): 15
Pot-Kolder 2016 [96]	Country: The Netherlands Allocation: randomized Blinding: SB Diagnostic criteria: DSM-IV Outcome scale: BDI-II Trial duration (weeks): 12 Setting: NA Overall risk of bias: Low	Participants (n): 116 Diagnosis: Psychotic disorder Gender distribution: - women (n): 34 - men (n): 82 Mean age duration of illness: - Cognitive Behavioral Therapy: 36,5 13,3 - Waitlist: 39,5 14,9	Cognitive Behavioral Therapy: - Participants (n): 58 - Number of sessions: 16 Waitlist: - Participants (n): 58

NA = not available; SB = single blind; OL = open label; DASS = Depression Anxiety Stress Scales [62]; PANSS = Positive and Negative Syndrome Scale[57]; BDI (-II) = Becks Depression Inventory [63] (II)[64]; SCL-27 plus = The symptom checklist-27-plus [65]; MADRS = Montgomery-Åsberg Depression Rating Scale [66]; DSM-IV(-TR)= Diagnostic and Statistical Manual of Mental Disorders [42] (-text revised) [44]; ICD-10 = International statistical Classification of Diseases and related health problems : tenth revision [41]

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Study	Methods	Participants	Intervention
Rathod 2013 [97]	Country: UK Allocation: randomized Blinding: SB Diagnostic criteria: ICD-10 Research Criteria Outcome scale: MADRS Trial duration (weeks): 20 Setting: In- and Outpatients Overall risk of bias: Moderate	Participants (n): 35 Diagnosis: Schizophrenia, schizoaffective disorder, delusional disorders Gender distribution: - women (n): 13 - men (n): 20 Mean age duration of illness (years): - Cognitive behavioral therapy: 31,4 8,6 - Treatment as Usual: 35,6 12,3	Cognitive Behavioral Therapy: - Participants (n): 17 - Number of sessions: 13,6 Treatment as Usual: - Participants (n): 18
Rector 2003 [98]	Country: Canada Allocation: randomized Blinding: SB Diagnostic criteria: DSM-IV Outcome scale: BDI Trial duration (weeks): 26 Setting: Outpatients Overall risk of bias: Moderate	Participants (n): 45 Diagnosis: Schizophrenia or schizoaffective disorder Gender distribution: - women (n): 22 - men (n): 20 Mean age duration of illness (years): - Cognitive Behavioral Therapy: 37,5 12,2 - Treatment as Usual: 41,2 18	Cognitive Behavioral Therapy: - Participants (n): 24 - Number of sessions: 20 Treatment as Usual: - Participants (n): 21
Schnackenberg 2017 [99]	Country: Germany Allocation: randomized Blinding: OL Diagnostic criteria: NA Outcome scale: BPRS depression and anxiety Trial duration (weeks): 44 Setting: NA Overall risk of bias: High	Participants (n): 22 Diagnosis: Schizophrenia and schizoaffective disorder Gender Distribution: - women (n): 5 - men (n): 7 Mean age duration of illness (years): - Experience Focused Counseling: 44,1 18 - Treatment as Usual: 40,2 18,6	Experience Focused Counseling: - Participants (n): 12 - Number of sessions: NA Treatment as Usual: - Participants (n): 10
Schrank 2016 [100]	Country: UK Allocation: randomized Blinding: OL Diagnostic criteria: Clinical Diagnosis Outcome scale: Short Depression Happiness Scale - Depression Trial duration (weeks): 11 Setting: In- and patients Overall risk of bias: High	Participants (n): 94 Diagnosis: Psychosis defined as schizophrenia and other psychoses including schizoaffective and delusional disorder but not depressive psychosis or psychosis due to substance misuse Gender distribution: - women (n): 38 - men (n): 56 Mean age duration of illness (years): - Group Therapy: 43 13 - Treatment as Usual: 42 14	Group Therapy: - Participants (n): 47 - Number of sessions: 7 Treatment as Usual: - Participants (n): 47

NA = not available; SB = single blind; OL = open label; DASS = Depression Anxiety Stress Scales [62]; PANSS = Positive and Negative Syndrome Scale[57]; BDI (-II) = Becks Depression Inventory [63] (II)[64]; SCL-27 plus = The symptom checklist-27-plus [65]; MADRS = Montgomery-Åsberg Depression Rating Scale [66]; DSM-IV(-TR)= Diagnostic and Statistical Manual of Mental Disorders [42] (-text revised) [44]; ICD-10 = International statistical Classification of Diseases and related health problems : tenth revision [41]

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Study	Methods	Participants	Intervention
Sensky 2000 [101]	Country: UK Allocation: randomized Blinding: SB Diagnostic criteria: ICD-10 research and DSM-IV Outcome scale: MADRS Trial duration (weeks): 39 Setting: NA Overall risk of bias: Moderate	Participants (n): 90 Diagnosis: Schizophrenia Gender distribution: - women (n): 37 - men (n): 53 Mean age duration of illness (years): - Cognitive Behavioral Therapy: 39 14 - Befriending: 40 15	Cognitive Behavioral Therapy: - Participants (n): 46 - Number of sessions: 19 Befriending: - Participants (n): 44 - Number of sessions: 19
Tarrier 2014 [102]	Country: UK Allocation: randomized Blinding: SB Diagnostic criteria: DSM-IV Outcome scale: Calgary Depression Scale Trial duration (weeks): 16 Setting: NA Overall risk of bias: Moderate	Participants (n): 49 Diagnosis: Schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder or psychotic disorder not otherwise specified Gender distribution: - women (n): 18 - men (n): 31 Mean age (years): - Cognitive Behavioral Therapy: 34,9 - Treatment as Usual: 34,9	Cognitive Behavioral Therapy: - Participants (n): 25 - Number of sessions: 24 Treatment as Usual: - Participants (n): 24
Trower 2004 [103]	Country: UK Allocation: randomized Blinding: SB Diagnostic criteria: ICD-10 Outcome scale: Calgary Depression Scale Trial duration (weeks): 26 Setting: NA Overall risk of bias: High	Participants (n): 38 Diagnosis: Schizophrenia or related disorder Gender distribution: - women (n): 14 - men (n): 24 Mean age duration of illness (years): - Cognitive Behavioral Therapy: 36,6 13,4 - Treatment as Usual: 35,1 10	Cognitive Behavioral Therapy: - Participants (n): 18 - Number of sessions: 16 Treatment as Usual: - Participants (n): 20
Turkington 2000 [104]	Country: UK Allocation: randomized Blinding: SB Diagnostic criteria: ICD-10 research criteria Outcome scale: MADRS Trial duration (weeks): 8 Setting: In- and Outpatients Overall risk of bias: Moderate	Participants (n): 19 Diagnosis: Schizophrenia Gender distribution: - women (n): 9 - men (n): 9 Mean age duration of illness (years): - Cognitive Behavioral Therapy: 37,4 9,2 - Befriending: 44,2 13	Cognitive Behavioral Therapy: - Participants (n): 13 - Number of sessions: 6 Befriending - Participants (n): 6

NA = not available; SB = single blind; OL = open label; DASS = Depression Anxiety Stress Scales [62]; PANSS = Positive and Negative Syndrome Scale[57]; BDI (-II) = Becks Depression Inventory [63] (II)[64]; SCL-27 plus = The symptom checklist-27-plus [65]; MADRS = Montgomery-Åsberg Depression Rating Scale [66]; DSM-IV(-TR)= Diagnostic and Statistical Manual of Mental Disorders [42] (-text revised) [44]; ICD-10 = International statistical Classification of Diseases and related health problems : tenth revision [41]

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Study	Methods	Participants	Intervention
Turkington 2002 [105]	Country: UK Allocation: randomized Blinding: SB Diagnostic criteria: ICD-10 research criteria Outcome scale: MADRS Trial duration (weeks): 20 Setting: NA Overall risk of bias: Moderate	Participants (n): 422 Diagnosis: Schizophrenia Gender distribution: - women (n): 97 - men (n): 325 Mean age (years): - Cognitive Behavioral Therapy: 39,9 - Treatment as Usual: 41,1	Cognitive Behavioral Therapy: - Participants (n): 257 - Number of sessions: 6 Treatment as Usual: - Participants (n): 165
White 2011 [106]	Country: UK Allocation: randomized Blinding: SB Diagnostic criteria: ICD-10 Outcome scale: Hospital Anxiety and Depression Scale - Depression Trial duration (weeks): 13 Setting: NA Overall risk of bias: High	Participants (n): 27 Diagnosis: Schizophrenia, schizoaffective disorder, schizophreniform disorder, delusional disorder, brief psychotic disorder, psychotic disorder NOS), bipolar disorder (with psychotic features), or depressive disorder with psychotic symptoms Gender distribution: - women (n): 6 - men (n): 21 Mean age (years): - Acceptance and commitment therapy: 33,6 - Treatment as Usual: 34,5	Acceptance and commitment therapy: - Participants (n): 14 - Number of sessions: 14,3 Treatment as Usual: - Participants (n): 13

NA = not available; SB = single blind; OL = open label; DASS = Depression Anxiety Stress Scales [62]; PANSS = Positive and Negative Syndrome Scale[57]; BDI (-II) = Becks Depression Inventory [63] (II)[64]; SCL-27 plus = The symptom checklist-27-plus [65]; MADRS = Montgomery-Åsberg Depression Rating Scale [66]; DSM-IV(-TR)= Diagnostic and Statistical Manual of Mental Disorders [42] (-text revised) [44]; ICD-10 = International statistical Classification of Diseases and related health problems : tenth revision [41]

3.2 Description of psychological interventions

We included all studies that investigated any psychological treatment. The following interventions were investigated in the included studies: Acceptance and Commitment Therapy (n = 1), AVATAR Therapy (n = 1), Cognitive Behavioral Therapy (n = 27), Experience Focused Counseling (n = 1), Eye movement desensitization and reprocessing (n = 1), Family Intervention (n = 2), Group Psychotherapy (n = 1), Metacognitive Training (n = 5), Mindfulness (n = 1), Music Therapy (n = 1), Progressive Muscle Relaxation (n = 1), Art Therapy (n = 1). A description of all psychological treatments and the control conditions can be found in table 3.2 together with the category under which the interventions were analysed.

Table 3.2: Table of Psychological Interventions and Control Conditions

Name	Category	Description
Acceptance and Commitment Therapy (RCT = 1)	Third Wave Therapies	This intervention is based on mindfulness and acceptance strategies and belongs to the third wave behavioral therapy. It focuses on strengthening the psychological flexibility, so patients gain strategies on how to react to negative feelings and thoughts.
AVATAR therapy (RCT = 1)	Various Therapies	Central element of this therapy is the creation of a computerized representation of the entity that the patients believed was the source of their main voice. The therapist was going to communicate with them via this avatar in further sessions. He or she sat in a second room with a control panel that allowed them to speak in his or her own voice, or as the avatar. A video link allowed the therapist to see and hear the participant's responses, enabling them to adjust therapeutic interventions. The progress of sessions was determined by a discussion in each session concerning any change in the patients condition. (Therapist encouraged assertive responding the dialogue gradually evolved as the avatar conceded ground and acknowledged the strengths and good qualities of the participant. There is an explicit focus on self-esteem and acknowledgments of the participant's strengths and capabilities.) [73]
Befriending (RCT = 2)	Inactive Control	Befriending is an inactive control condition in which the therapist takes the role of a good friend. He concentrates on creating an area of Empathy and support and leads a non-directiv conversation about every life topics, e.g. sports, hobbies, friends, intentionally excluding a discussion about the patients symptoms or problems.[101]

Table 3.2 – continued from previous page

Name	Category	Description
Cognitive Behavioral Therapy (CBT) (RCT = 27)	CBT	This therapy's basic assumption is, that the way people interpret and react to situations, fundamentally influences emotions and behaviors. By detecting and changing negative thinking and acting behaviors, analyzing existing and creating new coping strategies it aims to improve and strengthen patients cognition and emotional regulation. In patients with schizophrenia especially the handling of distress caused by hallucination or other psychotic symptoms is tackled.
Cognitive Remediation (RCT = 4)	Active Control	It aims to improve cognitive functions, like working memory, processing speed, executive functions, social or metacognition, problem solving and attention.
Experience Focused Counseling (RCT = 1)	Various Therapies	This psychological intervention has as basic assumption that the hallucination voices are not something to be cured, but to be seen as a normal human experience. It is based on the theory by Romme and Escher ([107]) and aims to teach participants coping strategies, that, when employed creatively and yet in a structured manner, aid the process of bringing order, life context, and increasing calmness to what can often be experienced as a very chaotic and anxiety-provoking experience of voice-hearing. [99]
Eye movement desensitization and reprocessing therapy (EMDR) (RCT = 1)	Various Therapies	EMDR was first created to help patients with posttraumatic stress disorder. The patient is guided to follow the finger of therapist with his eyes while concentrating on parts of distressing memories, that he has not processed so far. Therapist were targeting all stressful life events, including psychotic experiences, traumatic incidences in childhood or adulthood or treatment related adverse events. [83]

Table 3.2 – continued from previous page

Name	Category	Description
Family inter- vention (RCT = 2)	Various Thera- pies	This therapy focuses additionally on the care- givers and family of the patients. On the one hand it aims to help the patient by improving the caregivers' problem-solution or communi- cation skills and knowledge of the disease. On the other hand it ensures the caregivers' well- being and tries to teach them strategies to re- duce stress. [108]
Group Positive Psychotherapy (RCT = 1)	Various Thera- pies	This psychological intervention targets four areas of development: increasing positive ex- periences; amplifying strengths; fostering pos- itive relationships; and creating a more mean- ingful self-narrative. [100]
Metacognitive Training (MCT) (RCT = 5)	Third Wave Therapies	MCT is psychological treatment that aims to raise awareness of participants on cognitive bi- ases and cognitive dysfunction that may cause or maintain delusional beliefs. It consists of 8 modules, each one addressing a bias that is typical in patients with psychosis. [67]
Mindfulness (RCT = 1)	Third Wave Therapies	This intervention focuses on raising and train- ing awareness for experiences without judg- ment. As part of a therapy in schizophrenia it mainly tackles the perception of voices and other symptoms causing distress. It aims to lessen negative reactions by teaching patients to first allow psychotic experiences and then calmly observing them without reacting. It of- ten uses tools like meditation or discussion in groups to strengthen self-acceptance and in- sight.
Music therapy (RCT = 1)	Creative Ther- apy	This psychological treatment involves active and passive music interventions in a group set- ting. [89]
Progressive muscle relax- ation (PMR) (RCT = 1)	Active Control	It consists of guided training by a thera- pist and homework for patients. PMR in- volves tensing and relaxing 16 different muscle groups, while focusing the participant's atten- tion toward the resulting sensations. [83]

Table 3.2 – continued from previous page

Name	Category	Description
Art therapy (RCT = 1)	Creative Therapy	In this psychological intervention the therapist aimed on supporting the art process and helping to understand the image with a special focus on the patient's autonomous decision-making about the handling of his or her art work. [90]
Psychoeducation (RCT =1)	Active Control	Psychoeducation is an intervention that targets patients and caregivers to improve their understanding of illness and therapy trying to achieve a higher commitment to therapy and a lower re-hospitalization rate. In schizophrenia it focuses especially on symptoms and models of the illness, effects, side-effects and maintenance of medication and relapse prevention by teaching early signs of psychosis.
Supportive counselling (RCT = 3)	Inactive Control	It aims to match the investigated psychological intervention in time and contact. It involves basic support like empathic and supporting environment, psychoeducation, talking about coping strategies with minimal non directive therapist guidance. [73, 79]
Supportive Therapy (RCT =2)	Active Control	Supportive therapy is a guided group therapy session, which may e.g. comprises emotional support and counseling of non-symptom related problems, such as improving social relations with others [94, 109] or has a non structured psychoeducation style and the therapist helps participants to share experiences and promote verbal interaction [71].
Treatment as usual (TAU) (RCT = 26)	Treatment as Usual	Treatment as usual consists of the interventions, including psychopharmaca that are part of the psychiatric care at the study site. It involves psychiatrist consultations, psychoeducation, social work care, antipsychotic medication, group treatment and activities and in out-patient setting community-based rehabilitative activities and follow-ups.

Table 3.2 – continued from previous page

Name	Category	Description
Waitlist Control (WLC)(RCT = 2)	Waitlist Con- trol	A control condition, where participants after the time of the trial duration receive the same intervention as in the experimental arm.

A detailed description of the intervention conducted in each RCT can be found in the appendix in table 7.1- 7.14.

3.3 Scales for the measurement of depression

Depressive symptoms in included RCTs were assessed with 14 different scales. Most often used was the Calgary Depression Scale (RCT = 9) [110], followed by the Becks Depression Inventory II (RCT = 7)[64], the Becks Depression Inventory I (RCT = 4) [63], the Hamilton Depression Scale (RCT = 4) [111], the Hospital Anxiety and Depression Scale - Subscale Depression (RCT = 4) [112] and the Montgomery-Asberg Depression Rating Scale (RCT = 4) [66]. Only once were used the BPRS-E Depression [113], the Depression, Anxiety, Stress Scale - Depression [62], the Hospital Anxiety and Depression Scale [112], the PANSS-Depression [57], the PANSS Depression - 5 Factor [114, 115], the PANSS Depression Factor [116], the SCL-27 plus - Depression subscale [65] and the Short Depression-Happiness Scale - Depression [117]. A detailed description of each scale can be found in Table 3.3.

The Becks Depression Inventory was first established in 1961 to have a reliable and valid method to identifying depression [63]. It was revised in 1993 to BDI-IA [118] . A major revision was in 1996, when the authors adapted the items to the DSM-IV criteria [42] for depressive disorders [64]. In comparison to the BDI-A four items were dropped (weight loss, body image change, somatic preoccupation and work difficulty) and replaced with concentration difficulty, worthlessness, agitation and loss of energy items. In addition some items were reworded.

The Calgary Depression Scale was especially invented to assess depression in schizophrenic patients [110]. It contains items of the Hamilton Depression Scale [111] and items for depression out of the Present State Examination [119].

Table 3.3: Depression Scales - The content of "Items and Categories" and of "Scoring System" refer to the scale mentioned in column one with the source noted there.

Name	Items and Categories	Scoring System
Beck Depression Inventory (BDI-I) (RCT = 4) [63]	21 symptom-attitude categories: • Mood • Pessimism • Sense of Failure • Lack of Satisfaction • Guilty Feeling • Sense of Punishment • Self-Hate • Self Accusations • Self Punitive Wishes • Crying Spells • Irritability • Social Withdrawal • Indecisiveness • Body Image • Work Inhibition • Sleep Disturbance • Fatigability • Loss of Appetite • Weight Loss • Somatic Preoccupation • Loss of Libido	• Each category describes a specific behavioral manifestation of depression and consists of a graded series of 4 to 5 self-evaluative statements. • Numerical values from 0-3 are assigned each statement to indicate the degree of severity.

Table 3.3 – continued from previous page

Name	Items and Categories	Scoring System
Beck Depression Inventory-II (BDI-II) (RCT = 7)[64]	21 symptom-attitude categories: • Sadness • Pessimism • Past Failure • Loss of Pleasure • Guilty Feelings • Punishment Feelings • Self-Dislike • Self-Criticalness • Suicidal Thoughts • Crying • Agitation • Loss of Interest • Indecisiveness • Worthlessness • Loss of Energy • Change in Sleeping • Irritability • Change in Appetite • Concentration Difficulty • Tiredness or Fatigue • Loss of Interest in Sex	• Each category describes a specific behavioral manifestation of depression and consists of a graded series of 4 to 5 self-evaluative statements. • Numerical values from 0-3 are assigned each statement to indicate the degree of severity. • Differences between BDI-I and BDI-II: Agitation, Concentration Difficulty, Loss of Energy and Worthlessness were added.

Table 3.3 – continued from previous page

Name	Items and Categories	Scoring System
BPRS-E depression and anxiety (RCT = 1) [120]	2 Items: • Depression: – Included: sadness, unhappiness, anhedonia, and preoccupation with depressing topics, hopelessness, loss of self-esteem – Not included: vegetative symptoms, e.g., motor retardation, early waking, or the amotivation that accompanies the deficit syndrome • Anxiety: – Reported apprehension, tension, fear, panic or worry. – Observed anxiety is not rated	Scale from 2 to 7; 2 for very mild and 7 extremely severe

Table 3.3 – continued from previous page

Name	Items and Categories	Scoring System
Calgary Depression Scale for Schizophrenia (RCT = 9) [121]	9 items: • Depressed mood • Hopelessness • Self depreciation • Guilty ideas of reference • Pathological guilt • Morning depression • Early wakening • Suicide • Observed depression	• 8 structured questions and one observation item • Range from 0 (absent) to 3 (severe)
Depression, Anxiety, Stress Scales (DASS) - Depression (RCT = 1) [62]	14 items divided into subscales of 7 items with similar content: • dysphoria • hopelessness • devaluation of life • self-deprecation • lack of interest/involvement • anhedonia • inertia	• self-report scale • 4-point severity/frequency scales to rate the extent

Table 3.3 – continued from previous page

Name	Items and Categories	Scoring System
Hamilton Depression Scale (RCT = 4)[111]	17 variables • Depressed mood • Guilt • Suicide • Work and interests • Insomnia – initial – middle – delayed • Retardation • Agitation • Anxiety – psychic – somatic • Somatic symptoms – gastro-intestinal – general • Genital symptoms • Hypochondriasis • Loss of insight • Loss of weight + 4 four additional variables • Diurnal variation • Paranoid symptoms • Obsessional symptoms	• Two raters: summing the score, one rater: doubling the score • Five point scales for (0 no problem – 5 highest weight) for all except a • Three point scales (0-3) for: - Agitation, loss of weight, insomnia (initial, middle, delayed), Insight • Either scored on a three point rating scale, if the item is not easy to be assessed – 0: absent – 1: slight or doubtful – 2: clearly present • Or on a five point rating scale : – 0: absent – 1: mild or trivial – 2+3: moderate – 4: severe

Table 3.3 – continued from previous page

Name	Items and Categories	Scoring System
Hospital Anxiety and Depression Scale (HADS) (RCT = 1) [112]	14 items in two subscales (7 each): • Depression – I still enjoy the things I used to enjoy – I can laugh and see the funny side of things – I feel cheerful – I feel as if I am slowed down – I have lost interest in my appearance – I look forward with enjoyment to things – I can enjoy a good book or radio or TV programme • Anxiety – I feel tense or 'wound up' – I get a sort of frightened feeling as if something awful is about to happen – Worrying thoughts go through my mind – I can sit at ease and feel relaxed – I get a sort of frightened feeling like 'butterflies' in the stomach – I feel restless as if I have to be on the move – I get sudden feelings of panic	self-assessment on 4 point scales • 0 absent/hardly to • 3 often/severe

Table 3.3 – continued from previous page

Name	Items and Categories	Scoring System
Hospital Anxiety and Depression Scale - Depression (RCT = 4) [112]	Same as HADS (above), only items in subscale "Depression" are counted	Same as HADS
Montgomery-Åsberg Depression Rating Scale (RCT = 4) [66]	10 items • Apparent sadness • Reported sadness • Inner tension • Reduced sleep • Reduced appetite • Concentration difficulties • Lassitude • Inability to feel • Pessimistic thoughts • Suicidal thoughts	Score of 0 to 6 • 0 no problems • 6 highest severity of symptoms
PANSS depression (RCT = 1) [57]	30 parameters in 3 subscales • Positive Scale: 7 items • Negative Scale: 7 items • General Psychopathology Scale: 16 items and one of them is Depression	Score 1 to 7 • 1 = absent • 2 = minimal • 3 = mild • 4 = moderate • 5 = moderate-severe • 6 = severe • 7 = extreme

Table 3.3 – continued from previous page

Name	Items and Categories	Scoring System
PANSS depression - 5 Factor (RCT = 1) [114, 115]	urther development of the PANSS [57] with reorganization of the items (n) under 5 factors by Lindenmayer et al.: • Positive component (5) • Negative component (6) • Cognitive component (5) • Excitement component (4) • Depression component (5): Guilt Feelings, Anxiety, Depression, Tension, Lack of judgement and insight	Score 1 to 7 • 1 = absent • 2 = minimal • 3 = mild • 4 = moderate • 5 = moderate-severe • 6 = severe • 7 = extreme
PANSS depression factor (RCT = 1) [116]	Further development of the PANSS [57] with reorganization of the items (n) under 5 factors by Wallwork et al.: • Positive (4) • Negative (5) • Disorganize (3) • Excited (4) • Depressed (3): Guilt Feelings, Anxiety, Depression Posturing	Score 1 to 7 • 1 = absent • 2 = minimal • 3 = mild • 4 = moderate • 5 = moderate-severe • 6 = severe • 7 = extreme

Table 3.3 – continued from previous page

Name	Items and Categories	Scoring System
SCL-27 plus - depression subscale (RCT = 1) [65]	5 items in depression subscale • Melancholy • Would rather be dead • Hopelessness • Feeling blank inside • Loss of Joy	5 point rating scale: • 0: never • 1: 1 – 2 days • 2: 3 – 7 days • 3: 8 – 12 days • 4: 13 – 14 days in the last two weeks
Short Depression-Happiness Scale - Depression (RCT = 1)[117]	6 items: • I felt dissatisfied with my life* • I felt happy • I felt cheerless* • I felt pleased with the way I am • I felt that life was meaningless*	Self-assessment on a 4 point rating scale • never (0), rarely (1), sometimes (2), and often (3) • Items with * are reverse scored

3.4 Risk of bias assessment

We rated the analyzed studies for their possible risk of bias:

- Selection bias
A total of 23 studies had a low risk of bias in sequence generation and 13 in allocation concealment. All other studies are of unclear risk of bias in sequence generation and allocation concealment.
- Performance bias
All analyzed trials have a high risk of bias in blinding of participants and therapists, as expected in studies on psychological treatments, since a blinding of therapist and patient is not possible.
- Detection bias
15 studies have a low, 5 a high and 20 an unclear risk of bias in blinding of outcome assessors.

- **Attrition bias**
In Attrition bias 6 studies were rated with a low risk, 26 with high risk and 8 with unclear risk of bias.
- **Reporting bias**
A total of 9 studies were rated with a low risk of bias, 12 with high risk of bias and 19 with an unclear risk of bias in selective reporting.
- **Researcher Allegiance**
Four trials had a low risk of bias, 29 a high risk of bias and 7 an unclear risk of bias in Researcher Allegiance.
- **Other biases**
33 studies were rated with low, one with high and six with an unclear other risk of bias. There is a possible high risk of bias in the study by Montag et al.. They stated, that "baseline SANS values in the AT group were significantly higher than in control group" [90].

In evaluating the Overall risk of bias the risk of performance bias (In psychological therapies neither the patient nor the therapist can be blind) and the Researcher Allegiance were not taken in consideration. After applying the rule by Furukawa et al. [50] 6 studies had a low overall risk of bias, 21 a moderate overall risk of bias and 13 had a high overall risk of bias (Table 3.1).

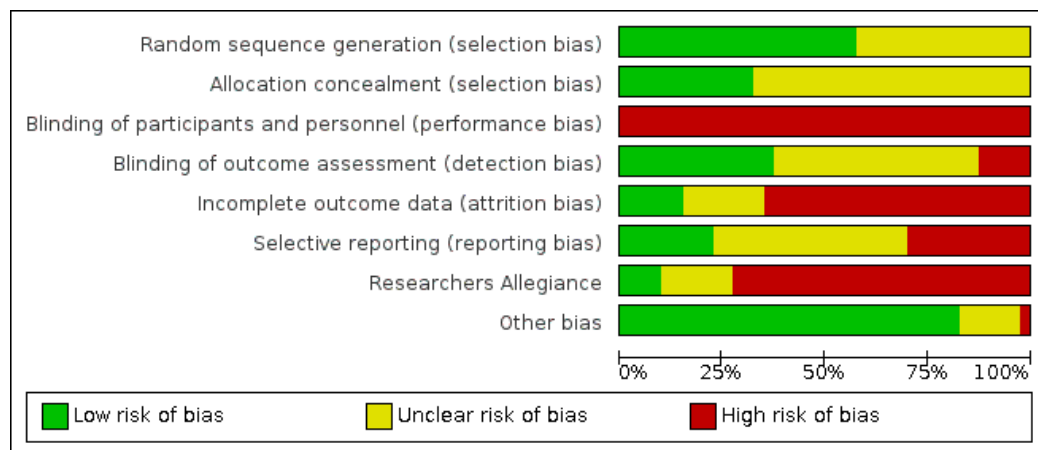


Figure 3.2: The studies were rated by evaluators with regard to their qualitative study methodology using the Cochrane Risk of Bias tool. The picture above shows the relative composition of the assessments in each risk of bias. Explanation: Green: Low risk of bias, Yellow: Unclear risk of bias, Red: High risk of bias

A summary of risk of bias judgements is shown in Figure 3.2 and Figures 3.3 & 3.4.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Researchers Allegiance	Other bias
ACTRN12616000976482	+	?	-	?	?	?	?	+
Andreou 2017	+	?	-	?	+	?	-	+
Barrowclough 2006	+	+	-	+	-	+	?	+
Birchwood 2014	+	+	-	+	+	-	-	?
Briki 2014	?	?	-	?	-	-	+	+
Chadwick 2016	?	+	-	+	?	+	-	?
Craig 2018	+	+	-	+	+	+	-	+
Farhall 2009	+	?	-	-	-	?	-	+
Freeman 2014	+	?	-	+	?	+	-	+
Garety 2008	+	+	-	+	-	+	-	+
Gottlieb 2017	?	?	-	?	-	+	-	+
Granholm 2005	+	?	-	+	-	?	-	+
Granholm 2013	?	?	-	?	-	-	-	+
Granholm 2014	+	?	-	+	-	-	-	+
Hazell 2016	?	+	-	?	?	?	-	+
Jenner 2004	+	+	-	-	-	?	-	+

Figure 3.3: Risk of Bias Summary (1)

Kim 2010	?	?	-	?	-	?	?	+
Klingberg 2011	+	+	-	+	-	?	-	?
Kowalski 2017	?	?	-	?	-	-	-	+
Kuipers 2004	+	?	-	?	-	?	-	+
Lee 2012	?	?	-	?	-	?	?	+
Lincoln 2012	+	?	-	-	+	-	-	+
Lu 2013	?	?	-	?	-	?	?	+
Montag 2014	?	+	-	?	-	-	-	-
Morrison 2014	+	+	-	+	+	-	-	+
Ochoa 2017	+	?	-	?	-	-	-	+
Penades 2006	+	?	-	?	?	?	+	?
Penn 2009	+	?	-	+	?	?	-	+
Pinninti 2010	+	?	-	?	-	?	+	+
Pot-Kolder 2016	+	+	-	+	+	?	?	+
Rathod 2013	?	+	-	?	-	+	-	+
Rector 2003	?	?	-	+	-	+	-	?
Schnackenberg 2017	?	?	-	-	-	?	?	+
Schrank 2016	?	+	-	-	-	+	-	+
Sensky 2000	?	?	-	?	?	-	-	+
Tarrier 2014	?	?	-	+	-	?	-	+
Trower 2004	+	?	-	?	-	-	-	+
Turkington 2000	?	?	-	?	-	?	-	+
Turkington 2002	+	?	-	?	?	?	-	?
White 2011	+	?	-	+	-	-	+	+

Figure 3.4: Risk of Bias Summary (2)

3.5 Effect of psychological interventions

3.5.1 Any psychological intervention versus any control

For this comparison 40 studies were included. Scales used for this comparison were Beck Depression Inventory [63] ($n = 4$) the Beck Depression Inventory II [64] ($n = 7$), the BPRS-E depression and anxiety [120] ($n = 1$), the Calgary Depression Scale ($n = 9$) [110], The Depression, Anxiety and Stress Scale [62] ($n = 1$), the Hospital Anxiety and Depression Scale [112] ($n = 1$) and Hospital Anxiety and Depression Scale-Depression [112] ($n = 4$), the Hamilton Test [111] ($n = 4$), the Montgomery-Åsberg Depression Rating Scale [66] ($n = 4$), the PANSS depression item [57] ($n = 1$), the PANSS depression factor [116] ($n = 1$), the PANSS depression - 5 factor [114, 115], SCL-27 plus depression subscale [65] ($n = 1$) and the Short Depression-Happiness Scale - Depression [117] ($n = 1$).

Psychological interventions led to a greater improvement on depression in patients with schizophrenia in comparison with any control condition (RCT = 41, $n = 3039$, SMD = -0,16; 95%CI: [-0,26 , -0,06], moderate $I^2 = 42\%$). (3.5).

Analyzing the different interventions versus the control condition, there is a clear benefit for reducing depressive symptoms in comparison to control conditions for CBT (RCT = 27, $n = 2117$, SMD = -0,15; 95%CI = [-0,27 , -0,03], moderate $I^2 = 37\%$), for Music Therapy (RCT = 1, $n = 75$, SMD = -0,67; 95%CI = [-1,14 , -0,21]), AVATAR Therapy (RCT = 1, $n = 124$, SMD = -0,39; 95%CI = [-0,75 , -0,04]) and Group Therapy (RCT = 1, $n = 84$, SMD = -0,47; 95%CI = [-0,91 , -0,04]).

No clear benefit was seen for Metacognitive Training (RCT = 5, $n = 314$, SMD = 0,06; 95%CI = [-0,21 , 0,32], non important $I^2 = 26\%$), Mindfulness (RCT = 1, $n = 93$, SMD = -0,38; 95%CI = [-0,79 , 0,03]), Family Intervention (RCT = 2, $n = 103$, SMD = 0,08; 95%CI = [-1,03 , 1,19]; considerable $I^2 = 84\%$), EMDR (RCT = 1, $n = 20$, SMD = 0,49; 95%CI = [-0,44 , 1,42]), PMR (RCT = 1, $n = 20$, SMD = 0,04, 95%CI = [-0,92 , 0,99]), Art Therapy (RCT = 1, $n = 53$; SMD = 0,12; 95%CI = [-0,42 , 0,66]), Acceptance and Commitment Therapy (RCT = 1, $n = 24$; SMD = -0,8; 95%CI = [-1,65 , 0,05]) and Experience Focused Counseling (RCT = 1, $n = 12$, SMD = -0,39; 95%CI = [-1,56 , 0,77]). (3.5).

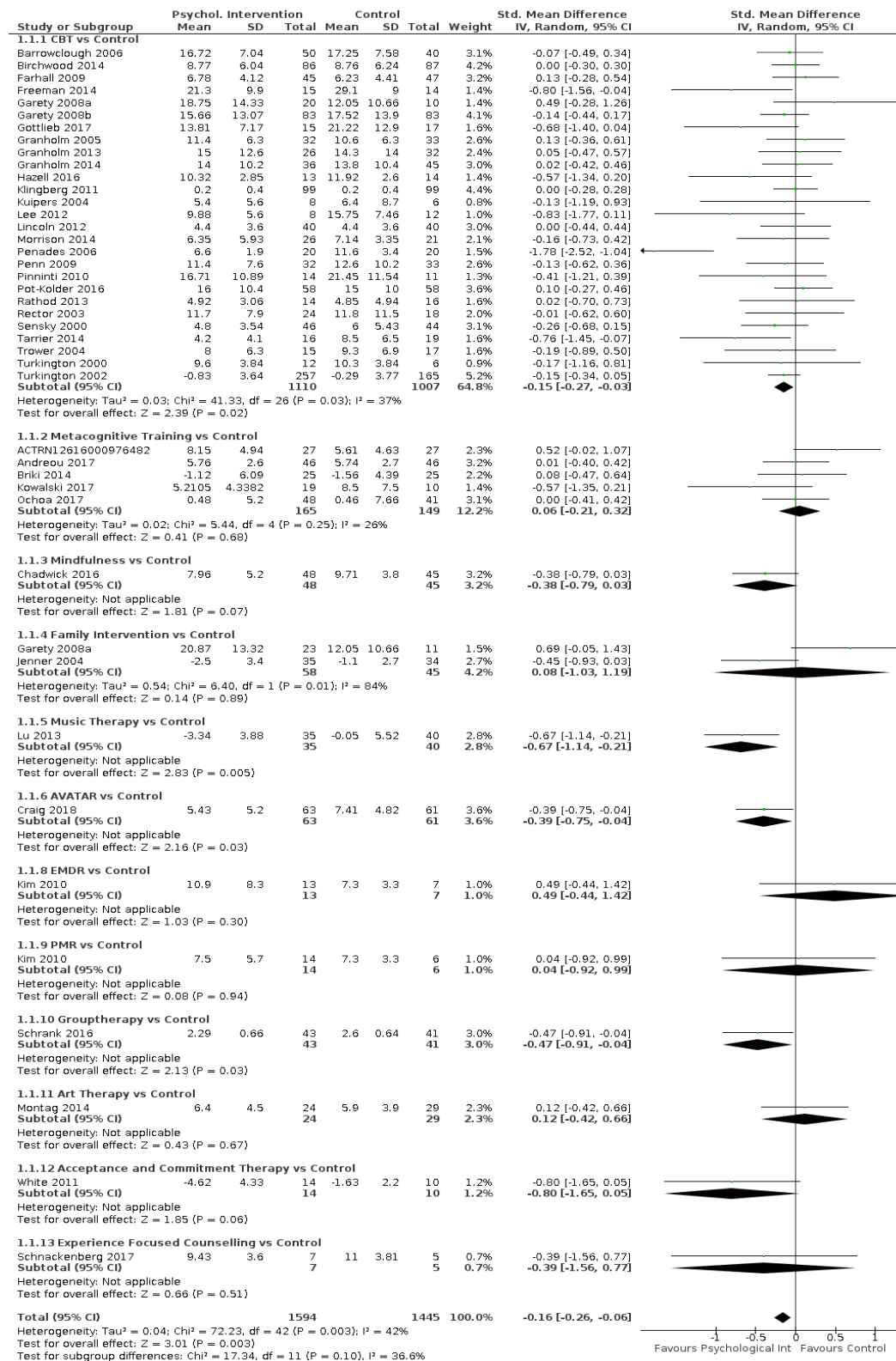


Figure 3.5: Comparison any psychological intervention versus any control condition (Random-Effects)

Subgroup analysis

Control Condition Intensity The benefit of psychological interventions is clear when they are compared to TAU or Waitlist Control (WLC) (RCT = 28, n = 2051, SMD = -0,17, 95%CI = [-0,29 , -0,05], moderate $I^2 = 34\%$) and to non-active control (RCT = 6, n = 400, SMD = -0,21, 95%CI = [-0,41 , -0,02], not important $I^2 = 0\%$). No clear difference is found when psychological interventions are compared to active controls (RCT = 7, n = 588, SMD = -0,12, 95%CI = [-0,48 , 0,23], substantial $I^2 = 77\%$).

The test for subgroup differences of depression between different control conditions did not reveal a difference between subgroups (-0,17 vs -0,21 vs -0,12; $p = 0,89$). Further details can be found in Figure 3.6.

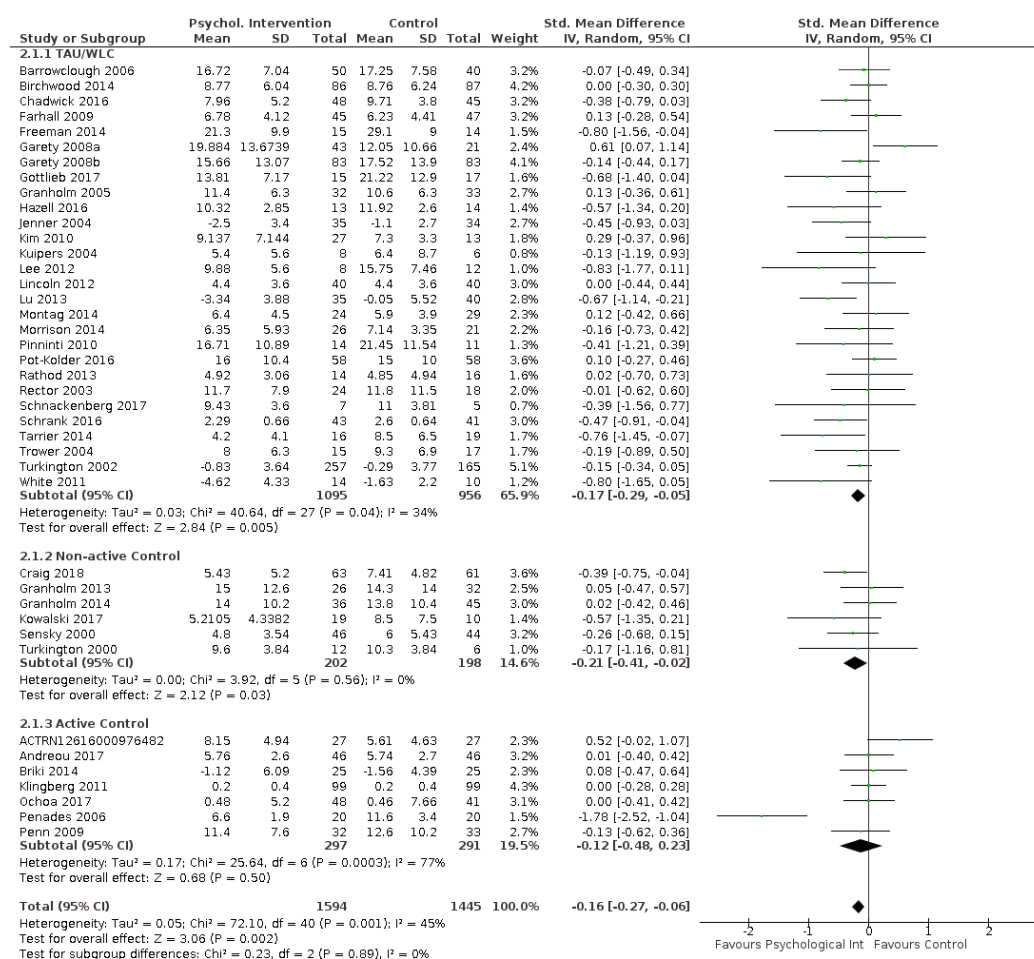


Figure 3.6: Subgroup analysis (Control Condition Intensity) of all psychological Interventions versus Control Conditions (Random-Effects)

Therapy setting Concerning the different therapy settings, both the group therapy (RCT = 13, n = 852, SMD = -0,17, 95%CI = [-0,33 , 0,01], not important $I^2 = 24\%$) and the individual therapy (RCT = 27, n = 2085, SMD = -0,16, 95%CI = [-0,30 , -0,03], moderate $I^2 = 48\%$) show a a clear benefit in comparison to a control condition. In Family intervention setting, psychological interventions show no benefit in comparison to control conditions (RCT = 2, n = 102, SMD = 0,08, 95%CI = [-1,03 , 1,18], considerable $I^2 = 84\%$)

The test for subgroup differences of depression between different therapy settings did not reveal a difference between subgroups (-0,17 vs -0,16 vs 0,08; p = 0,91). See more in Figure 3.7.

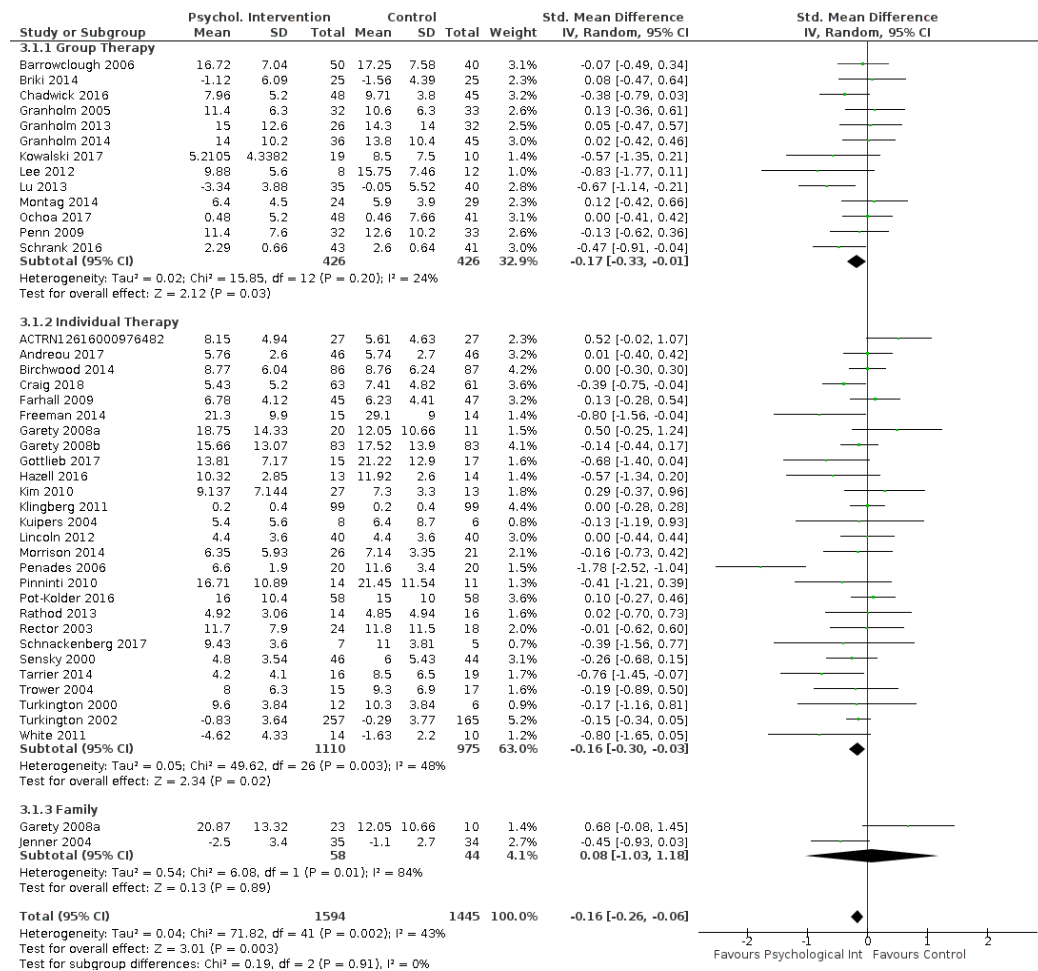


Figure 3.7: Subgroup analysis (Therapy Setting) in all psychological interventions versus control condition(Random-Effects)

Blinding of outcome assessors The subgroup analysis of the blinding of outcome assessors shows a benefit for studies in which the outcome assessor was blind for any psychological intervention versus any control condition (RCT = 36, n = 3039, SMD = -0.15, 95%CI = [-0.27, -0.06], moderate $I^2 = 44\%$). There is no clear benefit for open label studies (RCT = 5, n = 337, SMD = -0.20, 95%CI = [-0.47, 0.07], moderate $I^2 = 32\%$). Details can be found in Figure 3.8.

The test for subgroup differences did not reveal a difference between subgroups ($p = 0.77$).

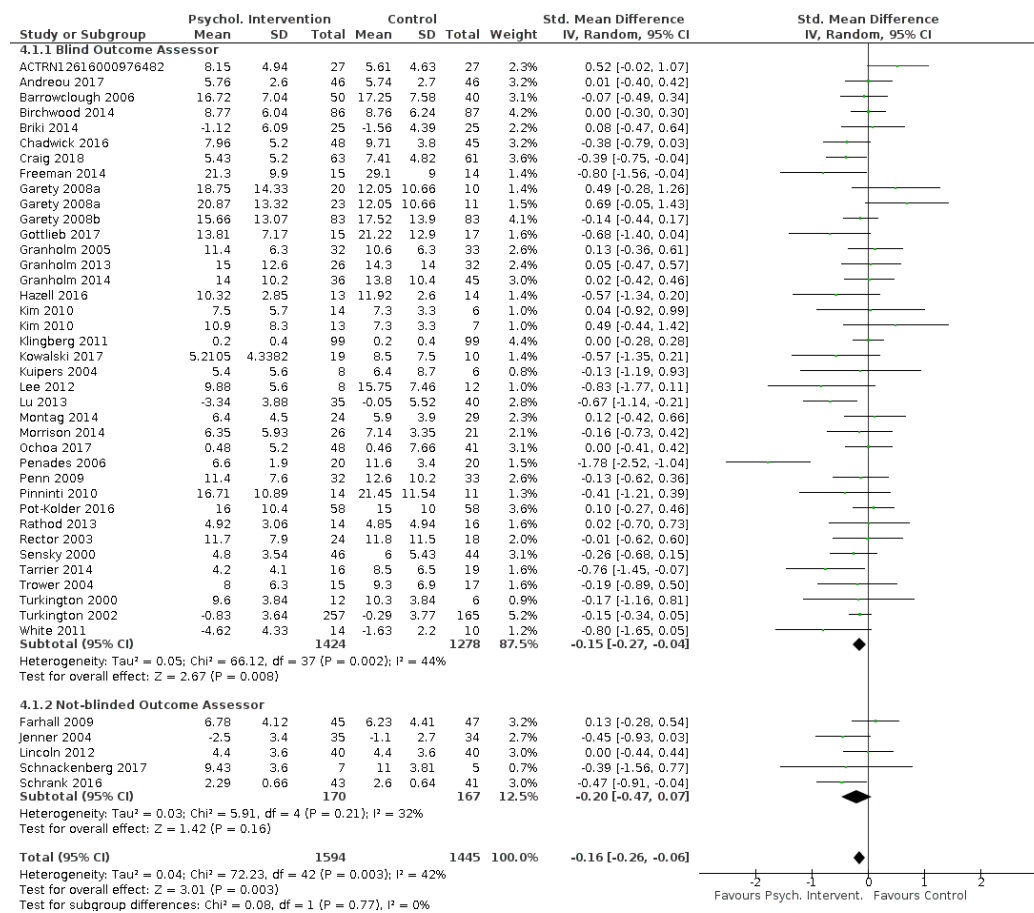


Figure 3.8: Subgroup analysis on blinding of outcome assessor in any psychological intervention versus any control condition (Random-effects)

Treatment resistant participants A subgroup analysis of studies with treatment resistant patients do not show a clear benefit in depressive symptoms for any psychological intervention (RCT = 4, n = 287, SMD = -0.14, 95%CI = [-0.37, 0.10], not important $I^2 = 0\%$). In studies with all other patients psychological intervention do have a clear benefit (RCT = 37, n = 2752, SMD = -0.16, 95%CI = [-0.28, -0.05], moderate $I^2 = 47\%$).

The test for subgroup differences did not reveal a difference between subgroups (-0.14 vs -0.16, $p = 0.83$). More information can be found in Figure 3.9.

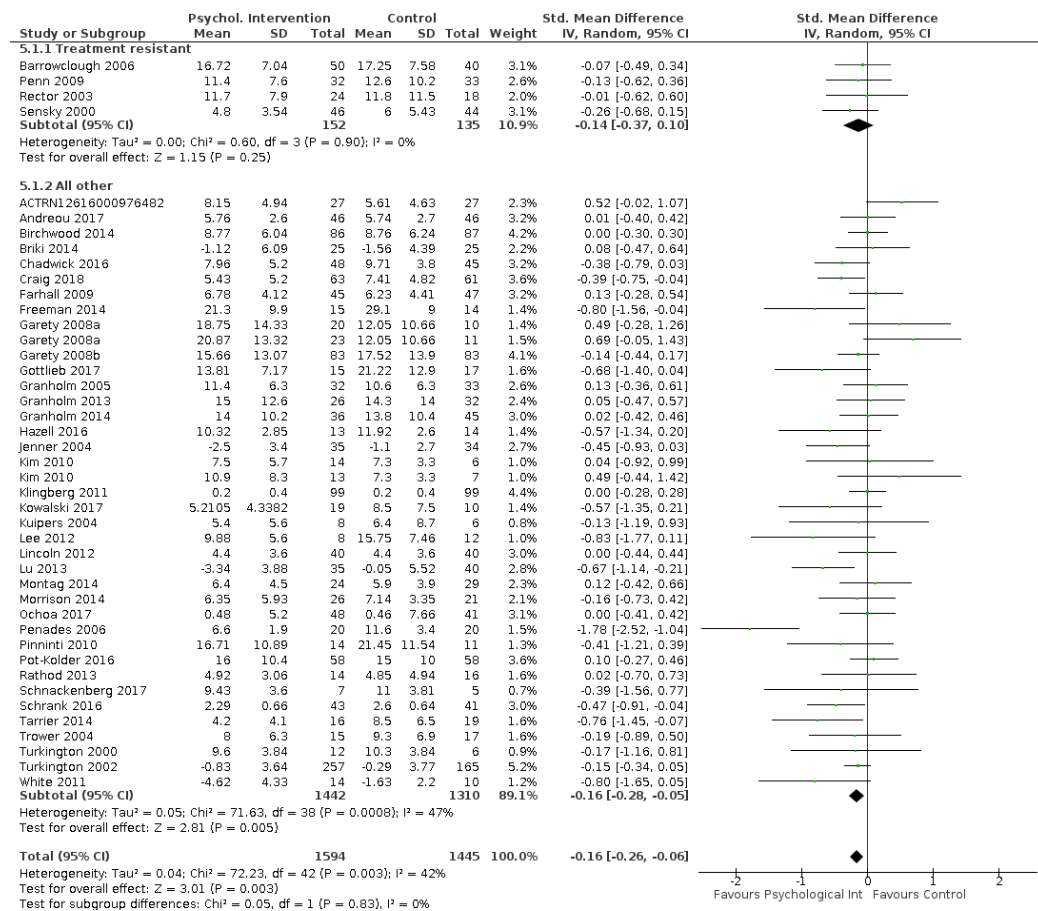


Figure 3.9: Subgroup analysis on studies with treatment resistant patients in the comparison any psychological intervention vs any control (random-effects).

Participants with predominantly negative symptoms A subgroup analysis of studies with patients with predominantly negative symptoms do not show a clear benefit for any psychological intervention in comparison to a control condition (RCT = 2, n = 238, SMD = -0,85, 95%CI = [-2,60 , 0,89], considerable $I^2 = 95\%$). In studies with all other patients any psychological interventions do have a clear benefit (RCT = 39, n = 2801, SMD = -0,14, 95%CI = [-0,23 , -0,04], not important $I^2 = 24\%$).

The test for subgroup differences did not reveal a difference between subgroups (-0,85 vs -0,14, $p = 0,42$). More information can be found in Figure 3.10.

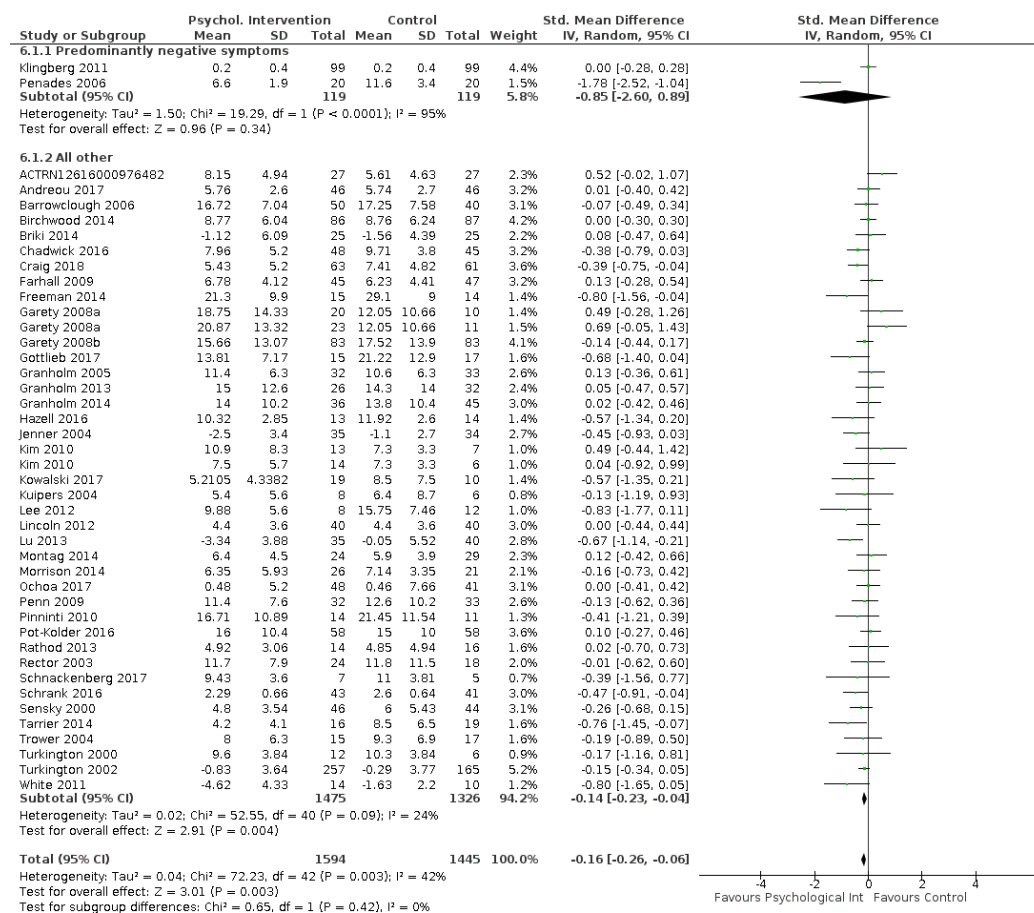


Figure 3.10: Subgroup analysis: Predominantly negative symptoms in any psychological intervention versus any control condition.

Different risk of bias in Researcher Allegiance A subgroup analysis of studies with high risk of bias in Researcher Allegiance show a clear benefit for any psychological intervention (RCT = 30, n = 2493, SMD = -0,13, 95%CI = [-0,22 , -0,04], not important $I^2 = 14\%$). In studies with unclear risk of bias in Researcher Allegiance (RCT = 7, n = 407, SMD = -0,09, 95%CI = [-0,44 , 0,26], substantial $I^2 = 62\%$) or low risk of bias in Researcher Allegiance (RCT = 4, n = 139, SMD = -0,71, 95%CI = [-1,54 , 0,13], considerable $I^2 = 81\%$) any psychological interventions do not have a benefit in depressive symptoms in comparison to a control condition. The test for subgroup differences did not reveal a difference between subgroups (-0,13 vs -0,09 vs -0,71, $p = 0,39$). More information can be found in Figure 3.11.

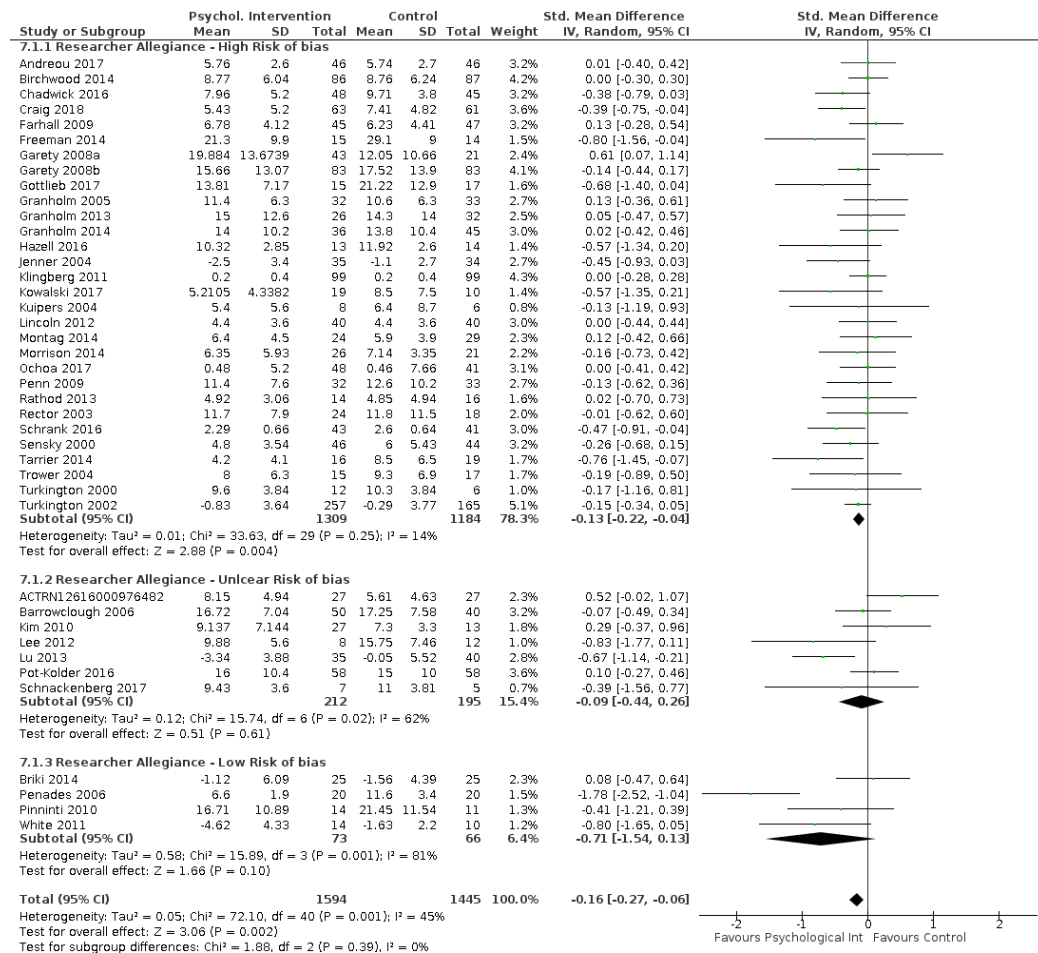


Figure 3.11: Subgroup analysis - Researcher Allegiance (High, unclear or low risk of bias) on the comparison any psychological intervention versus any control condition

Different overall risk of bias A subgroup analysis of studies with different overall risk of bias shows a borderline benefit for studies with a overall moderate risk of bias for any psychological intervention (RCT = 22, n = 1767, SMD = -0,16, 95%CI = [-0,32 , 0,00], moderate $I^2 = 55\%$). In studies with overall low risk of bias (RCT = 6, n = 519, SMD = -0,21, 95%CI = [-0,43 , 0,02], moderate $I^2 = 36\%$) or overall high risk of bias (RCT = 13, n = 753, SMD = -0,12, 95%CI = [-0,26 , 0,03], not important $I^2 = 4\%$) any psychological interventions do not have clear benefit in comparison to a control condition.

The test for subgroup differences did not reveal a difference between subgroups (-0,16 vs -0,21 vs -0,12, $p = 0,78$). More information can be found in Figure 3.12.

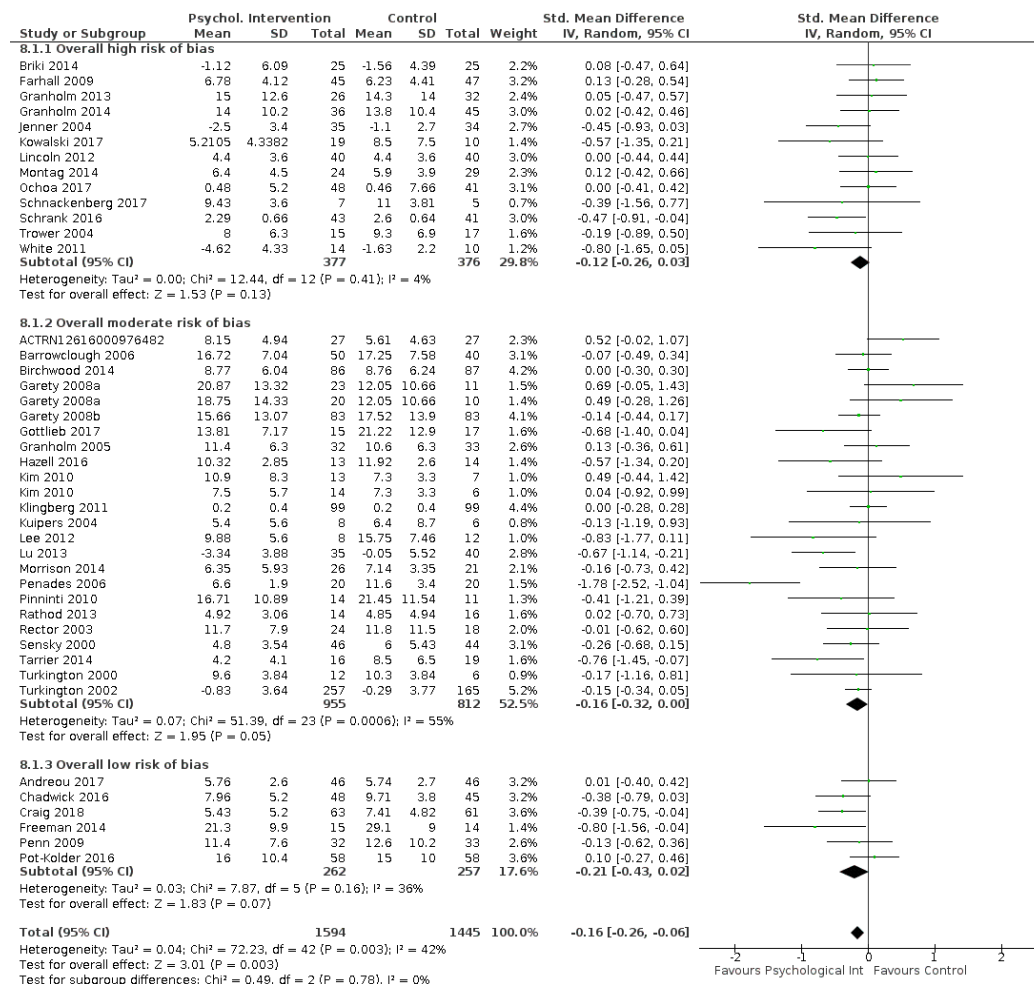


Figure 3.12: Subgroup analysis: Overall risk bias in any psychological intervention versus any control condition

Meta-regression

A meta-regression was performed to investigate the role of the following variables as potential effect modifiers.

Table 3.4: Meta-regression analysis - Depression

Moderator	Coefficient	95%CI	Z-value	P-value
Number of sessions	0,0195	0,0046; 0,0344	2.5646	0,0103
Study duration	0,0042	-0,0038; 0,0123	1.0291	0,3034
Baseline severity	0,0067	-0,0172 ; 0,0306	0.5512	0,5815

Number of sessions For the meta-regression for the possible moderator "number of session" 41 pairwise comparisons provided data and were analyzed. Number of sessions was found to have a role in moderating depression on the comparison psychological interventions versus any control condition with standardized mean differences changing from negative to positive values (higher SMD favors the control condition) the higher the number of sessions was ($p = 0,0103$).

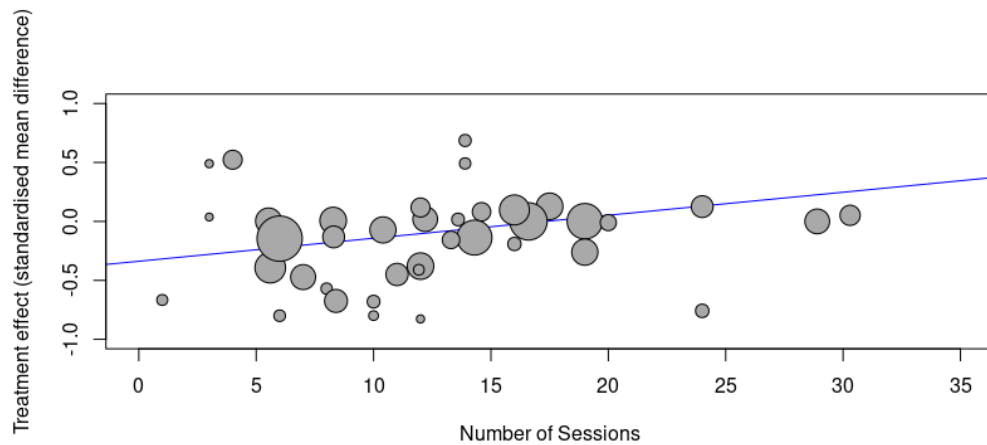


Figure 3.13: Meta-regression: Number of Sessions on comparison any Psychological Intervention versus any Control Condition

Study duration For the meta-regression on possible moderator "Study Duration" 43 pairwise comparisons provided data and were analyzed. The outcome depression was not found to be associated with the study duration

for any psychological interventions versus any control condition ($p = 0,3034$).

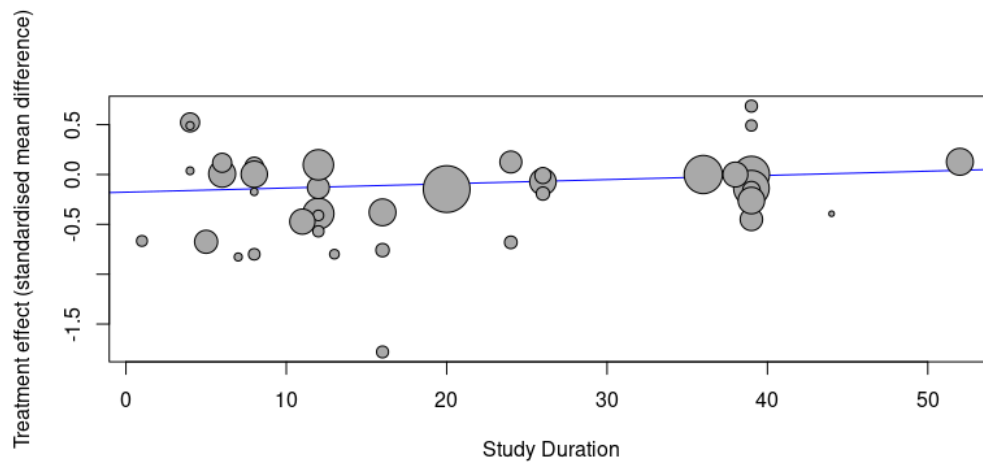


Figure 3.14: Meta-regression: Study Duration on comparison any Psychological Intervention versus any Control Condition

Baseline severity in primary outcome (PANSS) For the meta-regression on possible moderator "Baseline Severity" 26 pairwise comparisons provided data and were analyzed. Baseline Severity was not found to have a role in moderating depression in the comparison any psychological interventions versus any control condition ($p = 0,5815$).

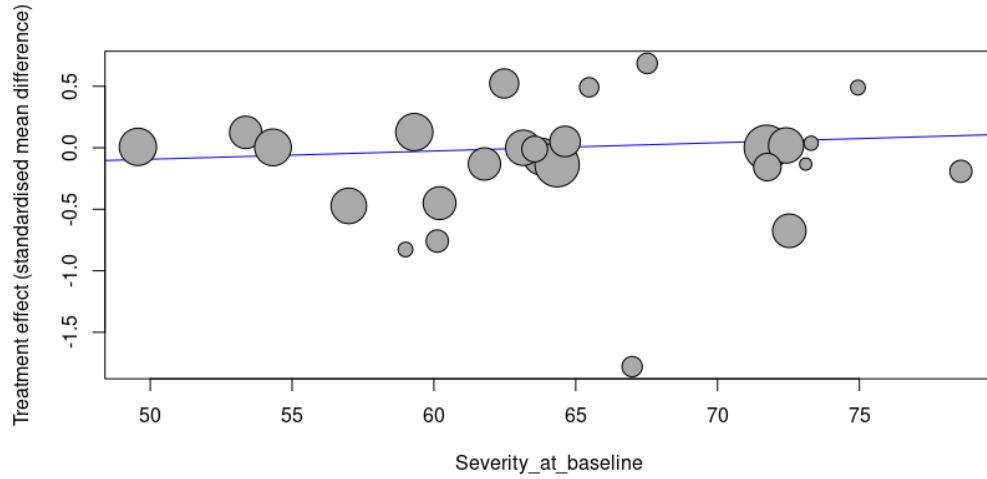


Figure 3.15: Meta-regression: Baseline Severity on comparison any Psychological Intervention versus any Control Condition

An overview and detailed numbers can be found in Table 3.4 and in the Graphs 3.14, 3.15 and 3.13.

Sensitivity analysis

The sensitivity analyses were performed on the following decisions:

Studies with imputed SD When excluding studies with imputed SD ([104]) the result did not change in comparison with the main analysis (RCT = 40, $n = 3021$, $SMD = -0,16$, $95\%CI = [-0,26, -0,05]$, moderate $I^2 = 43\%$).

Studies with only completer analysis When studies with only completer analysis were excluded ([69, 71, 76–79, 83, 85–87, 89, 90, 92, 95, 97–99, 102–104, 106]) the result was consistent with the main analysis (RCT = 19, $n = 1976$, $SMD = -0,18$, $95\%CI = [-0,33, -0,04]$, moderate $I^2 = 58\%$).

3.5.2 Cognitive behavioural therapy versus any control condition

For this comparison 27 studies were included. Scales used for this comparison

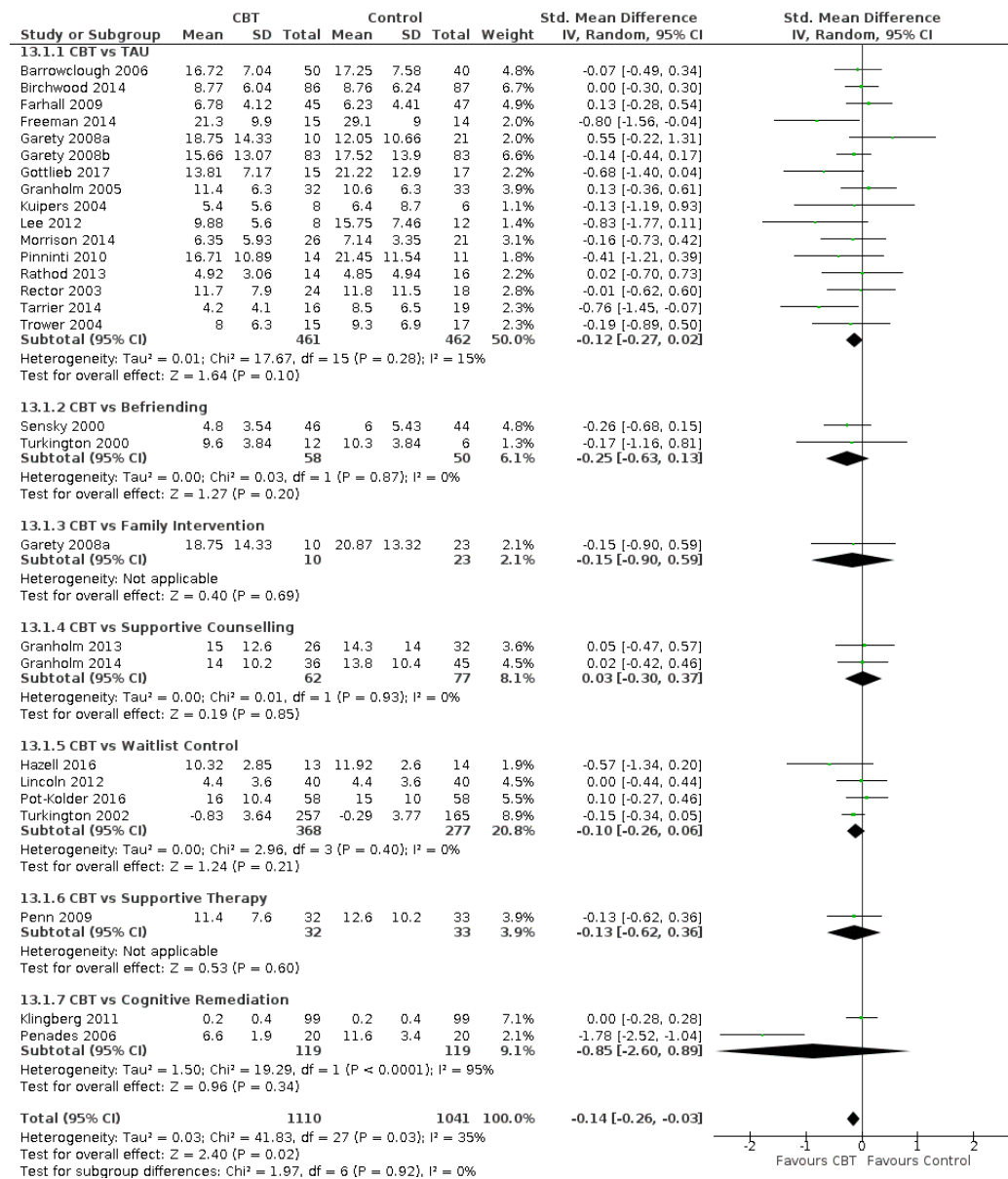


Figure 3.16: Comparison: CBT versus any Control Condition (Random-Effects Model)

were Beck Depression Inventory [63] ($n = 3$) the Beck Depression Inventory II [64] ($n = 7$), the Calgary Depression Scale ($n = 5$)[110], the Hospital

Anxiety and Depression Scale [112] ($n = 1$) and Hospital Anxiety and Depression Scale-Depression [112] ($n = 2$), the Hamilton Test [111] ($n = 3$), the Montgomery-Åsberg Depression Rating Scale [66] ($n = 4$) and the PANSS depression -5 factor [114, 115] ($n = 1$).

Cognitive behavioral therapy shows a clear beneficial effect on depression in patients with schizophrenia in comparison with any control condition (RCT = 27, $n = 2151$, SMD = -0,14; 95%CI: [-0,26 , -0,03]; moderate $I^2=35\%$) (Figure 3.16).

Looking at the comparisons in detail no clear benefit was seen for CBT in comparison to TAU, but at the limit of significance (RCT = 16, $n = 923$, SMD = -0,12, 95%CI = [-0,27 , 0,02], not important $I^2 = 15\%$), to Befriending (RCT = 2, $n = 108$, SMD = -0,25, 95%CI = [-0,63 , 0,13], not important $I^2 = 0\%$), to Family intervention (RCT = 1, $n = 33$, SMD = -0,15, 95%CI = [-0,90 , 0,59]), to Supportive Counseling (RCT = 2, $n = 139$, SMD = 0,03, 95%CI = [-0,30 , 0,37], not important $I^2 = 0\%$), to Waitlist Control (RCT = 4, $n = 645$, SMD = -0,10, 95%CI = [-0,26 , 0,06], not important $I^2 = 0\%$), to Supportive Therapy (RCT = 1, $n = 65$, SMD = -0,13, 95%CI = [-0,62 , 0,36]) and to Cognitive Remediation (RCT = 2, $n = 238$, SMD = -0,85, 95%CI = [-2,6 , 0,89], considerable $I^2 = 95\%$). More details can be found in Figure 3.16.

Subgroup analysis

Control Condition Intensity There is a borderline benefit for CBT in comparison to TAU and WLC (RCT = 20, n = 1568, SMD = -0.11, 95%CI = [-0.22, 0.00], non important $I^2 = 8\%$). In the subgroups of inactive controls (RCT = 4, n = 247, SMD = -0.09, 95%CI = [-0.34, 0.16], not important $I^2 = 0\%$) and active controls (RCT = 4, n = 336, SMD = -0.46, 95%CI = [-1.13, 0.20], considerable $I^2 = 85\%$) there is no clear benefit for CBT. The test for subgroup differences of depression between different control conditions did not reveal a difference between subgroups (-0.11 vs -0.09 vs -0.46; $p = 0.57$). Further details can be found in Figure 3.17.

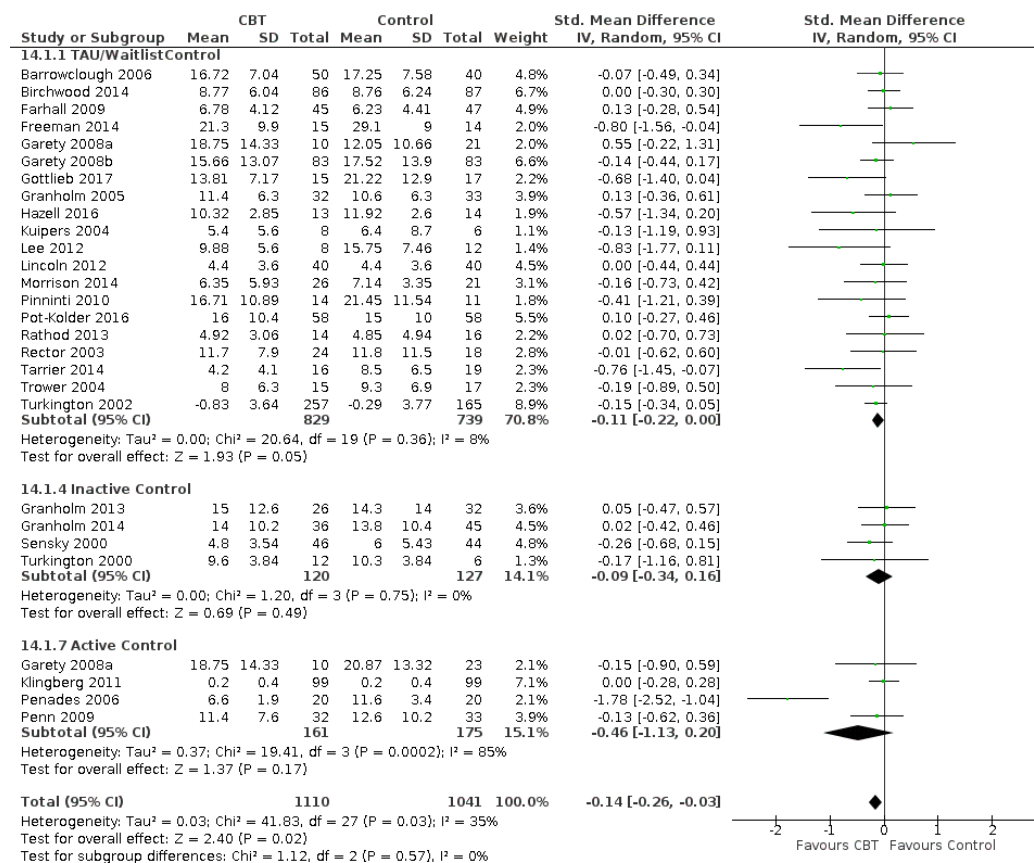


Figure 3.17: Subgroup analysis: Different Control Conditions in CBT vs Control (Random-Effect)

Therapy setting A subgroup analysis for therapy setting, studies with a group therapy setting do not show a clear benefit for CBT (RCT = 6, n = 379, SMD = -0,04, 95%CI = [-0,25 , 0,16], not important $I^2 = 0\%$). Studies in which CBT was delivered in an individual therapy setting show a clear advantage for the therapy (RCT = 21, n = 1772, SMD = -0,18, 95%CI = [-0,32 , -0,03], moderate $I^2 = 44\%$) to any control condition.

The test for subgroup differences did not reveal any differences between subgroups (-0,18 vs -0,04, $p = 0,29$). More information can be found in Figure 3.18.

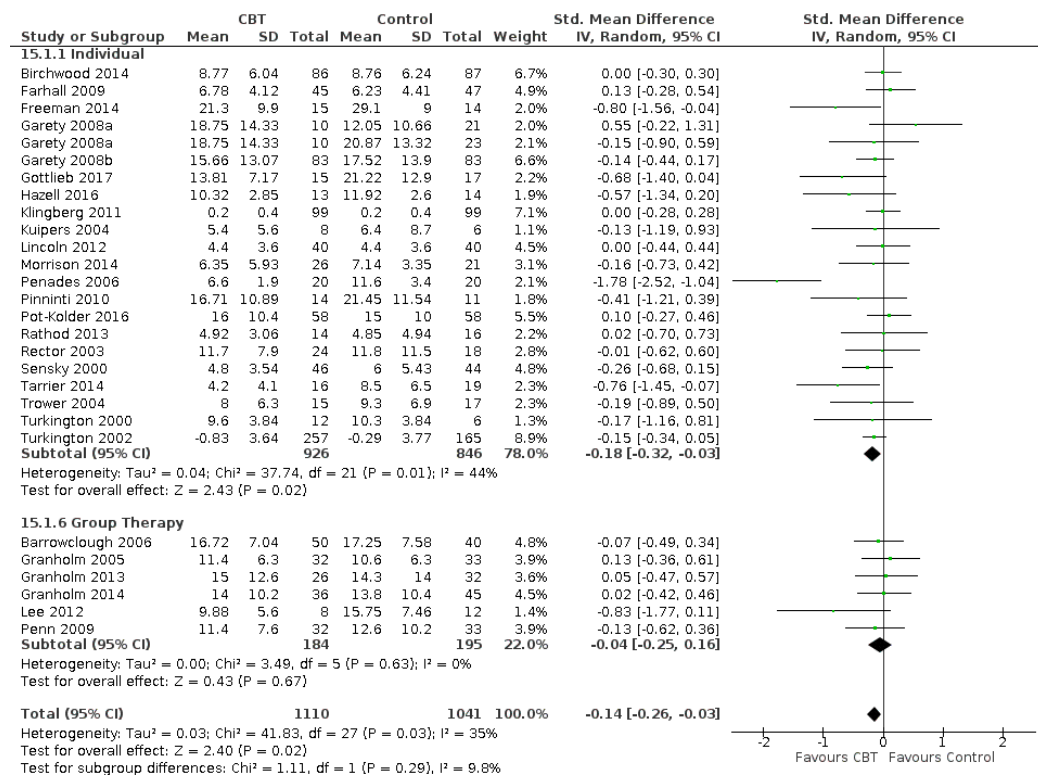


Figure 3.18: Subgroupanalysis: Therapy Setting in CBT versus any Control Condition

Blinding of outcome assessors The subgroup analysis of the blinding of outcome assessors shows a clear benefit for studies, that are single blind, for CBT versus any control condition (RCT = 25, n = 1979, SMD = -0,17, 95%CI = [-0,29 , -0,04], moderate $I^2 = 38\%$). There is no clear benefit for open label studies (RCT = 2, n = 172, SMD = 0,07, 95%CI = [-0,23 , 0,37], not important $I^2 = 0\%$). Details can be found in Figure 3.19.

The test for subgroup differences did not reveal any differences between subgroups (-0,17 vs 0,07, $p = 0,15$).

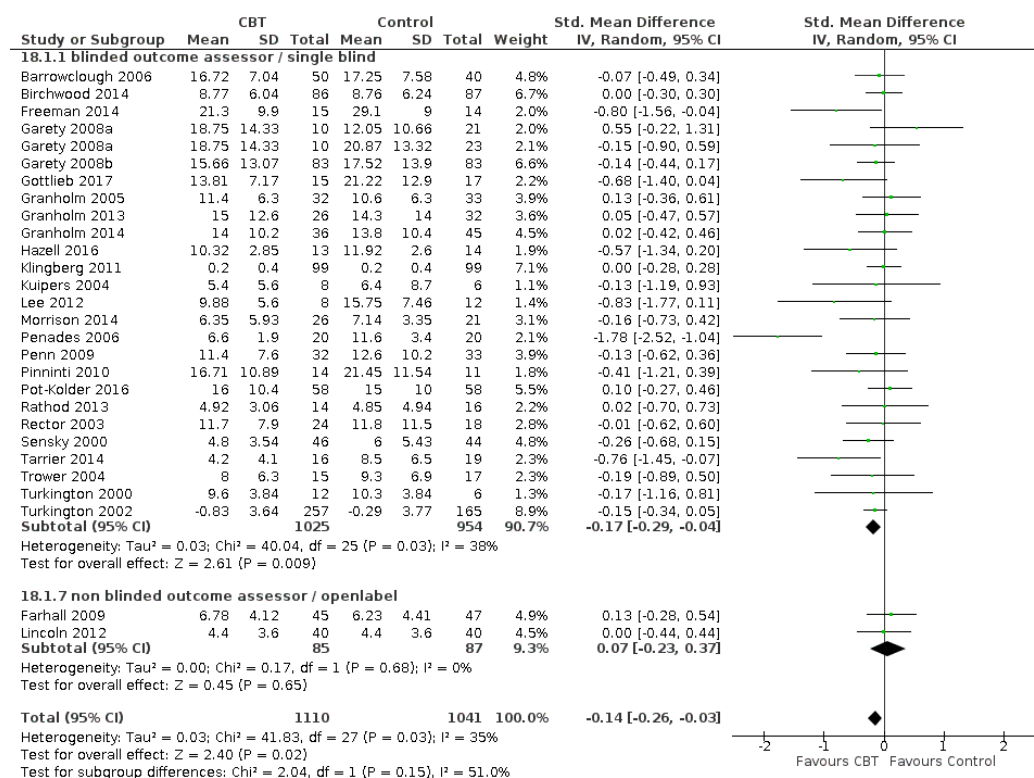


Figure 3.19: Subgroup analysis: Blinding of outcome assessor in CBT vs any Control Condition (Random-Effects)

Treatment resistant participants A subgroup analysis of studies with treatment resistant patients does not show a clear benefit for CBT (RCT = 4, n = 287, SMD = -0,14, 95%CI = [-0,37 , 0,10], not important $I^2 = 0\%$). In studies with all other patients CBT does have a clear benefit in comparison to a control condition (RCT = 23, n = 1864, SMD = -0,16, 95%CI = [-0,30 , -0,02], moderate $I^2 = 44\%$).

The test for subgroup differences did not reveal any differences between subgroups (-0,16 vs -0,14, $p = 0,88$). More information can be found in Figure 3.20.

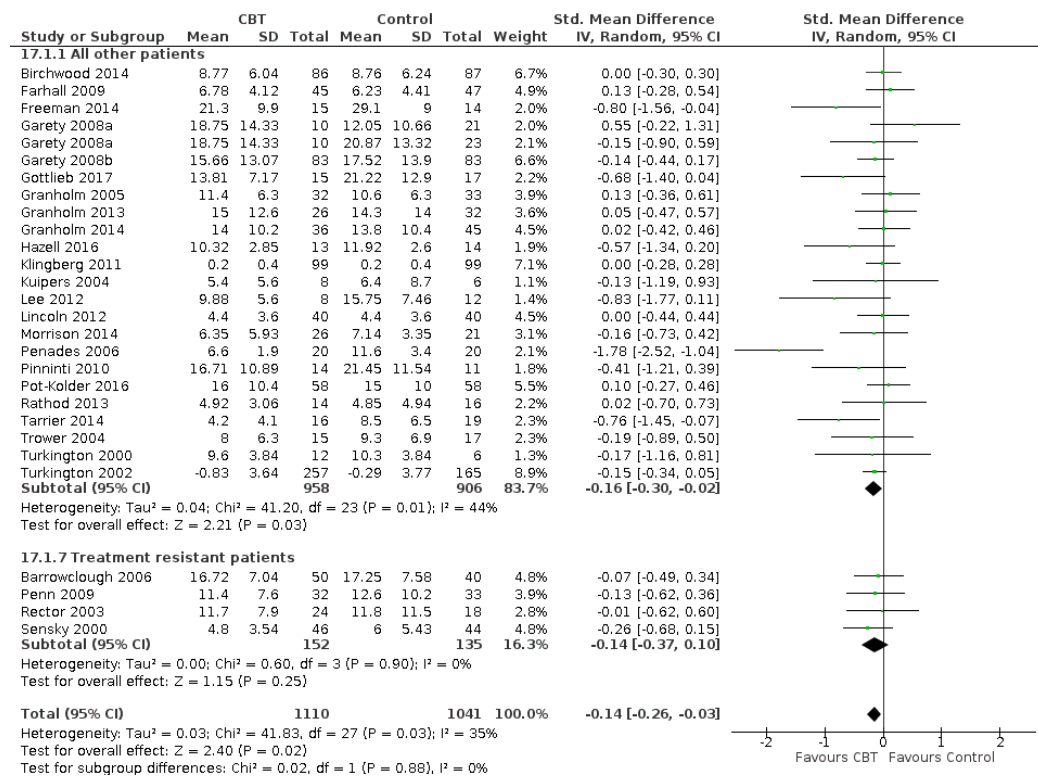


Figure 3.20: Subgroup analysis: Treatment resistant patients in CBT vs Control

Participants with predominantly negative symptoms A subgroup analysis of studies with patients with predominantly negative symptoms do not show a clear benefit for CBT in comparison to any control condition (RCT = 2, n = 238, SMD = -0,85, 95%CI = [-2,60 , 0,89], considerable $I^2 = 95\%$). In studies with all other patients CBT does have a clear benefit in depressive symptoms (RCT = 25, n = 1913, SMD = -0,11, 95%CI = [-0,20 , -0,01], not important $I^2 = 0\%$).

The test for subgroup differences did not reveal differences between subgroups (-0,85 vs -0,11, $p = 0,40$). More information can be found in Figure 3.21.

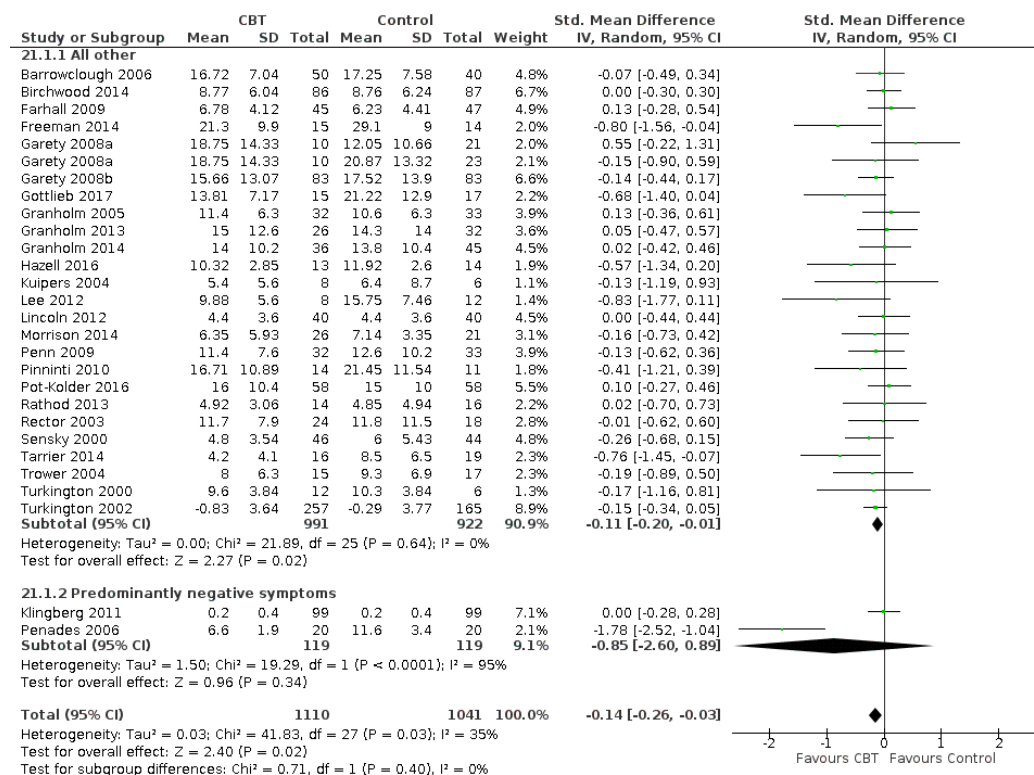


Figure 3.21: Subgroup analysis: Predominantly negative symptoms in CBT versus any control condition (Random-effects).

Different risk of bias in Researcher Allegiance A subgroup analysis of studies with high risk of bias in Researcher Allegiance show a clear benefit for CBT (RCT = 22, n = 1860, SMD = -0,10, 95%CI = [-0,19 , -0,01], not important $I^2 = 0\%$). In studies with unclear risk of bias in Researcher Allegiance (RCT = 3, n = 226, SMD = -0,09, 95%CI = [-0,46 , 0,28], moderate $I^2 = 39\%$) or low risk of bias in Researcher Allegiance (RCT = 2, n = 65, SMD = -1,10, 95%CI = [-2,44 , 0,24], considerable $I^2 = 83\%$) CBT does not have a clear benefit in depressive symptoms in comparison to a control condition. The test for subgroup differences did not reveal differences between subgroups (-0,10 vs -0,09 vs -1,10, $p = 0,34$). More information can be found in Figure 3.22.

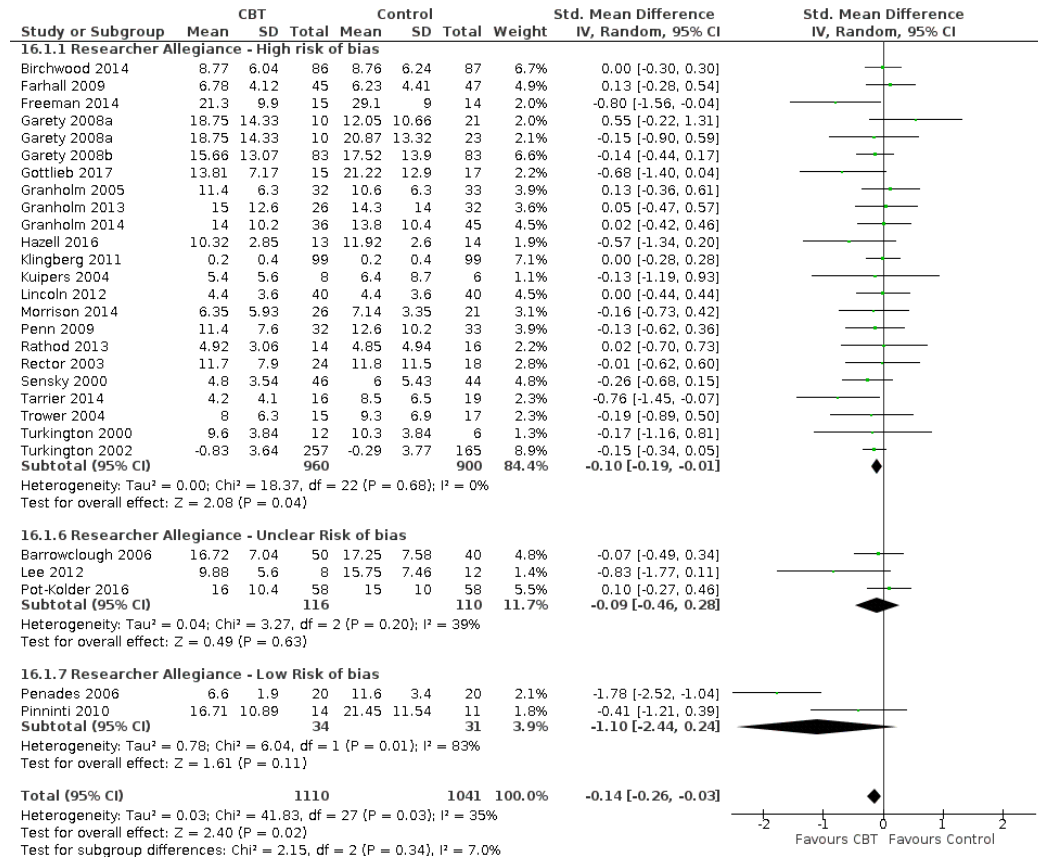


Figure 3.22: Subgroup analysis: Risk of bias in Researcher Allegiance in CBT vs any Control Condition

Different overall risk of bias A subgroup analysis of studies with different overall risk of bias shows a clear benefit for studies with a overall moderate risk of bias for CBT (RCT = 19, n = 1598, SMD = -0,20, 95%CI = [-0,36 , -0,05], moderate $I^2 = 45\%$). In studies with overall low risk of bias (RCT = 3, n = 210, SMD = -0,18, 95%CI = [-0,61 , 0,26], moderate $I^2 = 54\%$) or overall high risk of bias (RCT = 5, n = 343, SMD = 0,03, 95%CI = [-0,18 , 0,24], not important $I^2 = 0\%$) CBT does not have a clear benefit. The test for subgroup differences did not reveal differences between subgroups (-0,36 vs -0,18 vs 0,03, $p = 0,21$). More information can be found in Figure 3.23.

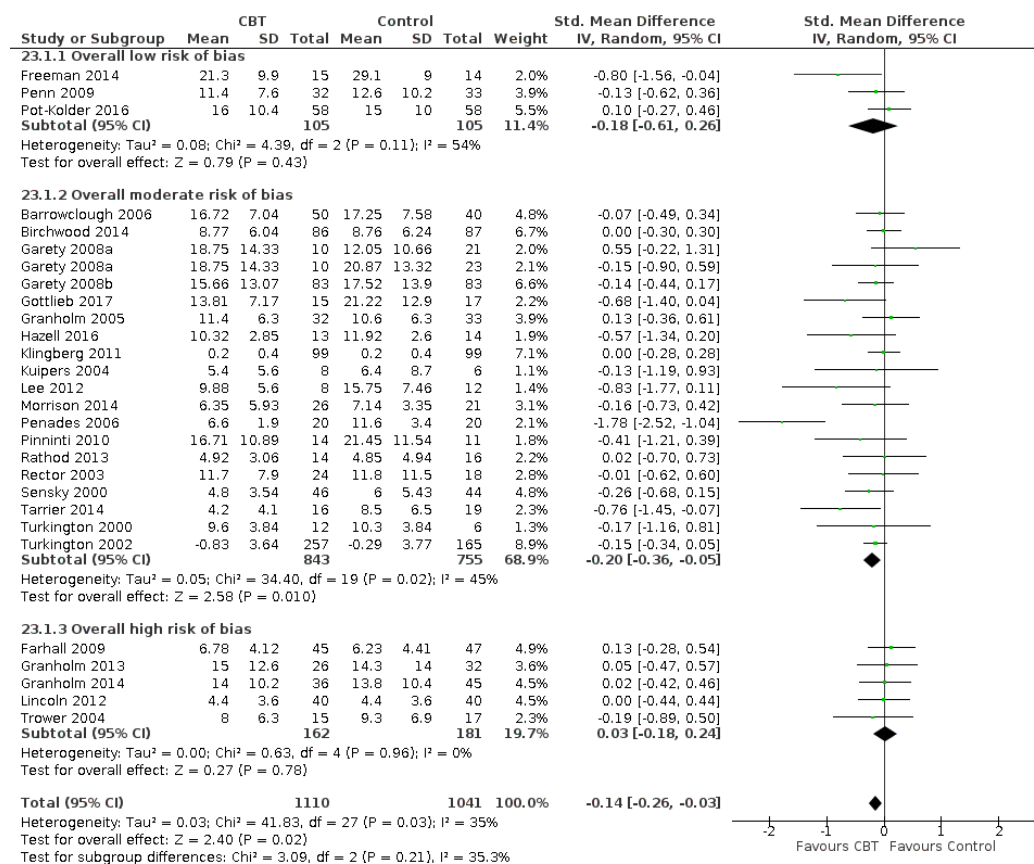


Figure 3.23: Subgroup analysis: Overall risk of bias in CBT vs any control condition. (Random-effects)

Meta-regression

A meta-regression was performed on the following possible continuous moderator variables.

Table 3.5: Meta-regression analysis - Depression CBT vs Control

Moderator	Coefficient	95%CI	Z-value	P-value
Number of sessions	0.0241	0.0064; 0.0418	2.6756	0.0075
Study duration	0.0052	-0.0053; 0.0158	0.9685	0.3328
Baseline severity	0.0051	-0.0281; 0.0384	0.3027	0.7622

Number of sessions The meta-regression for the possible moderator "Number of Session" had 26 pairwise comparisons, that provided data and were analyzed. Number of sessions was found to have moderating role in depression in the comparison CBT versus any control condition with effect sizes changing from negative to positive values the higher the number of sessions was ($p = 0,0075$). For more details see Figure 3.5 and Figure 3.24.

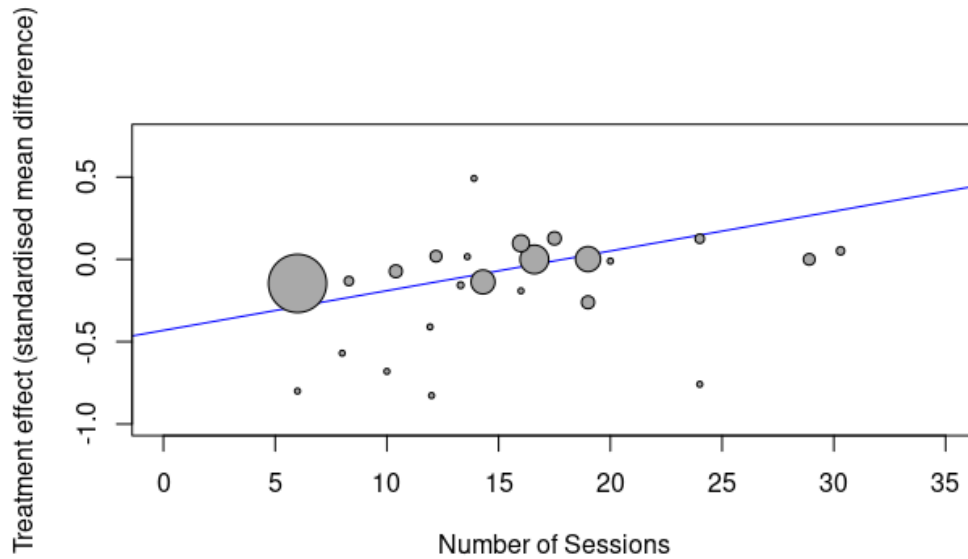


Figure 3.24: Meta-regression: Number of Session on comparison CBT versus any Control Condition.

Study duration For the meta-regression for the possible moderator "Study Duration" 27 pairwise comparisons provided data and were analyzed. Depression was not found to be associated with Study Duration for the comparison CBT versus any control condition ($p = 0,3328$). See Figure 3.25

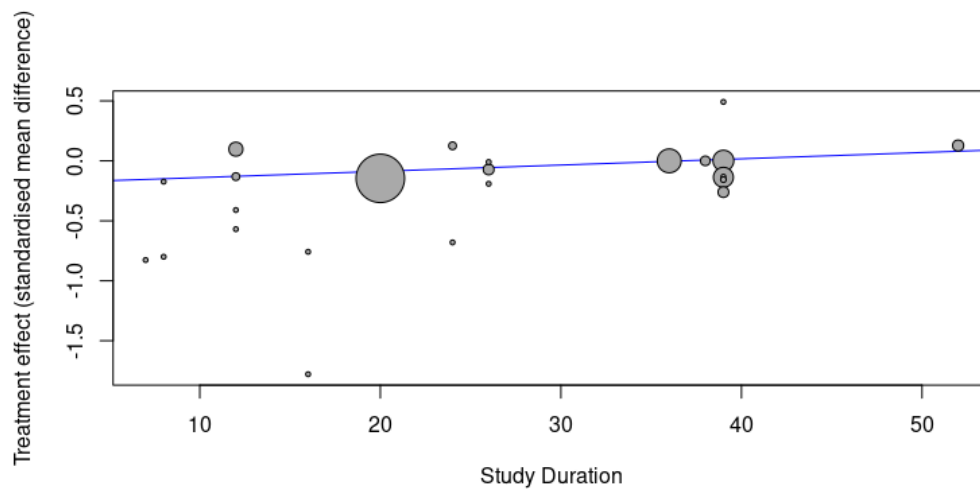


Figure 3.25: Meta-regression: Study duration on comparison CBT versus any Control Condition.

Baseline severity in schizophrenic symptoms outcome (PANSS)

For the meta-regression for the possible moderator "Baseline severity" 17 pairwise comparisons provided data and were analyzed. Depression was not found to be associated with baseline severity in schizophrenic symptoms for the comparison CBT versus any control condition ($p = 0,7622$). For more details see Figure ??

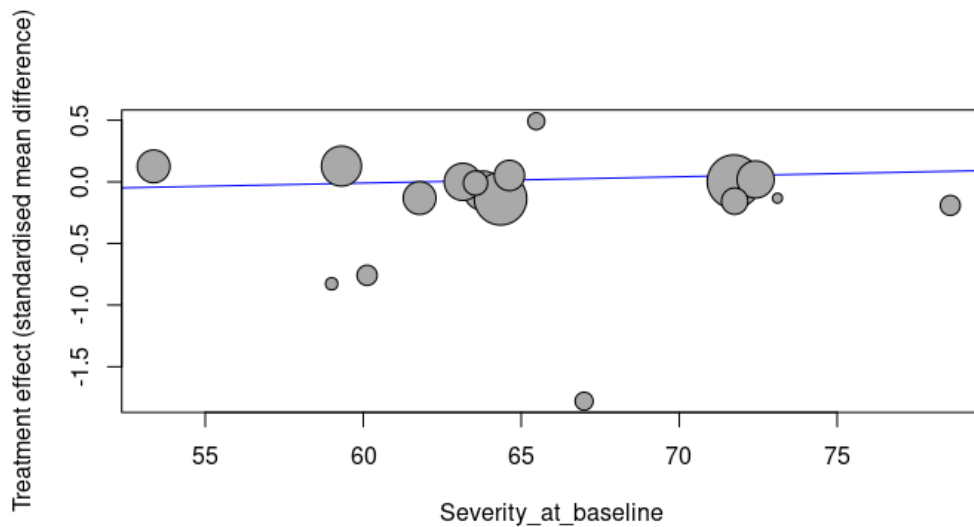


Figure 3.26: Meta-regression: Baseline Severity on comparison CBT versus any Control Condition.

Sensitivity analysis

Studies with imputed SD When excluding studies with imputed SD ([104]) the result did not change in comparison with the main analysis (RCT = 26, $n = 2133$, SMD = -0,15, 95%CI = [-0,27 , -0,03], moderate $I^2 = 38\%$)

Studies with only completer analysis When studies with only completer analysis were excluded ([69, 76–79, 86, 87, 95, 97, 98, 102–104]) the result changed and there was no clear benefit for CBT (RCT = 13, $n = 1460$, SMD = -0,16, 95%CI = [-0,34 , 0,01], moderate $I^2 = 58\%$).

3.5.3 Third Wave Cognitive Behavioural Therapies versus any Control Condition

Third wave therapies are forms of therapy based on traditional behavioral therapy that incorporate additional elements. These include amongst others mindfulness or acceptance and commitment therapy. For this comparison 7 studies were included.

Scales used for this comparison were Beck Depression Inventory [63] ($n = 1$), the Calgary Depression Scale [110] ($n = 1$), The Depression, Anxiety and Stress Scale [62] ($n = 1$), Hospital Anxiety and Depression Scale-Depression [112] ($n = 2$), the PANSS depression factor [116] ($n = 1$) and SCL-27 plus depression subscale [65] ($n = 1$).

Overall there was no clear benefit for 3rd wave cognitive behavioral therapies in comparison to any control conditions in reducing depression in schizophrenic patients (RCT = 7, $n = 431$, SMD = -0,10, 95%CI = [-0,38 , 0,18], moderate $I^2 = 49\%$). See Figure 3.27.

Metacognitive training was not associated with a decrease in depressive

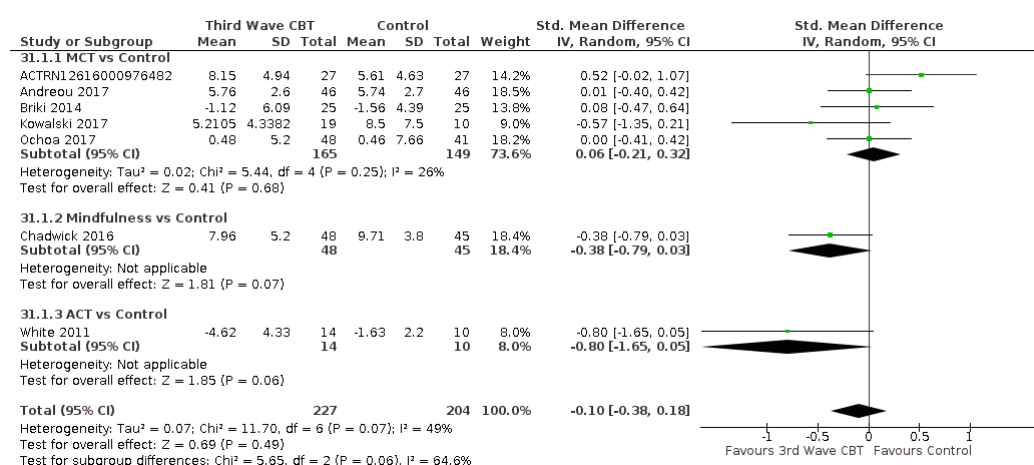


Figure 3.27: Comparison: 3rd Wave Cognitive Behavioral Therapies versus any Control Condition (Random-Effects).

symptoms (RCT = 5, $n = 314$, SMD = 0,06, 95%CI = [-0,21 , 0,32], not important $I^2 = 26\%$) versus any control condition. No clear benefit was seen for Mindfulness (RCT = 1, $n = 93$, SMD = -0,38, 95%CI = [-0,79 , 0,03]) and Acceptance and Commitment Therapy (RCT = 1, $n = 24$, SMD = -0,80, 95%CI = [-1,65 , 0,05]).

3.5.4 Creative Therapy versus any Control Condition

For this comparison 2 studies were included. The scale used for this comparison was the Calgary Depression Scale [110] ($n = 2$). Overall there was no clear benefit for creative therapies in comparison to any control condition on depression in schizophrenic patients (RCT = 2, $n = 128$, SMD = -0,29, 95%CI = [-1,07 , 0,49], substantial $I^2 = 79\%$). See Figure 3.28.

There was a clear benefit in reducing depressive symptoms for Music Ther-

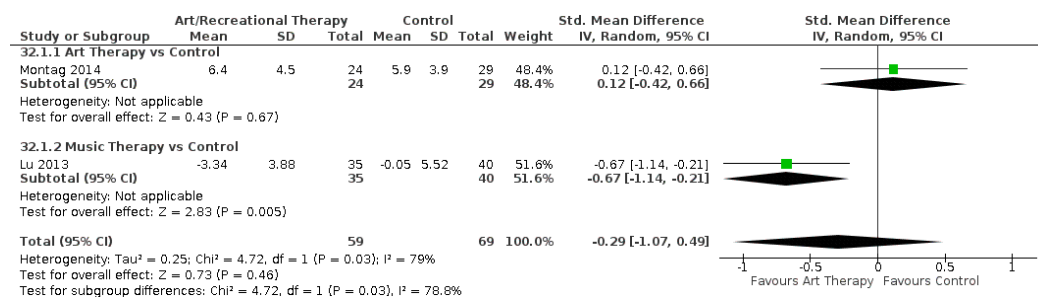


Figure 3.28: Comparison Creative Therapy vs any Control Condition (Random-Effects).

apy in comparison to any Control Condition (RCT = 1, $n = 75$, SMD = -0,67, 95%CI = [-1,14 , -0,21]). But for Art Therapy no difference was found in comparison to any control condition (RCT = 1, $n = 53$, SMD = 0,12, 95%CI = [-0,42 , 0,66]).

3.5.5 Various Therapies versus any Control Condition

For this comparison 6 studies were included. Scales used for this comparison were the Beck Depression Inventory II [64] ($n = 1$), the BPRS-E depression and anxiety [120] ($n = 1$), the Calgary Depression Scale [110] ($n = 1$), the Hamilton Test [111] ($n = 1$), the PANSS depression item [57] ($n = 1$) and the Short Depression-Happiness Scale - Depression [117] ($n = 1$).

Overall various psychological interventions show no clear benefit in reducing depression in patients with schizophrenia in comparison with any control condition (RCT = 6, $n = 373$, SMD = -0,13; 95%CI: [-0,49 , 0,23], moderate $I^2 = 59\%$). See Figure 3.29.

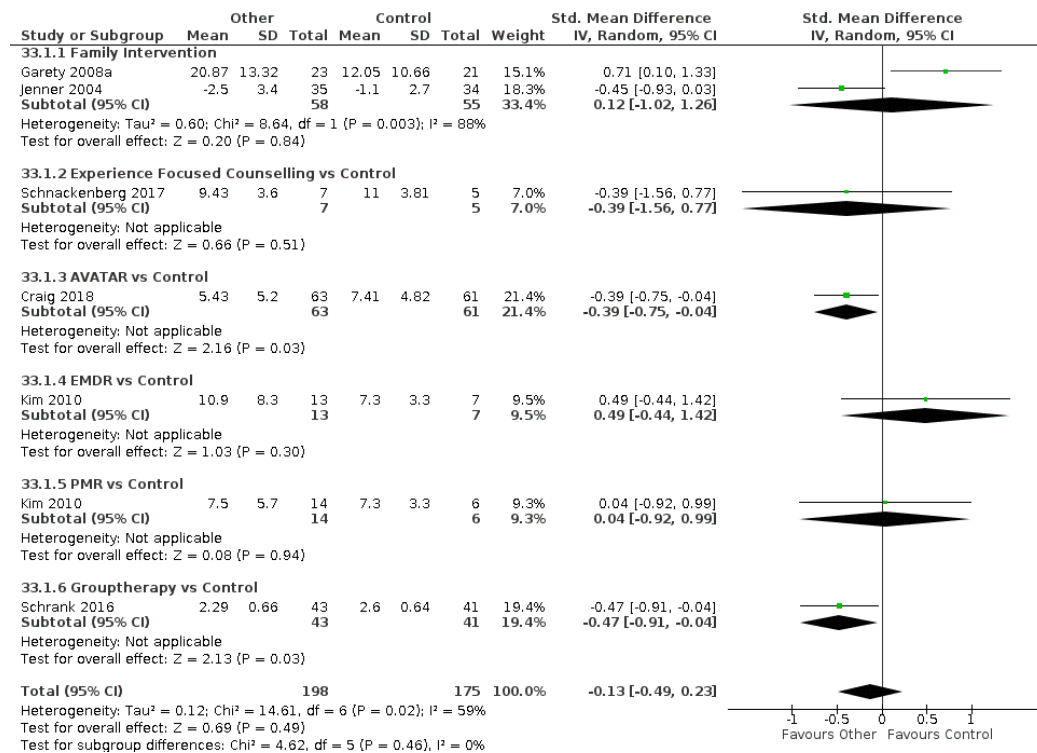


Figure 3.29: Comparison Various Therapies versus any Control Condition (Random-Effects).

No advantage in improving depressive symptoms was seen for Family intervention ($RCT = 2$, $n = 113$, $SMD = 0.12$; $95\%CI$: [-1.02, 1.26], considerable $I^2 = 88\%$), Experience Focused Counseling ($RCT = 1$, $n = 12$, $SMD = -0.39$; $95\%CI$: [-1.56, 0.77]), EMDR ($RCT = 1$, $n = 20$, $SMD = 0.49$; $95\%CI$: [-0.44, 1.42]) or PMR ($RCT = 1$, $n = 20$, $SMD = 0.04$; $95\%CI$: [-0.92, 0.99]) in comparison to any control condition. There was a clear benefit in reducing depressive symptoms for AVATAR Therapy ($RCT = 1$, $n = 124$, $SMD = -0.39$; $95\%CI$: [-0.75, -0.04]) and Group therapy ($RCT = 1$, $n = 84$, $SMD = -0.47$; $95\%CI$: [-0.91, -0.04]) versus any control condition.

3.6 Publication bias

Funnel plots were calculated for comparisons with more then ten studies.

3.6.1 Any psychological intervention versus any control condition

The funnel plot did not show a possible publication bias for psychological interventions considered together versus any control condition. (Figure 3.30). The Egger's Test confirms the visual interpretation of the funnel plot ($p=0,1300$).

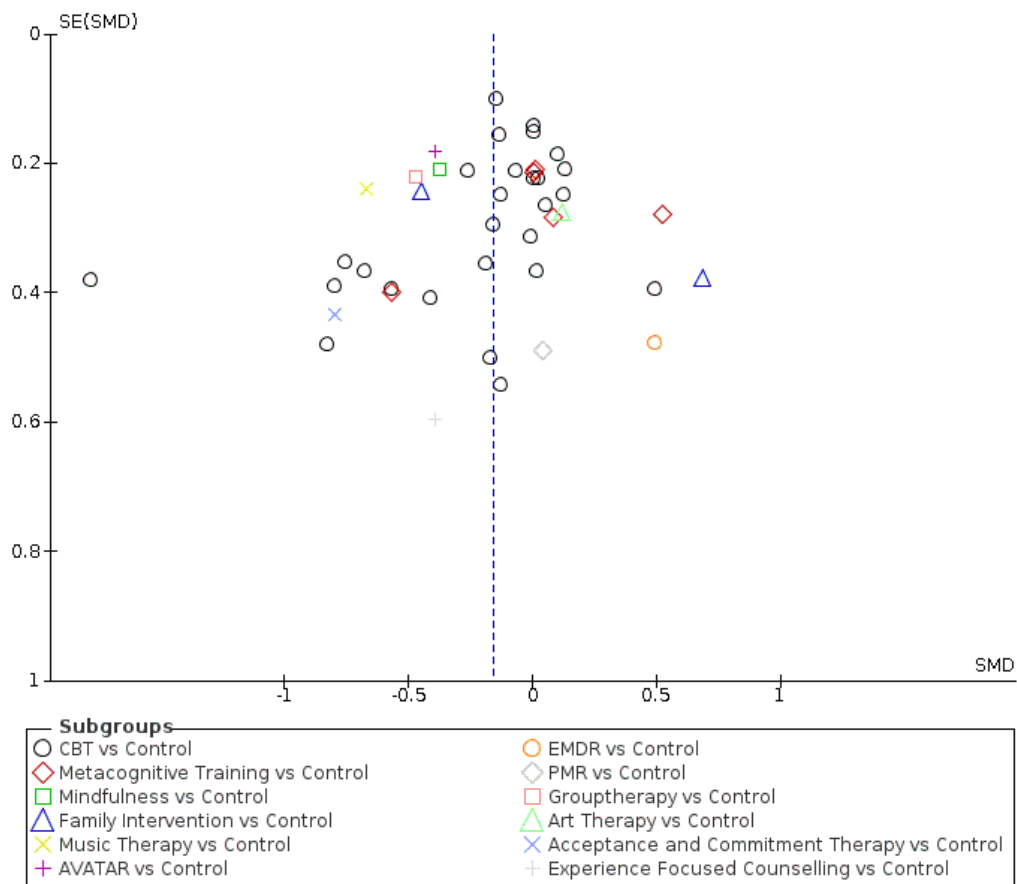


Figure 3.30: Funnel plot for any psychological intervention versus any control condition

3.6.2 CBT vs any control condition

For the comparison CBT versus any control condition there was an slightly unequally distribution of reported outcomes. The funnel plot suggests a lack of small studies, that favor the control condition (Figure 3.31). The Egger's Test confirmed the presence of a funnel plot asymmetry ($p = 0,0133$).

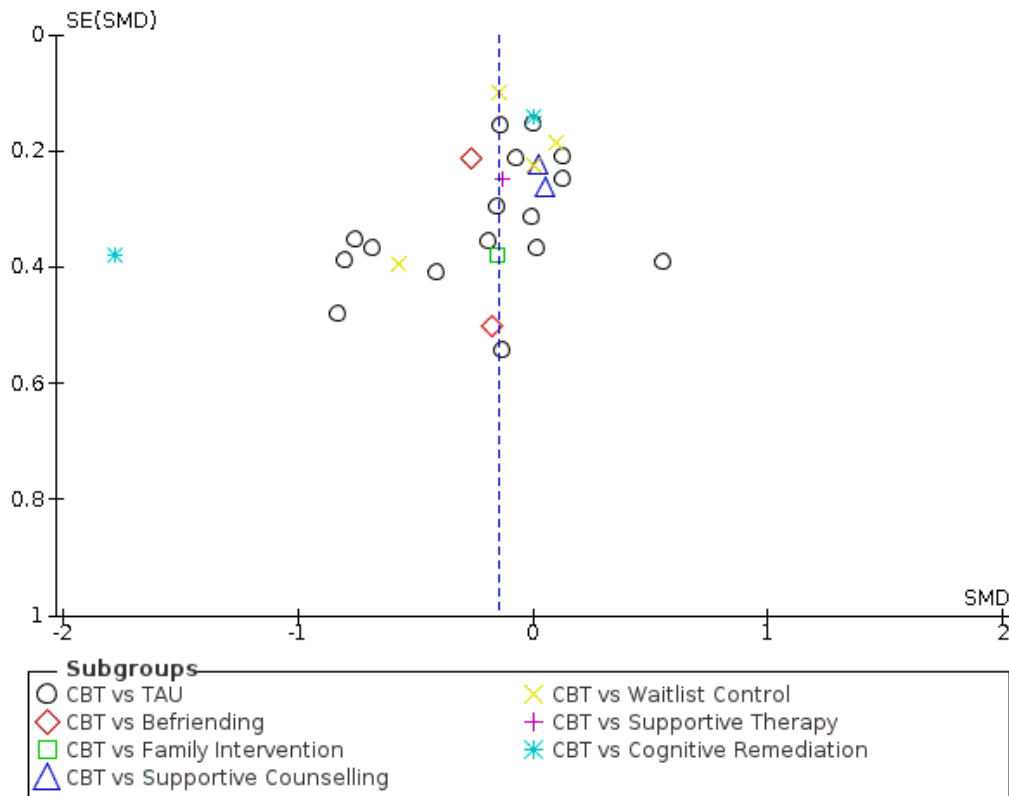


Figure 3.31: Funnel-plot: CBT versus any Control Condition (Random-Effects)

Chapter 4

Discussion

This meta-analysis was conducted to investigate whether psychological interventions have an effect on depressive symptoms in patients with schizophrenia. The data used for this purpose was extracted in the context of a larger project about psychological interventions for schizophrenia [1].

4.1 Main results

In the following section the main results will be discussed.

4.1.1 Quantitative results

Any psychological intervention vs any control condition

For interpreting the effect sizes of control and intervention the standardized mean differences were calculated. The analysis of included studies showed that all psychological interventions combined had a positive effect on depressive symptomatology in individuals with schizophrenia (SMD = -0.16; 95%CI: [-0.26 , -0.06]). In psychological studies Cohens d is often used to interpret the effect size. Cohen categorizes SMDs in small ($\geq 0,2$ and $\leq 0,5$), medium ($\geq 0,5$ and $\leq 0,8$) and large ($\geq 0,8$) effect, see Cohen [122]. By using this categorization the overall effect of any psychological intervention versus any control condition can be interpreted as a small effect. Even though there is discussion whether Cohens d is applicable for standardized mean differences [123] it is an orientation for interpreting the results. When the individual therapies/interventions are considered in isolation, a very heterogeneous picture emerges. Four interventions show an improvement in depressive symptomatology, when compared to control conditions: CBT (RCT = 27; SMD = -0.15; 95%CI = [-0.27 , -0.03]), Music Therapy

(RCT = 1; SMD = -0.67; 95%CI = [-1.14 , -0.21]), AVATAR-Therapy (RCT = 1; SMD = -0.39; 95%CI = [-0.75 , -0.04]) and Group Therapy (RCT = 1, n = 84, SMD = -0.47; 95%CI = [-0.91 , -0.04]). It should be emphasized that according to Cohen's categorization, the effect size of music therapy is 0.67, which is a medium effect, although the result is based on one study only. The effect size of AVATAR-Therapy with 0.39 and Group therapy with 0.47 is a small effect according to Cohen. The comparison CBT to all control conditions with an effect size of 0.15 cannot be assigned to any category by Cohen [122]. However, it should be noted that for the comparison of music therapy ([89]), AVATAR-Therapy ([73]), and Group Therapy([100]) to a control condition, only one study is available, so the evaluation of this effect has poor statistical power. Geretsegger et al. 2017 were also able to show a positive effects of music therapy on depressive symptoms, especially in the long term. However, only a few studies and a problem with different scales were described [124]. Only for CBT a considerable number of studies (n = 27) is available. This means that the majority of the studies examined in this meta-analysis used CBT as the treatment modality, so the overall effect is highly dependent on the effect of CBT. Comparisons with a few studies of other forms of therapy therefore carry less weight.

Looking at the available literature it is notable that CBT has been widely analyzed and different authors showed its effectiveness especially in positive symptomatology of schizophrenia [38, 125]. Outcomes in depression were examined by Jones et al. [37, 38] with small effects for CBT in comparison to other psychological interventions or only standard care. But Jones et al. noted that the evidence for the comparison CBT versus standard care is very low quality and the evidence for CBT versus other psychological treatments is inconsistent.

In this current work no clear advantage was found for the psychological interventions against the control group in the other forms of therapy. However, this meta-analysis also did not show that any of these therapies could have a relevant negative effect on depressive symptoms in patients with schizophrenia.

A priori to the analysis, different subgroups were defined, in order to investigate the role of variables that could have an influence on the results. However, when tested for subgroup differences, there were no relevant differences in the different subgroup analyses comparing any psychological interventions against the control groups. An interesting point was nevertheless the subgroup analysis of intensity of control groups. Control groups varied in the studies from standard therapy only to more active comparators, such as Cognitive Remediation. We investigated the potential role of the control group intensity as moderator of the intervention effect by examining

the studies using these different comparators as separate subgroups: active control group, waitlist control (WLC) & treatment as usual (TAU) and inactive control group. In the WLC/TAU and inactive control subgroups, there was still a relevant effect of psychological interventions compared to these control conditions. No relevant effect of psychological interventions could be shown against the active control conditions. However, the test for subgroup differences showed no relevant difference. A similar result was stated by Michopoulos et al. in a network meta-analysis of psychotherapy in depression. The authors found that different control conditions produce different effect estimates and claim that therefore should not be lumped into a single group [126].

Looking at different study populations there was no clear benefit for psychological interventions with patients that are treatment resistant ($RCT = 4$). On the other side there was a advantage for psychological interventions in studies enrolling non treatment-resistant participants. The test for subgroup differences did not reveal a relevant difference. Similar were the results for a subgroup analysis for studies with patients who have predominantly negative symptoms ($RCT = 2$). There was no clear advantage for any psychological interventions versus control conditions in studies with patients with predominantly negative symptoms. The test for subgroup differences did not show a relevant difference. It is an interesting fact that neither for treatment resistant nor for patients with predominantly negative symptoms psychological interventions seem to have a clear benefit in reducing depressive symptoms. In the meta-regression, the number of therapy hours was shown to be a relevant moderator of the effect size, which resulted in a decrease of the effect with an increase of the number of therapy session ($p = 0.0103$) cf. 3.13. Possible reasons for the decreasing effect on depressive symptoms with increasing number of sessions in this meta-analysis could be chronification of suffering under depression or some kind of habituation. Another explanation could be that the interventions most effective have lower number of sessions (for CBT 16 sessions are recommended [7, 21]). No relevant effect was found for the other possible influencing factors examined. In other meta-analyses on psychotherapy a larger number of sessions was related to a larger effect size [124, 127].

CBT vs any control condition

In advance, the different psychological interventions were grouped together based on the similarity of their therapeutic content. Looking at the comparison of those groups, the following picture emerges. CBT in comparison to the control conditions has a positive effect on depressive symptoms in persons

with schizophrenia. (RCT = 27; SMD = -0.14; 95%CI: [-0.26 , -0.06], $I^2 = 35\%$). A subgroup analysis shows no relevant differences between subgroups. In the meta-regression, number of sessions can be defined as a relevant moderator ($p = 0.0075$), with the positive effect on depressive symptomatology decreasing with increasing number of therapy sessions. Possible reasons are discussed above. Duration of study or baseline severity could not be shown to be moderating factors. A Meta-analysis by Jones 2012 [26] compared CBT with other psychological interventions in patients with schizophrenia and analyzed various outcomes. It showed that in the long term 3 studies demonstrated a significant improvement in depressive symptoms. In a 2018 update of this meta-analysis by Jones, there was only a small advantage with very low evidence for CBT when comparing CBT versus CBT plus standard care [37]. The comparison of CBT versus other psychological treatment also showed only an inconsistent picture for the effect of CBT on depressive symptomatology [38].

Further comparisons

In the further comparisons of Third Wave Therapies, Creative Therapies or all other therapies, no relevant advantage of psychological interventions over a control group could be shown. Several meta-analyses of psychological interventions for schizophrenia have now been published. Among others, music therapy [128], metacognitive training [29, 129], mindfulness [130] or family therapy [32]. None of these reviews has analyzed depression as an outcome, so it is difficult to assess whether these therapies have a relevant effect on the depressive symptoms of schizophrenia patients.

4.1.2 Qualitative results

Analyzed in this work were 40 studies with 30039 participants, which were published in a period from 2000 to 2018 and had recorded depressive symptomatology.

Types of psychological interventions

It should be noted here that a majority of the studies analysed, examined the effect of CBT. Third wave therapies or creative therapies were investigated in a small number of studies only. The large group of other forms of therapy that could not be categorized into a defined group is also striking. These include specially developed forms of therapy, difficult to categorise into a group of interventions. Since often a combination of therapy forms combined

in one intervention is investigated, such as in AVATAR therapy, it is difficult to draw conclusions about the effectiveness of these interventions, as they have often only been tested by their developer and a reproduction of the results in further studies has not yet taken place. For a meta-analysis investigating the effect of any psychological intervention on depressive symptoms, such a variety of individual therapies has the effect that the field of therapies is very heterogeneous and the investigation of moderators or influencing factors is difficult. Even in a meta-analysis of the effect of CBT the author stated, that "a range of interventions were included under "CBT" "[38]. And Hodann-Caudevilla et al. also found differences in applying therapy protocols of mindfulness applications in their meta-analysis [130].

However, even if there was a clear defined form of therapy, it is difficult to examine the true effect of therapy. A fixed definition of the intensity of the intervention and the composition of the intervention is not possible, in contrast to pharmacological studies with active substance, for example Haloperidol, and active substance dose given, for example in milligram. Moreover, as Jones et al. noted in 2012, CBT contains a lot of components and the effective part is hardly ascertainable. In addition, according to Jones et al., there is also an increasing shift in CBT from affective symptoms as therapy target to psychotic symptoms, which further complicates a homogeneous analysis [26].

This is probably one of the greatest limitations of meta-analyses of psychological interventions, in contrast to meta-analyses of pharmacological studies. In pharmacological studies, there is an active substance with a fixed dose for the participants. This is not possible with psychological interventions.

Scales

Overall there were 14 different scales for measuring depression included in this analysis. An attempt to adjust these scales statistically is by using SMD for a meta-analysis. This is an useful method, if the measurement type is different, but cannot help if the scales differ in their content. The scales included in this work measure different items. Some assess only a few items, some more than 20. Notably, also the content of these scales can differ. Some measure somatic and psychological symptoms some only psychological. One scale was especially invented to unmask psychiatric disorders in patients suffering from bodily diseases [112]. This also provides scatter in the results or can mask a true effect, since the target of the measurement is always somewhat different between scales.

Noticeable is that most of the scales used were originally designed for mood disorders, and are not fitted for assessing depression in schizophrenia. Adding-

ton et al. observed that using those scales in patients with schizophrenia causes problems [110]. There is an overlapping in extrapyramidal syndroms due to antipsychotic medication [131] and negative symptoms [132] and additionally the self-evaluation by the patients and the assessment of raters does not correspond [133]. The problem of using different scales for outcome measurement has also been described in other reviews [26, 37, 38, 125].

Risk of bias

By applying the rule by Furukawa et al. [50] only 6 studies had a overall low risk of bias. Whereas 21 studies had a moderate overall risk of bias and 13 had a high overall risk of bias.

Looking at this phenomenon in detail, it was noticeable that a very large part of the studies had a high risk of bias in researcher allegiance. This means that leading persons of the studies developed the manual for the therapy or the therapy itself and thus could have had an interest in the success of the study. On closer examination, it was found that in the comparison of all psychological interventions against a control group there was a relevant positive effect of the RCTs with high risk of bias in Researcher Allegiance on depressive symptomatology. No relevant effect was found for unclear or low risk of bias in this domain. The test for subgroup differences showed no relevant differences between these studies, but it has to be noted, that because of the small number of studies with low risk of bias in Researcher Allegiance the statistical power of this comparison is low.

Turner et al. 2014 also found a high risk of bias in Researcher Allegiance in their meta-analysis in the majority of included studies. A sensitivity analysis showed a decreasing positive effect of the intervention studied. Given the small number of studies without this bias, further analyses of this anomaly were hardly possible [125]. Eichner et al. also found higher effects in studies with high risk of bias in contrast to studies with low risk bias. However, the effect was still significant for this intervention [129].

In a further examination of subgroup differences concerning the risk of bias in blinding of the outcome assessor, there was no relevant subgroup difference in any comparison. In their meta-analysis on CBT, Jauhar et al found a difference between studies that employed a masked outcome assessor and studies that did not, with better results for studies with no masking [134]. Whereas Bighelli et al. still found a relevant effect in studies employing a masked outcome assessor [1]. In a further examination of this discrepancy the authors found out that this difference might be caused by the different inclusion criteria employed in the two systematic reviews. [135].

4.2 Strengths and Limitations

This work presents some methodological strengths. It was planned and conducted following the PRISMA guidelines [60] and the rules applied by the Cochrane Collaboration. Additionally it is a very comprehensive review, since all psychological interventions were systematically considered for inclusion. This current work also presents some limitations, mostly because of lack of evidence, which is discussed in the following sections.

Low number of studies

There are only a few systematic reviews investigating the effect of specific psychological interventions on depressive symptoms in patients with schizophrenia [26, 37–39, 130]. The aim of the present work was to conduct a more comprehensive analysis by including all psychological interventions. However, even for this meta-analysis, only a few studies could be included for further subgroup analyses. The problem was that few RCTs reported depression as an outcome. Of the nearly 200 studies eligible for inclusion, only 40 reported depressive symptoms. One reason for the small number of studies that reported depressive symptoms as an outcome could be the focus on positive and negative symptomatology in patients with schizophrenia. Law's et al. meta-analysis on CBT in schizophrenia also found an imbalance in favor of reporting positive and negative symptoms as outcome [136]. And Jones et al. also complain that "not all trials reported data on all prespecified outcomes, hence, often there are only a handful of small trials contributing data to any given outcome." [37]. It seems therefore that depression is not often investigated as an outcome in clinical trials on psychological interventions for people with schizophrenia.

Heterogeneity

The primary analysis of this work has a moderate heterogeneity [47]. The first reason to be discussed are the various therapies that were included in the main analysis. Looking at the specific therapeutic interventions in detail the heterogeneity for those comparisons drop (Figure 3.5). One possible other reason might be that there is no agreement among studies authors on how to measure which treatment effects. As a result, RCTs define many different primary and secondary outcomes, which are additionally measured with different scales [26, 37, 38]. As mentioned above some scale on depression measure somatic (weight loss, gastro-intestinal or general somatic symptoms [111]) and some only psychological/mood symptoms e.g. the Hospital Anxi-

ety and Depression Scale [112]. We aimed to investigate possible reasons for heterogeneity by conducting subgroup analyses, but this was made difficult by the small number of studies available. A similar conclusion was reached by Eichner et al.[129].

High risk of bias

Many studies with high risk of bias were included in this work. This may lead to a general shift in the results. In the subgroup analysis investigating the role of risk of bias, no significant differences were found, but due to the small number of studies in the individual comparisons, no strong conclusions were possible. The methodologically poor quality of many RCTs was also noted by authors in other meta-analyses [32].

Real therapy effect

The strength of this work to include all psychological interventions is also a relevant limitation. The analyzed RCTs focus on psychological interventions with different therapeutic target outcomes. Thus, a psychological intervention does not generally aim to improve all of a patient's symptoms. Rather, depending on the focus of the therapy, it has different effects, e.g., more on negative or positive symptoms as primary target [125]. In this paper, however, only the outcome depression is analyzed and whether the actual effect of psychotherapy on depression was thus measured is questionable. More likely this work analyzed an indirect therapy effect on depression: an improved general symptomatology (related to positive and negative symptomatology) may lead to a reduced depressive symptomatology. Moreover, an attempt to analyze the actual effect of different forms of psychological therapy on depressive symptoms is difficult to determine given the small number of studies per comparison. Jones et al. reach a similar conclusion [38]. So one possible interpretation of the results is that an aspecific therapeutic effect improves depressive symptomatology. Additionally, it should be mentioned that it is generally a problem to measure the effect of psychotherapeutic interventions. Many of the scales were developed in relation to pharmacological therapy and that base on concepts of depression, that leave out factors like self-esteem, well-being and more. These are often key topics in psychotherapeutic approaches. Thus, in their analysis, Geretsegger et al. also question how to measure the effect of music therapy in the first place[124]. In addition, there is an overlap between the clinic of negative symptoms of schizophrenia and symptoms of depression. Thus, one can assume that an improvement on a scale for negative symptoms can also lead to an improvement on a depression

scale. Lutgens et al. showed that psychological interventions (especially for CBT, music treatments, exercise, skills-based training) provided a benefit for the improvement of negative symptoms [137] and Jones et al. found a benefit for CBT versus standard care in negative symptoms on the PANSS subscale [37]. These are similar results to those shown in this work and could support the assumption that improvement in negative and depressive symptoms are mutually dependent.

4.3 Conclusion and Implications

As a conclusion from above points, it can be said that psychological interventions have a small relevant positive effect in reducing depressive symptoms in patients with schizophrenia. Among them, CBT, music therapy, AVATAR therapy and group therapy have shown a benefit in comparison to control conditions. Whereby it must be considered that only the comparison about CBT included a relevant number of studies ($n = 27$), while the other interventions were investigated in only a number of studies too small to draw strong conclusions. It should be said in general that there are few studies investigating psychological interventions for depression in patients with schizophrenia, even though it is very important. Notably the included studies employed 14 different scales for measuring depression, which causes heterogeneity and poor comparability.

One implication for future research is, that RCTs on psychological interventions for patients with schizophrenia should include depression as outcome in their analysis so that the evidence of data is stronger. In addition, future studies should be conducted with a sound methodology, especially with regard to researcher allegiance. Furthermore, when planning an RCT, attention should be paid to defined therapeutic objectives. It is important that in addition to the positive and negative symptoms, other life domains of the patient should be treated, such as depression, distress, functioning, quality of life, among others. Moreover, a scientific discussion should be conducted with regard to the scales for measuring therapy effects. So that in the future a better comparability of studies in meta-analyses is realizable. A similar suggestion is formulated by Turner et al. and Jones et al. [37, 38, 125]. It would also be interesting for further meta-analyses on this topic to investigate to what extent an improvement of schizophrenic symptoms leads to an improvement of other symptoms. An analysis of whether this is a relevant moderator is desirable.

Chapter 5

Summary

Schizophrenia is a serious illness, which has far-reaching consequences for the patients, their relatives and society. It is most frequently diagnosed in young adulthood [5, 7]. A multifactorial genesis is assumed [7, 8]. An imbalance of the neurotransmitter systems [9] leads to the typical positive and negative symptoms [7]. However, affected persons do often additionally suffer from somatic and psychiatric comorbidities [7]. Comorbid depression very often presents with severe negative effects that lead to a increased risk of death [10, 13, 14]. In addition the socioeconomic impact is high due to direct costs, e.g. for hospitalizations, and indirect costs, e.g. loss of productivity of patients and care givers [15, 17–20]. Therapeutically, the group of antipsychotics continue to be the first choice therapy for schizophrenia. In order to strengthen the affected person and his integration into society accompanying psychotherapy is gaining more and more importance and is recommended by German and British professional societies [7, 21]. For depression in schizophrenia it is recommended to adjust antipsychotic medication, to use antidepressants and to add psychotherapy. Whereas the effect of additive psychotherapy in patients suffering from schizophrenia on general symptoms is studied in various works [1, 24–26, 28, 32], the effect on depression is poorly studied. In this current work, we investigate whether additional psychological interventions have an effect on depressive symptoms in patients suffering from schizophrenia. All psychological interventions were compared against a control condition and additionally the interventions were grouped according to their main therapeutic method against control conditions. Included were randomized-controlled trials that measured depressive symptoms as a primary or secondary outcome and had at least one treatment arm with a psychological intervention. Study participants were adults and had a diagnosis of schizophrenia or schizophrenia-related disorder, as defined in various diagnostic manuals. Patients with comorbidities, first episode of

psychosis, or prodromal phase were excluded. As psychological interventions, all interactions between therapist and patient were included and grouped according to the main intervention method. The outcome depression had to be measured with a peer reviewed scale. Methodological quality was also assessed. To compare the effect between different scales we calculated the standardized mean differences. Negative values showed an advantage for the intervention group. The results were presented graphically with a forest plot. The degree of heterogeneity was determined by calculating I^2 . According to the Cochrane Collaboration [47], substantial heterogeneity can be assumed from a degree of 50% I^2 . To identify possible moderators of the effect estimates, different subgroups were defined in advance. These were examined in subgroup analyses when comparisons were made with more than ten studies. For meta-regression possible moderators were pre-specified and analysed. For this study, 192 RCTs met the inclusion criteria after full text analysis, of which 40 studies with a total of 3039 study participants reported data on depression and could be analyzed. 12 different psychological interventions were investigated in pairwise comparisons. There are 14 different scales used by the included RCTs for assessing depression. The methodological quality of the studies was poor. After applying the rule by Furukawa et al [50] 6 studies had a low overall risk of bias, 21 a moderate overall risk of bias and 13 had a high overall risk of bias.

All psychological interventions compared to any control condition showed a relevant advantage in improving depressive symptoms (effect size = 0,16). Subgroup tests for all of the predefined subgroup comparisons were not significant. Only the number of therapy sessions could be analyzed as a relevant moderator for the comparison of all additional psychological interventions against all control condition.

The comparison of additional CBT against all control conditions showed a clear advantage for CBT (effect size = 0.14). Subgroup tests for all of the predefined subgroup comparisons were not significant. In the meta-regression, the number of therapy sessions was also shown to be a relevant moderator. Further comparisons of therapy groups showed no relevant benefit for Third Wave therapies (n=7), a relevant benefit for Creative Therapies (n=2), and no clear benefit for the intervention group for the group of Various Therapies (n = 6).

For publication bias the Egger's Test confirmed the presence of funnel plot asymmetry for the comparison CBT versus a control condition, but not for all psychological interventions versus any control conditions. In summary, it can be concluded that psychological interventions in addition to medication against control conditions are superior in their positive effect on depression in patients with schizophrenia. However, the effect size is small. In further

comparisons of therapy groups against control conditions, only CBT shows a relevant advantage. Most of the psychological interventions analyzed were CBT ($n = 27$). It is noticeable that there was a large group of therapy forms that could not be categorized. It emerges a very heterogeneous picture of interventions. In sum there were 14 different scales used by the included RCTs for assessing depression in schizophrenic patients. Because of different included items irrespective different targets of assessing this leads to further heterogeneity and uncertainty about the true effect of the investigated interventions. In addition most of the used scales were invented for assessing mood disorders and are therefore not suitable for measuring depression in schizophrenia. The overall poor methodological quality of the studies was conspicuous. High risk of bias can lead to a shift in results, and thus the exclusion of studies with high risk of bias in Researcher Allegiance also showed a decreasing to disappearing effect of the tested interventions.

One strength of this work is, that it was planned and conducted following the PRISMA guidelines [60] and the rules applied by the Cochrane Collaboration. Additionally it is a very comprehensive review, since all psychological interventions were systematically considered for inclusion. Complicating a thorough analysis was the small number of studies, due in part to the fact that few of the included studies measured or reported depression as an outcome. In many comparisons, this resulted in very low statistical power to the extent that no further analysis of the comparisons was possible. The reason for this could be that the focus of the effect is on positive and negative symptoms. This work shows a moderate heterogeneity, which could be caused by a non-agreement of study authors on what and how to measure outcome effects of psychological interventions. This disagreement leads to many different outcomes defined and measured with different scales. Another limitation is the overall poor methodological quality of the studies which can cause a general shift in the results.

As a conclusion from above points, it can be said that psychological interventions have a small relevant positive effect in reducing depressive symptoms in patients with schizophrenia. But analyzing this effect and possible moderators further was obstructed by low number of studies, heterogeneity and poor methodological quality of studies. So further research in this field is needed. This implicates to include depression as outcome, to take care of high methodological quality, to pay attention to defined therapeutic objectives and to lead scientific discussion with regard to the scales measuring therapy effects.

Chapter 6

Note of Thanks

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Chapter 7

Appendix

7.1 Detailed description of interventions of each study

The description of intervention refer to passages in the respective studies. Sources to each study are given in the captions.

Study	Name of intervention	Description intervention	Main intervention strategy	Other intervention strategies	Grouped to
ACTRN12616000976482 [ACTRN.]	Metacognitive Training	- Metacognitive therapy (MCT+) is a novel psychotherapeutic approach that builds on the concepts and goals of cognitive-behavioural therapy for psychosis. 8 modules covering six cognitive biases common in psychosis (...) and an introductory and relapse prevention module.	MCT	CBT	MCT 3rd Wave CBT
	Cognitive remediation	- active control group - covering four cognitive domains	Cognitive Remediation		Cognitive Remediation Active Control
Andreou 2017 [68]	Metacognitive Training	- MCTp is a manualized intervention that comprises 12 twice-weekly individual therapy sessions - goal is to highlight the fallibility of cognition in general and encourage patients to reflect on their own thinking styles in relation to symptoms, but also to everyday life - Most sessions included homework tasks according to the principles of CBT.	MCT	CBT	MCT
	Computerized cognitive remediation	- active control group - computerized cognitive training program that targets cognitive dysfunctions commonly encountered in patients with psychosis	Cognitive Remediation		Cognitive Remediation Active Control
Barrowclough 2006 [69]	Cognitive behavioural therapy	- group intervention ran for 6 months, with 18 sessions - session 1, introduction to the CBT approach to psychosis; session 2, what is CBT? Session 3, identification of patient problems (delusional beliefs and voices were the main focus); session 4, formulating problems in terms of thoughts, feelings and behaviours; session 5, negative thinking patterns and thought monitoring; sessions 6, 7 and 8, thought challenging; sessions 9, 10 and 11, behavioural strategies: experiments and action plans; sessions 12 and 13, stress, arousal and medication; sessions 14 and 15, staying-well plans; session 16, emergency staying-well plans; sessions 17 and 18, follow-up and revision.	CBT		CBT
	Treatment as usual	Standard psychiatric care in the UK (...)	TAU		TAU
Birchwood 2014 [70]	Cognitive therapy for command hallucinations	- cognitive behaviour therapy techniques are used to assess and modify conviction in four beliefs linked to the construct of voice power (...): (..)it adheres to a staged process informed by our cognitive model	CBT	Cognitive Therapy	CBT

Figure 7.1: [ACTRN., 68–70]

7.1. DETAILED DESCRIPTION OF INTERVENTIONS OF EACH STUDY⁹⁷

Study	Name of intervention	Description intervention	Main intervention strategy	Other intervention strategies	Grouped to
	Treatment as usual	Treatment as usual was provided by community mental health and assertive outreach and early intervention teams.	TAU		TAU
Briki 2014 [71]	Metacognitive Training	The MCT programme included 8 modules (cycle A) and a single cognitive bias was explored in a module. A second 8-module cycle (cycle B) was then administered, reviewing the same biases but using different examples and exercises	MCT		MCT 3rd Wave CBT
	Supportive Therapy	- an active intervention, aimed to help participants share experiences with each other, and to promote verbal interaction. - lements of psycho-education were given, especially during sessions focusing on pathology and treatment	Supportive Therapy	Psychoeducation	Supportive Therapy Active Control
Chadwick 2016 [72]	Group Person-Based Cognitive Therapy (PBCT)	- integrates cognitive therapy and mindfulness to target distinct sources of distress in psychosis - All sessions began with mindfulness practice and discussion - Sessions 1–3 socratically drew out participants' voice hearing experiences (...) and framed them using the ABC cognitive model. - Sessions 4–6 explored personal control, socratically weakening voice omnipotence and enhancing autonomy. - Sessions 7–12 added focus on identifying and decentring from negative schemata, and building positive schematic beliefs (...) - Participants were encouraged to practice mindfulness daily at home	Mindfulness	Cognitive therapy	Mindfulness 3rd Wave CBT
	TAU	2–3 monthly outpatient appointments with their psychiatrist, antipsychotic medication, and contact with care team members every two weeks	TAU		TAU
Craig 2018 [73]	AVATAR therapy	- computerised representation of the entity that they believed was the source of their main voice. - each session involved face-to-face work with the avatar, wherein the therapist facilitated a direct dialogue between the participant and the avatar - The therapist sat in a second room with a control panel that allowed them to speak in his or her own voice, or as the avata			AVATAR therapy Various Therapies
	Supportive counselling	more than a simple attention or time control and augmented the manual to deliver an emotion-focused psychological intervention that facilitated exploration of issues of fundamental importance in the person's life, in the context of an	Supportive counselling		Supportive counselling Inactive Control

Figure 7.2: [71–73]

Study	Name of intervention	Description intervention	Main intervention strategy	Other intervention strategies	Grouped to
		empathic, non-directive therapeutic relationship			
Farhall 2009 [74]	Cognitive behavioural therapy	• CBTp intervention included psychoeducation, positive symptom, and co-morbid problem components • Therapy proceeded on the basis of individual formulation, collaborative goals and utilization of opportunities to address change issues as they arose, thus cases varied greatly in the number and mix of therapy components addressed.	CBT	Psychoeducation	CBT
	TAU				TAU
Freeman 2014 [75]	Cognitive behavioural therapy	• There was an explicit agenda made with the patient to focus upon three areas: 1. negative thoughts about the self, 2. positive activities, and 3. positive thoughts about the self. • Tasks were set between sessions and there were supportive telephone calls or texts, and a graduate psychologist could visit to help with carrying out of an activity.	CBT		CBT
	Standard care	• Standard care was delivered according to national and local service protocols and guidelines.	TAU		TAU
Garety 2008a [76]	Cognitive-behavioural therapy	• The therapy was an adaptation of our generic CBT for psychosis manual 18 specifically aimed to target key aspects of relapse prevention highlighted by our cognitive model. • A central focus of the work was developing a shared formulation of relapse. • Therapists then attempted to target the key problems associated with vulnerability to relapse • The last stage involved developing a set of self-regulatory strategies to manage relapse.	CBT		CBT
	Family intervention	• Family intervention followed the manual of Kuipers et al. with an emphasis on improving communication, offering discussion of up-to-date information about psychosis, problem-solving, reducing criticism and conflict, improving activity, and the emotional processing of grief, loss and anger. • There was a particular focus on relapse prevention	Family intervention		Family intervention Active Control
	TAU		TAU		TAU
Garety 2008b [76]	Cognitive-behavioural therapy	• The therapy was an adaptation of our generic CBT for psychosis manual 18 specifically aimed to target key aspects of relapse prevention highlighted by our	CBT		CBT

Figure 7.3: [74–76]

7.1. DETAILED DESCRIPTION OF INTERVENTIONS OF EACH STUDY99

Study	Name of intervention	Description intervention	Main intervention strategy	Other intervention strategies	Grouped to
		cognitive model. • A central focus of the work was developing a shared formulation of relapse. • Therapists then attempted to target the key problems associated with vulnerability to relapse • The last stage involved developing a set of self-regulatory strategies to manage relapse.			
	TAU		TAU		TAU
Gottlieb 2017 [77]	Coping With Voices program	• CWV takes a skills-based approach that incorporates many of the traditional elements of CBT and CBTp • overarching goal of the CWP program is to teach users CBT-based skills in order to reduce the distress, preoccupation, and day-to-day interference of voices, and to improve overall quality of life •	CBT		CBT
	Usual care	•	TAU		TAU
Granholtm 2005 [78]	Cognitive behavioural social skills training	• The components of social skills training were based on social skills training interventions available from Psychiatric Rehabilitation Consultants • he components of cognitive behavior therapy were developed specifically for patients with schizophrenia • Cognitive behavioural social skills training, therefore, targeted the multidimensional deficits that lead to disability in aging patients with schizophrenia. • patients used thought records and homework assignments to identify relationships among thoughts, feelings, and behaviors, and they identified mistakes in thinking • to improve communication skills and social interactions • problem-solving skills were taught	CBT	Social Skills Training	CBT
	TAU		TAU		TAU
Granholtm 2013 [79]	Cognitive behavioural social skills training	• CBSST integrates CBT and SST techniques to target the different factors that contribute to poor functioning • CBSST integrates CBT and SST techniques to target the different factors that contribute to poor functioning • cognitive therapy components were focused on the practice of simplified thought challenging skills and behavioural experiment activities • The primary goal of Social Skills	CBT	Social Skills Training Problem Solving Skills	CBT

Figure 7.4: [77–79]

Study	Name of intervention	Description intervention	Main intervention strategy	Other intervention strategies	Grouped to
		Training module was to improve communication skills through behavioural role plays Basic problem-solving skills were trained in the Problem-Solving Module using the acronym, SCALE – Specify the problem, Consider all possible solutions, Assess the best solution, Lay out a plan, and Execute and Evaluate the outcome			
	Goal-Focused Supportive Contact	- The GFSC intervention was enhanced supportive contact that included a primary focus, like CBSST, on setting and achieving functioning goals - Sessions typically included components of psychoeducation, empathy, and non-directive reinforcement of health, coping, and symptom management behaviors, that grew out of group discussions, with minimal therapist guidance	Supportive Counselling	Psychoeducation	Supportive Counselling Inactive Control
Granholtm 2014 [80]	Cognitive behavioural social skills training	- The three CBSST modules were the Cognitive Skills Module, Social Skills Module, and Problem-Solving Skills Module - Training thought-challenging skills was the exclusive focus of the Cognitive Skills Module, but thought challenging was also used throughout the other two modules - cognitive therapy components focused on the practice of simplified thought-challenging skills and behavioural experiment activities - primary goal of the Social Skills Module was to improve communication skills - problem-solving skills were trained in the Problem-Solving Skills Module using the acronym, SCALE: Specify the problem, Consider all possible solutions, Assess the best solution, Lay out a plan, and Execute and Evaluate the outcome	CBT	Social Skills Training Problem Solving Skills	CBT
	Goal-Focused Supportive Contact	- enhanced supportive contact control condition with a primary focus, like CBSST, on setting and achieving functioning goals - Sessions typically included components of psychoeducation, empathy, and nondirective reinforcement of health, coping, and symptom management behaviors, which grew out of group discussions, with minimal therapist guidance.	Supportive counselling	Psychoeducation	Supportive Counselling Inactive Control
Hazell 2016 [81]	Cognitive behavior therapy for distressing	- is based on and guided by the self-help book Overcoming Distressing Voices - The therapists and participants will have the same therapy materials (book and	CBT		CBT

Figure 7.5: [80, 81]

7.1. DETAILED DESCRIPTION OF INTERVENTIONS OF EACH STUDY 101

Study	Name of intervention	Description intervention	Main intervention strategy	Other intervention strategies	Grouped to
	voices	workbook) - current coping strategies will be evaluated, and new ones considered - address self-esteem - target unhelpful beliefs - work on a difficult relationship - plan for taking learning from the self-help course forward into the future.			
	Wait list control	- Participants allocated to delayed therapy will join a waiting list for the intervention. - Throughout the trial (including the waiting period), participants will continue with their usual mental health care.	Waitlist	TAU	Waitlist Control Inactive Control
Jenner 2004 [82]	Hallucination Focused Integrative Treatment	- The approach is a directive style of single-family therapy that integrates motivational interventions, training in coping skills, CBT, and operant conditioning with medication, psychoeducation, and rehabilitation (Jenner 2001, 2002; Jenner and van de Willige 2001). - Motivational interviewing (Miller and Rollnick 1991) helps accommodate interventions to the patient's degree of illness awareness - Coping training teaches patients and relatives how to manage their anxiety, distract their attention from voices, and selectively focusing on voices. - Psychoeducation focuses on symptoms and problem solving. In family treatment, social support is pivotal; ideas about voices are simultaneously shared and challenged	Family Intervention	Motivational Interview CBT Psychoeducation Skills training	Family intervention
	Routine Care	Multidisciplinary teams in these centers provide psychiatric, social, and financial management; psychoeducation; supportive and job counseling; home visits; and around-the-clock ambulatory crisis intervention.	TAU		TAU
Kim 2010 [83]	Eye movement desensitization and reprocessing (EMDR)	- An eight-phase standard protocol of EMDR was delivered - targets included stressful life events which may have contributed to the patient's current admission, traumatic incidents from childhood or adulthood, treatment-related adverse events(e.g., involuntary admission or seclusion), or the experience of distressing psychotic symptoms(i.e., delusions or hallucinations)	EMDR		EMDR Other Therapies
	Progressive	attention placebo control, progressive	PMR		Active

Figure 7.6: [82, 83]

Study	Name of intervention	Description intervention	Main intervention strategy	Other intervention strategies	Grouped to
	muscle relaxation (PMR)	muscle relaxation - involves tensing and relaxing 16 different muscle groups - first session consisted of explaining the model of stress and anxiety(20minutes), teaching the rationale and the procedure muscle relaxation training (40minutes), and then performing a round of APRT with the patient (20 minutes)			Control PMR
	TAU	no experimental treatments but received a routine treatment at the ward, both of which the EMDR and PMR groups also received	TAU		TAU
Klingberg 2011 [84]	Cognitive behavioural Therapy	- CBT applies general principles of cognitive behavior therapy (eg, case formulation based on a cognitive model, goal setting, discussion of cognitive processes, homework assignments, role-play) for the treatment of negative symptoms. - CBT aims at developing a shared formulation and a shared concept of treatment.	CBT		CBT
	Cognitive remediation	- It applies the principles of restitution as well as compensation. - The program follows the principles of errorless learning, overlearning, and immediate positive feedback (verbal), which are combined with alternative cognitive strategies such as systematic elaboration of information, verbalization, self-instruction, and structuring of information.	Cognitive Remediation		Cognitive Remediation Active Control
Kowalski 2017 [85]	Jumping to conclusion group - MCT	The JTC subgroup attended a module of metacognitive training – “Jumping to Conclusions” version	MCT		MCT 3rd Wave CBT
	Theory of mind group - MCT	The ToM subgroup attended a module of metacognitive training – “To empathize” version A	MCT		MCT 3rd Wave CBT
	Control	Patients allocated to the control condition participated in an approximately one hour long discussion about current events.	Control		Control
Kuipers 2004 [86]	Croydon Outreach and Assertive Support Team (COAST)	- COAST offered a range of interventions, including optimum atypical medication, psychological interventions (individual cognitive behavioural therapy and family intervention if appropriate) and a range of vocational and welfare help according to need covering four cognitive domains - All participants were offered medication review and monitoring, vocational and benefits help, information about psychosis, individual therapy for residual	CBT	Family intervention	CBT

Figure 7.7: [84–86]

7.1. DETAILED DESCRIPTION OF INTERVENTIONS OF EACH STUDY 103

Study	Name of intervention	Description intervention	Main intervention strategy	Other intervention strategies	Grouped to
		positive symptoms of psychosis (CBT) (based on Fowler et al. 1995), family meetings and intervention if appropriate			
	TAU	People offered TAU remained with their referring team, and were offered all the usual services available to a local multidisciplinary team; medication, monitoring and access to services, but no specialised psychological interventions, nor information geared towards early intervention issues	TAU		TAU
Lee 2012 [87]	Cognitive behavioural therapy and social skills training	- active control group - covering four cognitive domains	CBT	Social Skills Training	CBT
	TAU		TAU		TAU
Lincoln 2012 [88]	Cognitive behavioural Therapy for Psychosis	- CBTp was delivered according to a German language manual (Lincoln, 2006) that is based on manuals by the pioneers of CBTp (Chadwick, Birchwood, & Trower, 1996; Fowler et al., 1995; Kingdon & Turkington, 1994) and on well-established cognitive and behavioural interventions for comorbid depression and anxiety. - Metacognitive (e.g., challenging beliefs about the omniscience or omnipotence of voices), cognitive (e.g., challenging thoughts about the self or others), and behavioural techniques (e.g., coping strategy enhancement) were used to change the triggering and maintaining factors and increase perceived control - Relevant factors were tackled with problem solving, social skill training, exposure, Socratic questioning, and behavioural experiments	CBT	MCT Social Skills Training Problem Solving	CBT
	Wait list intervention	- The wait list group received standard psychiatric care - Thereafter, the wait list patients received the CBT intervention.	Waitlist Control		Waitlist Control Inactive Control
Lu 2013 [89]	Music intervention group	The MIG attended 60 min of group music therapy twice a week for 5 weeks. The music therapy comprised of 10 sessions of active and passive music interventions including music listening, singing popular Taiwanese songs, playing percussion instruments, watching music videos, and discussions	Music Therapy		Music Therapy Creative Therapy
	Usual care group	Usual care in the nursing home included 24-h care with activities of daily living, basic nursing care, meal provision, and social activities (e.g., TV watching, family visiting, and occasional parties for	TAU		TAU

Figure 7.8: [87–89]

Study	Name of intervention	Description intervention	Main intervention strategy	Other intervention strategies	Grouped to
		special events)			
Montag 2014 [90]	Psychodynamic Group Art Therapy	- The approach was non-directive – patients could choose to create whatever they wanted and use any available material they liked. - Interventions by the art therapist aimed at supporting the art process and helping to understand the image. - The patient's autonomous decision-making about the handling of his or her art work was crucial	Art Therapy		Art Therapy Creative Therapy
	TAU	In addition to supportive contact and pharmacotherapy, TAU covered a broad spectrum of verbal targeted psychotherapies for patients with psychoses like cognitive-behavioural therapy and modified psychodynamic interventions in individual and group settings, as well as occupational therapy, music therapy, cognitive and social skills training, excursions, relaxation and sports.	TAU		TAU
Morrison 2014 [91]	Cognitive therapy	- the therapy group received cognitive therapy on the basis of a specific cognitive model - Cognitive therapy requires an individualised, problem-oriented approach and incorporates a manualised process of assessment and formulation. The central features of our approach to treatment of psychosis involve normalisation and evaluation of the appraisals that people make, helping them to test such appraisals with use of behavioural experiments, and helping them to identify and modify unhelpful cognitive and behavioural responses	CBT		CBT
	TAU	TAU	TAU		TAU
Ochoa 2017 [92]	Metacognitive Training	The MCT program included eight modules: Attributional style (1), Jumping to conclusions (2, 7), Changing beliefs (3), Empathy (4, 6), Memory (5), and Depression and self-esteem (8), worked through with PowerPoint presentations with different examples and material on all these topics.	MCT		MCT 3rd Wave CBT
	Psychoeducation	In the psycho-educational group the modules were: Healthy habits (1); Risk Behaviors (2), Prevention of relapse (3), Video forum (4, 5), Resources of work (6), Leisure activities (7), and Resources available in the community (8). Material for each weekly module was previously agreed upon by all participating centers to unify interventions.	Psychoeducation		Psychoeducation Active Control

Figure 7.9: [90–92]

7.1. DETAILED DESCRIPTION OF INTERVENTIONS OF EACH STUDY 105

Study	Name of intervention	Description intervention	Main intervention strategy	Other intervention strategies	Grouped to
Penades 2006 [93]	Cognitive behavioural therapy	• CBT is a structured and time-limited approach to the management of problems faced by people with psychosis. • It has three main goals: to reduce the distress and disability associated with residual psychotic symptomatology; to reduce emotional disturbance; and to promote the active participation of the individual in the regulation of the risk of relapse and social disability.	CBT		CBT
	Cognitive Remediation Therapy	◦ The main instructional technique was scaffolding. • The “Cognitive Shift Module” aims to address flexibility in thinking and information-set maintenance both of which presumably require the capacity to effectively engage and disengage activated neural network processing. • The “Work-ing Memory Module” aims to target the executive processes central to memory control, and has patients work with as many as two to five information sets at a time. • The primary target of the “Planning Module” is self-ordered, goal-oriented, set/schema formation and manipulation, that is, the application of the practiced processes, such as Working Memory, to tasks requiring planning.	Cognitive Remediation		Cognitive Remediation Active Control
Penn 2009 [94]	Cognitive-behavioural therapy	• The sessions covered the following themes: Session #1) introduction to treatment, Sessions #2–3) psychoeducation, Sessions #4–5) content of auditory hallucinations (...), Sessions #6–7) behavioural analysis of auditory hallucinations, Sessions #8–9) increasing and decreasing strategies for auditory hallucinations (...), Sessions #10–12) coping strategies for auditory hallucination • CBT techniques, such as self-monitoring and coping strategies, were at the heart of the intervention	CBT		CBT
	Supportive therapy	• Enhanced ST is a 12-week manual-based intervention which comprises emotional support and counseling of non-symptom related problems, such as improving social relations with others • Thus, unlike CBT, the group leaders provided direct advice for client questions/problems, and solicited advice and suggestions from group members.	Supportive Therapy		Supportive Therapy Active Control
Pinninti 2010 [95]	Cognitive-behavioural Therapy	• The cognitive-behavioural therapy approach was not manualized, but it stressed engaging the patients in	CBT		CBT

Figure 7.10: [93–95]

Study	Name of intervention	Description intervention	Main intervention strategy	Other intervention strategies	Grouped to
		treatment; developing a cognitive formulation of the symptoms; and utilizing a normalizing rationale to reduce stigma associated with psychosis, with specific cognitive techniques to reduce distress and dysfunction associated with positive psychotic symptoms and relapse prevention techniques.			
	Control	to receive only second-generation antipsychotics	TAU		TAU Inactive Control
Pot-Kolder 2016 [96]	Virtual-reality-based cognitive behavioural therapy	- An individualised case formulation guided exposure to idiosyncratic social environmental cues that elicited fear, paranoid thoughts, and safety behaviours. Patients and therapists communicated during virtual-reality sessions to explore and challenge suspicious thoughts during social situations, drop safety behaviours during social situations - The VR-CBT manual described a structured treatment plan for all 16 sessions.	CBT		CBT
	Waiting list control	Patients in the waiting list control group received treatment as usual	Waitlist Control	TAU	Waitlist Control Inactive Control
Rathod 2013 [97]	Culturally adapted CBT for psychosis	The intervention group was offered 16 sessions of CaCBTp over a period of 16 to 20 weeks by trained CaCBTp therapists	CBT		CBT
	TAU	TAU can vary within NHS organisations in the UK. It involves pharmacotherapy, regular monitoring by a multi-disciplinary team including outpatient clinic appointments with a psychiatrist, reviews by a care co-ordinator and input from other professionals like support workers for social activities, occupational therapist or attendance at day centre for meaningful activities	TAU		TAU
Rector 2003 [98]	Cognitive – behavioural therapy	CBT approach in this study was guided by the principles and strategies developed by Beck et al. (1979, 1985) in the treatment of the emotional disorders and tailored to treat the specific symptoms of schizophrenia within a diathesis-stress framework	CBT		CBT
	Enriched treatment-as-usual	- comprehensive psychiatric management with medication optimization and clinical case management - The stated goals of ETAU were to optimize medication effectiveness and adherence; improve patient	TAU		TAU

Figure 7.11: [96–98]

7.1. DETAILED DESCRIPTION OF INTERVENTIONS OF EACH STUDY 107

Study	Name of intervention	Description intervention	Main intervention strategy	Other intervention strategies	Grouped to
		empowerment and choice; and increase social and occupational functioning			
Schnackenberg 2017 [99]	Experience Focused Counselling (EFC)	- EFC denotes a mutual process of making sense of the voice-hearing experience within the person's life context (Corstens & Longden, 2013), and of supporting the VH in learning to better deal with the experience as part of a recovery process - They were asked to engage in the sequential use of EFC tools such as the Maastricht Interview, Report and Construct, alongside the development of HVM-suggested coping strategies, including voice dialogue	Experience Focused Counselling (EFC)		Experience Focused Counselling (EFC) Other Therapies
	TAU	TAU generally comprised of antipsychotic medication, general rehabilitative life skills support and techniques for the distraction from voices or challenging beliefs, thus representing a classic mainstream biological model psychiatric approach.	TAU		TAU
Schrang 2016 [100]	Positive psychotherapy group intervention	In brief, it targets four areas of development: increasing positive experiences; amplifying strengths; fostering positive relationships; and creating a more meaningful self-narrative.	Group Therapy	Positive Therapy	Group Therapy Other Therapies
	TAU	Care is provided by multidisciplinary mental health teams, and treatments may include medication, social or psychological interventions.	TAU		TAU
Sensky 2000 [101]	Cognitive-behavioural therapy	- a collaborative understanding of the development of symptoms and work toward reducing distress and disability - Thereafter, specific techniques were used with positive psychotic symptoms	CBT		CBT
	Befriending	- This intervention was designed to provide patients with approximately the same amount of therapist contact as the CBT group, with sessions spaced at similar intervals. - The therapists aimed to be empathic and nondirective. Psychotic or affective symptoms were not directly tackled in any way. - The sessions focused on neutral topics, such as hobbies, sports, and current affairs.	Befriending		Befriending Active Control
Tarrier 2014 [102]	Cognitive behavioural prevention of suicide in psychosis	- CBSPp was based upon a treatment manual (Tarrier et al., 2008; Tarrier et al., 2013) and was derived from an explanatory model of suicide behaviour - In addition, the sessions focussed on the processes thought to underlie resilience to suicide.	CBT		CBT

Figure 7.12: [99–102]

Study	Name of intervention	Description intervention	Main intervention strategy	Other intervention strategies	Grouped to
	TAU		TAU		TAU
Trower 2004 [103]	Cognitive therapy for command hallucinations	- Using the methods of collaborative empiricism and Socratic dialogue, the therapist seeks to engage the client to question, challenge and undermine the power beliefs, then to use behavioural tests to help the client gain disconfirming evidence against the beliefs. - build clients' alternative beliefs in their own power and status, and finally, where appropriate, to explore the origins of the schema so clients have an explanation for why they developed those beliefs about the voice in the first place	CBT		CBT
	TAU	This was delivered by community mental health teams.	TAU		TAU
Turkington 2000 [104]	Cognitive behavioural techniques	- active control group - development of a shared explanation was a cornerstone of improved adherence and better coping - Attempts were also made to reduce distressing related affect and positive and negative types of behaviour - Techniques of reality testing of hallucinations were used to establish the uniqueness of the phenomena to the patients themselves as coming from within rather than from outside their own minds. - Not paying attention, distraction and focusing techniques, including rational responding, were taught systematically.	CBT		CBT
	Befriending	Interviews mostly consisted of non-directive discussion around neutral topics, such as the patient's interests and domestic matters.	Befriending		Befriending Active Control
Turkington 2002 [105]	Cognitive behavioural therapy	- All the phases of CBT were included in the brief approach, including assessment and engaging, developing explanations, case formulation, symptom management, adherence, working with core beliefs and relapse prevention. - Booklets covered treatment, self-care and lifestyle, leisure time and relationships, drug and alcohol advice, symptom management and sources of help, and were worked through in a flexible manner according to the patient's and carer's individual needs. Appropriate homework was generated	CBT		CBT
	TAU	The patients and carers randomised to receive treatment as usual were left to the care of their own community mental health teams but were aware that CBT would be offered at the end of the study	Waitlist Control	TAU	Waitlist Control

Figure 7.13: [103–105]

7.1. DETAILED DESCRIPTION OF INTERVENTIONS OF EACH STUDY 109

Study	Name of intervention	Description intervention	Main intervention strategy	Other intervention strategies	Grouped to
		period.			
White 2011 [106]	Acceptance and Commitment Therapy	- Focusing on the following themes: 1) Distinguishing between different types of experience: internal experience vs. 5-sense experience; (2) Recognizing how we get caught up struggling to move away from suffering; (3) Moving towards our values (4) Getting distance between us and our 'life stories', (5) Exploring how trying to control difficult mental experiences can be part of the problem rather than the solution, (6) Noticing that we can notice: focusing on the context in which mental experiences occur rather on the content of these experiences, (7) Exploring worry thoughts associated with psychosis. - ACT has a strong mindfulness component	ACT	Mindfulness	ACT 3rd Wave CBT
	TAU	TAU consisted of psychopharmacology, case management and/or psychotherapy	TAU		TAU

Figure 7.14: [106]

7.2 Search Strategies

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present> Searched 10th January 2018

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1 exp Schizophrenia/ (104582)
  2 exp Psychotic Disorders/ (51539)
  3 schizo$.mp. (166486)
  4 or/1-3 (201032)
  5 exp Psychotherapy/ or exp Behavior Therapy/ or exp Cognitive Therapy/ or exp Complementary Therapies/ or exp Psychoanalysis/ or exp Counseling/ or exp Hypnosis/ or Association/ or Association learning/ (424755)
  6 (abreaction or "acceptance and commitment therapy" or acting out or adlerian or analytical psychotherap$ or anger control or anger management or animal therap$ or art therap$ or assertive$ training or attention training technique or autogenic training or autosuggestion or aversion therap$ or balint group or befriending or behavior?r contracting or behavior?r modification or behavior?r regulation or behavior?r therap$ or bibliotherap$ or biofeedback or body psychotherap$ or brief psychotherap$ or caregiver support or cbt or client cent$ or cognitive behavior?r$ or cognitive intervention$ or cognitive rehabilit$ or cognitive remediation or cognitive technique$ or cognitive therap$ or cognitive treatment$ or colo?r therap$ or compassionate mind training or conjoint therap$ or contingency management or conversational therap$ or conversion therap$ or coping skills or counsel?ing or countertransference or couples therap$ or covert sensitization or crisis intervention or dance therap$ or dialectic$ or eclectic or emotion$ focus$ or emotional freedom technique or encounter group therap$ or existential therap$ or experiential psychotherap$ or exposure therap$ or expressive psychotherap$ or eye movement desensiti?ation or family intervention$ or family therap$ or feminist therap$ or free association or freudian or geriatric psychotherap$ or gestalt therap$ or griefwork or group intervention$ or group psychotherap$ or group therap$ or guided image$ or holistic psychotherap$ or humanistic psychotherap$ or hypnosis or hypnotherap$ or hypnoti?zability or imagery or implosive therap$ or individual psychotherap$ or insight therap$ or integrated psychological therapy or integrative psychotherap$ or integrative therap$ or interpersonal or jungian or kleinian or logotherap$ or marathon group therap$ or marital therap$ or meditation or mental healing or metacognitive therap$ or metacognitive training or milieu therap$ or mindfulness or morita therap$ or multimodal or music therap$ or narrative therap$ or nondirective therap$ or object relations or person cent$ therap$ or personal

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construct therap\$ or persuasion therap\$ or pet therap\$ or play therap\$ or primal therap\$ or problem solving or psychoanaly\$ or psychodrama or psychodynamic or psychoeducat\$ or psychologic\$ or psychological therap\$ or psychosocial treatment or psychotherap\$ or psychotherapeutic counsel\$ or psychotherapeutic processes or psychotherapeutic training or psychotherapeutic treatment\$ or rational emotive or reality therap\$ or reciprocal inhibition or rehabilitat\$ or relationship therap\$ or relaxation or reminiscence therap\$ or rogerian or role play\$ or self analys\$ or self esteem or sensitivity training or sex therap\$ or sleep phase chronotherap\$ or social skills education or social skills training or socioenvironmental therap\$ or sociotherap\$ or solution focused or stress management or support group\$ or supportive therap\$ or systematic desensiti?ation or systemic therap\$ or therapeutic communit\$ or transactional analysis or transference or transtheoretical or validation therap\$ or (dream\$ adj3 analys\$) or (support adj3 psycho\$)).mp. (1197308)

- 7 or/5-6 (1380129)
- 8 exp clinical trial/ (888265)
- 9 exp randomized controlled trials/ (130594)
- 10 exp double-blind method/ (162383)
- 11 exp single-blind method/ (27740)
- 12 exp cross-over studies/ (46911)
- 13 randomized controlled trial.pt. (515252)
- 14 clinical trial.pt. (561480)
- 15 controlled clinical trial.pt. (101720)
- 16 (clinic\$ adj2 trial).mp. (737165)
- 17 (random\$ adj5 control\$ adj5 trial\$).mp. (706490)
- 18 (crossover or cross-over).mp. (92834)
- 19 ((singl\$ or double\$ or trebl\$ or tripl\$) adj (blind\$ or mask\$)).mp. (236226)
- 20 randomi\$.mp. (844744)
- 21 (random\$ adj5 (assign\$ or allocat\$ or assort\$ or reciev\$)).mp. (233688)
- 22 or/8-21 (1388053)
- 23 4 and 7 and 22 (3485)
- 24 limit 23 to ed=20170625-20180110 (112)

Embase <1974 to 2018 Week 02> Searched 10-01-17

- 1 exp schizophrenia/ (168146)
- 2 exp psychosis/ (259209)
- 3 schizo\$.mp. (211911)
- 4 or/1-3 (298021)

5 exp Psychotherapy/ or exp Behavior Therapy/ or exp Cognitive Therapy/ or exp Psychoanalysis/ or exp Counseling/ or exp Hypnosis/ or Association/ (419285)

6 (abreaction or "acceptance and commitment therapy" or acting out or adlerian or analytical psychotherap\$ or anger control or anger management or animal therap\$ or art therap\$ or assertive\$ training or attention training technique or autogenic training or autosuggestion or aversion therap\$ or balint group or befriending or behavior?r contracting or behavior?r modification or behavior?r regulation or behavior?r therap\$ or bibliotherap\$ or biofeedback or body psychotherap\$ or brief psychotherap\$ or caregiver support or cbt or client cent\$ or cognitive behavior?r\$ or cognitive intervention\$ or cognitive rehabilit\$ or cognitive remediation or cognitive technique\$ or cognitive therap\$ or cognitive treatment\$ or colo?r therap\$ or compassionate mind training or conjoint therap\$ or contingency management or conversational therap\$ or conversion therap\$ or coping skills or counsel?ing or countertransference or couples therap\$ or covert sensitization or crisis intervention or dance therap\$ or dialectic\$ or eclectic or emotion\$ focus\$ or emotional freedom technique or encounter group therap\$ or existential therap\$ or experiential psychotherap\$ or exposure therap\$ or expressive psychotherap\$ or eye movement desensiti?ation or family intervention\$ or family therap\$ or feminist therap\$ or free association or freudian or geriatric psychotherap\$ or gestalt therap\$ or griefwork or group intervention\$ or group psychotherap\$ or group therap\$ or guided image\$ or holistic psychotherap\$ or humanistic psychotherap\$ or hypnosis or hypnotherap\$ or hypnoti?zability or imagery or implosive therap\$ or individual psychotherap\$ or insight therap\$ or integrated psychological therapy or integrative psychotherap\$ or integrative therap\$ or interpersonal or jungian or kleinian or logotherap\$ or marathon group therap\$ or marital therap\$ or meditation or mental healing or metacognitive therap\$ or metacognitive training or milieu therap\$ or mindfulness or morita therap\$ or multimodal or music therap\$ or narrative therap\$ or nondirective therap\$ or object relations or person cent\$ therap\$ or personal construct therap\$ or persuasion therap\$ or pet therap\$ or play therap\$ or primal therap\$ or problem solving or psychoanaly\$ or psychodrama or psychodynamic or psychoeducat\$ or psychologic\$ or psychological therap\$ or psychosocial treatment or psychotherap\$ or psychotherapeutic counsel\$ or psychotherapeutic processes or psychotherapeutic training or psychotherapeutic treatment\$ or rational emotive or reality therap\$ or reciprocal inhibition or rehabilitat\$ or relationship therap\$ or relaxation or reminiscence therap\$ or rogerian or role play\$ or self analys\$ or self esteem or sensitivity training or sex therap\$ or sleep phase chronotherap\$ or social skills education or social skills training or socioenvironmental therap\$ or sociotherap\$

or solution focused or stress management or support group\$ or supportive therap\$ or systematic desensiti?ation or systemic therap\$ or therapeutic communit\$ or transactional analysis or transference or transtheoretical or validation therap\$ or (dream\$ adj3 analys\$) or (support adj3 psycho\$)).mp. (1816360)

7 or/5-6 (1846489)

8 (clin\$ adj2 trial).mp. (1407667)

9 ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj (blind\$ or mask\$)).mp. (266326)

10 (random\$ adj5 (assign\$ or allocat\$)).mp. (159013)

11 randomi\$.mp. (1005968)

12 crossover.mp. (85226)

13 exp randomized-controlled-trial/ (481956)

14 exp double-blind-procedure/ (144978)

15 exp crossover-procedure/ (53823)

16 exp single-blind-procedure/ (30078)

17 exp randomization/ (76684)

18 or/8-17 (1980276)

19 4 and 7 and 18 (7787)

20 limit 19 to exclude medline journals (787)

PsycINFO <1806 to January Week 1 2018> Searched 10-01-18

1 exp Schizophrenia/ (83900)

2 exp psychosis/ (107318)

3 schizo\$.mp. (127877)

4 or/1-3 (146915)

5 exp psychotherapy/ or exp Behavior Therapy/ or exp Cognitive Therapy/ or exp PSYCHOANALYSIS/ or exp psychotherapeutic counseling/ or hypnosis/ or free association/ (218371)

6 (abreaction or "acceptance and commitment therapy" or acting out or adlerian or analytical psychotherap\$ or anger control or anger management or animal therap\$ or art therap\$ or assertive\$ training or attention training technique or autogenic training or autosuggestion or aversion therap\$ or balint group or befriending or behavior?r contracting or behavior?r modification or behavior?r regulation or behavior?r therap\$ or bibliotherap\$ or biofeedback or body psychotherap\$ or brief psychotherap\$ or caregiver support or cbt or client cent\$ or cognitive behavior?r\$ or cognitive intervention\$ or cognitive rehabilit\$ or cognitive remediation or cognitive technique\$ or cognitive therap\$ or cognitive treatment\$ or colo?r therap\$ or compassionate mind training or conjoint therap\$ or contingency management or conversational

therap\$ or conversion therap\$ or coping skills or counsel?ing or counter-transference or couples therap\$ or covert sensitization or crisis intervention or dance therap\$ or dialectic\$ or eclectic or emotion\$ focus\$ or emotional freedom technique or encounter group therap\$ or existential therap\$ or experiential psychotherap\$ or exposure therap\$ or expressive psychotherap\$ or eye movement desensiti?ation or family intervention\$ or family therap\$ or feminist therap\$ or free association or freudian or geriatric psychotherap\$ or gestalt therap\$ or griefwork or group intervention\$ or group psychotherap\$ or group therap\$ or guided image\$ or holistic psychotherap\$ or humanistic psychotherap\$ or hypnosis or hypnotherap\$ or hypnoti?ability or imagery or implosive therap\$ or individual psychotherap\$ or insight therap\$ or integrated psychological therapy or integrative psychotherap\$ or integrative therap\$ or interpersonal or jungian or kleinian or logotherap\$ or marathon group therap\$ or marital therap\$ or meditation or mental healing or metacognitive therap\$ or metacognitive training or milieu therap\$ or mindfulness or morita therap\$ or multimodal or music therap\$ or narrative therap\$ or nondirective therap\$ or object relations or person cent\$ therap\$ or personal construct therap\$ or persuasion therap\$ or pet therap\$ or play therap\$ or primal therap\$ or problem solving or psychoanaly\$ or psychodrama or psychodynamic or psychoeducat\$ or psychologic\$ or psychological therap\$ or psychosocial treatment or psychotherap\$ or psychotherapeutic counsel\$ or psychotherapeutic processes or psychotherapeutic training or psychotherapeutic treatment\$ or rational emotive or reality therap\$ or reciprocal inhibition or rehabilitat\$ or relationship therap\$ or relaxation or reminiscence therap\$ or rogerian or role play\$ or self analys\$ or self esteem or sensitivity training or sex therap\$ or sleep phase chronotherap\$ or social skills education or social skills training or socioenvironmental therap\$ or sociotherap\$ or solution focused or stress management or support group\$ or supportive therap\$ or systematic desensiti?ation or systemic therap\$ or therapeutic communit\$ or transactional analysis or transference or transtheoretical or validation therap\$ or (dream\$ adj3 analys\$) or (support adj3 psycho\$)).mp. (1068413)

7 or/5-6 (1068614)

8 ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj (blind\$ or mask\$)).mp. (23874)

9 (random\$ adj5 (assign\$ or allocat\$)).mp. (39290)

10 randomi\$.mp. (72094)

11 crossover.mp. (6680)

12 or/8-11 (114666)

13 4 and 7 and 12 (1873)

Cochrane Library Searched 10th January 2018

- #1 MeSH descriptor: [Schizophrenia] explode all trees [5749]
- #2 MeSH descriptor: [Psychotic Disorders] explode all trees [1902]
- #3 schizo*:ti,ab,kw (Word variations have been searched) [12880]
- #4 #1 or #2 or #3 [13755]
- #5 MeSH descriptor: [Psychotherapy] explode all trees [21548]
- #6 MeSH descriptor: [Behavior Therapy] explode all trees [14721]
- #7 MeSH descriptor: [Cognitive Therapy] explode all trees [7698]
- #8 MeSH descriptor: [Complementary Therapies] explode all trees [18611]
- #9 MeSH descriptor: [Psychoanalysis] explode all trees [16]
- #10 MeSH descriptor: [Counseling] explode all trees [4818]
- #11 MeSH descriptor: [Hypnosis] explode all trees [668]
- #12 MeSH descriptor: [Association] explode all trees [475]
- #13 MeSH descriptor: [Association Learning] explode all trees [345]
- #14 (abreaction or "acceptance and commitment therapy" or acting out or adlerian or analytical psychotherap* or anger control or anger management or animal therap* or art therap* or assertive* training or attention training technique or autogenic training or autosuggestion or aversion therap* or balint group or befriending or behavio?r contracting or behavio?r modification or behavio?r regulation or behavio?r therap* or bibliotherap* or biofeedback or body psychotherap* or brief psychotherap* or caregiver support or cbt or client cent* or cognitive behavio?r* or cognitive intervention* or cognitive rehabilit* or cognitive remediation or cognitive technique* or cognitive therap* or cognitive treatment* or colo?r therap* or compassionate mind training or conjoint therap* or contingency management or conversational therap* or conversion therap* or coping skills or counsel?ing or countertransference or couples therap* or covert sensitization or crisis intervention or dance therap* or dialectic* or eclectic or emotion* focus* or emotional freedom technique or encounter group therap* or existential therap* or experiential psychotherap* or exposure therap* or expressive psychotherap* or eye movement desensiti?ation or family intervention* or family therap* or feminist therap* or free association or freudian or geriatric psychotherap* or gestalt therap* or griefwork or group intervention* or group psychotherap* or group therap* or guided image* or holistic psychotherap* or humanistic psychotherap* or hypnosis or hypnotherap* or hypnoti?zability or imagery or implosive therap* or individual psychotherap* or insight therap* or integrated psychological therapy or integrative psychotherap* or integrative therap* or interpersonal or jungian or kleinian or logotherap* or marathon group therap* or marital therap* or meditation or mental healing or metacognitive therap* or metacognitive training or milieu therap* or mindfulness

or morita therap* or multimodal or music therap* or narrative therap* or nondirective therap* or object relations or person cent* therap* or personal construct therap* or persuasion therap* or pet therap* or play therap* or primal therap* or problem solving or psychoanaly* or psychodrama or psychodynamic or psychoeducat* or psychologic* or psychological therap* or psychosocial treatment or psychotherap* or psychotherapeutic counsel* or psychotherapeutic processes or psychotherapeutic training or psychotherapeutic treatment* or rational emotive or reality therap* or reciprocal inhibition or rehabilitat* or relationship therap* or relaxation or reminiscence therap* or rogerian or role play* or self analys* or self esteem or sensitivity training or sex therap* or sleep phase chronotherap* or social skills education or social skills training or socioenvironmental therap* or sociotherap* or solution focused or stress management or support group* or supportive therap* or systematic desensiti?ation or systemic therap* or therapeutic communit* or transactional analysis or transference or transtheoretical or validation therap* or (dream* near/3 analys*) or (support near/3 psycho*)):ti,ab,kw (Word variations have been searched)[411716]

#15 #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 [419239]

#16 #4 and #15 in Trials [6420]

Biosis Searched 25th June 2017

13 **684** #12 AND #11 AND #10

Indexes=BCI Timespan=All years

12 **403,516** **TITLE:**((abreaction or "acceptance and commitment therapy" or "acting out" or adlerian or "analytical psychotherap*" or "anger control" or "anger management" or "animal therap*" or "art therap*" or "assertive* training" or "attention training technique" or "autogenic training" or autosuggestion or "aversion therap*" or "balint group" or befriending or "behavior contracting" or "behavior modification" or "behavior regulation" or "behavior therap*" or "behaviour contracting" or "behaviour modification" or "behaviour regulation" or "behaviour therap*" or bibliotherap* or biofeedback or "body psychotherap*" or "brief psychotherap*" or "caregiver support" or cbt or "client cent*" or "cognitive behavior*" or "cognitive behaviour*" or "cognitive intervention*" or "cognitive rehabilit*" or "cognitive remediation" or "cognitive technique*" or "cognitive therap*" or "cognitive treatment*" or "color therap*" or "colour therap*" or "compassionate mind training" or "conjoint therap*" or "contingency management" or "conversational therap*" or "conversion therap*" or "coping skills" or counseling or counselling or countertransference or "couples therap*" or "covert sensitiza-

tion" or "covert sensitisation" or "crisis intervention" or "dance therap*" or dialectic* or eclectic or emotion* focus* or "emotional freedom technique" or "encounter group therap*" or "existential therap*" or "experiential psychotherap*" or "exposure therap*" or "expressive psychotherap*" or "eye movement desensitization" or "eye movement desensitisation" or "family intervention*" or "family therap*" or "feminist therap*" or "free association" or freudian or "geriatric psychotherap*" or "gestalt therap*" or griefwork or "group intervention*" or "group psychotherap*" or "group therap*" or "guided image*" or "holistic psychotherap*" or "humanistic psychotherap*" or hypnosis or hypnotherap* or hypnotizability or hypnotisability or imagery or "implosive therap*" or "individual psychotherap*" or "insight therap*" or "integrated psychological therapy" or "integrative psychotherap*" or "integrative therap*" or interpersonal or jungian or kleinian or logotherap* or "marathon group therap*" or "marital therap*" or meditation or "mental healing" or "metacognitive therap*" or "metacognitive training" or "milieu therap*" or mindfulness or "morita therap*" or multimodal or "music therap*" or "narrative therap*" or "nondirective therap*" or "object relations" or person cent* therap* or "personal construct therap*" or "persuasion therap*" or "pet therap*" or "play therap*" or "primal therap*" or "problem solving" or psychoanaly* or psychodrama or psychodynamic or psychoeducat* or psycholog* or "psychological therap*" or "psychosocial treatment" or psychotherap* or "psychotherapeutic counsel*" or "psychotherapeutic processes" or "psychotherapeutic training" or "psychotherapeutic treatment*" or "rational emotive" or "reality therap*" or "reciprocal inhibition" or rehabilitat* or "relationship therap*" or relaxation or "reminiscence therap*" or rogerian or "role play*" or "self analys*" or "self esteem" or "sensitivity training" or "sex therap*" or "sleep phase chronotherap*" or "social skills education" or "social skills training" or "socioenvironmental therap*" or sociotherap* or "solution focused" or "stress management" or "support group*" or "supportive therap*" or "systematic desensitization" or "systematic desensitisation" or "systemic therap*" or "therapeutic communit*" or "transactional analysis" or transference or transtheoretical or "validation therap*" or (dream* Near/3 analys*) or (support Near/3 psycho*)) ORTOPIC:((abreaction or "acceptance and commitment therapy" or "acting out" or adlerian or "analytical psychotherap*" or "anger control" or "anger management" or "animal therap*" or "art therap*" or "assertive* training" or "attention training technique" or "autogenic training" or autosuggestion or "aversion therap*" or "balint group" or befriending or "behavior contracting" or "behavior modification" or "behavior regulation" or "behavior therap*" or "behaviour contracting" or "behaviour modification" or "behaviour regulation" or "behaviour therap*" or bibliotherap* or

biofeedback or "body psychotherap*" or "brief psychotherap*" or "caregiver support" or cbt or "client cent*" or "cognitive behavior*" or "cognitive behaviour*" or "cognitive intervention*" or "cognitive rehabilit*" or "cognitive remediation" or "cognitive technique*" or "cognitive therap*" or "cognitive treatment*" or "color therap*" or "colour therap*" or "compassionate mind training" or "conjoint therap*" or "contingency management" or "conversational therap*" or "conversion therap*" or "coping skills" or counseling or counselling or countertransference or "couples therap*" or "covert sensitization" or "covert sensitisation" or "crisis intervention" or "dance therap*" or dialectic* or eclectic or emotion* focus* or "emotional freedom technique" or "encounter group therap*" or "existential therap*" or "experiential psychotherap*" or "exposure therap*" or "expressive psychotherap*" or "eye movement desensitization" or "eye movement desensitisation" or "family intervention*" or "family therap*" or "feminist therap*" or "free association" or freudian or "geriatric psychotherap*" or "gestalt therap*" or griefwork or "group intervention*" or "group psychotherap*" or "group therap*" or "guided image*" or "holistic psychotherap*" or "humanistic psychotherap*" or hypnosis or hypnotherap* or hypnotizability or hypnotisability or imagery or "implosive therap*" or "individual psychotherap*" or "insight therap*" or "integrated psychological therapy" or "integrative psychotherap*" or "integrative therap*" or interpersonal or jungian or kleinian or logotherap* or "marathon group therap*" or "marital therap*" or meditation or "mental healing" or "metacognitive therap*" or "metacognitive training" or "milieu therap*" or mindfulness or "morita therap*" or multimodal or "music therap*" or "narrative therap*" or "nondirective therap*" or "object relations" or person cent* therap* or "personal construct therap*" or "persuasion therap*" or "pet therap*" or "play therap*" or "primal therap*" or "problem solving" or psychoanal* or psychodrama or psychodynamic or psychoeducat* or psychologic* or "psychological therap*" or "psychosocial treatment" or psychotherap* or "psychotherapeutic counsel*" or "psychotherapeutic processes" or "psychotherapeutic training" or "psychotherapeutic treatment*" or "rational emotive" or "reality therap*" or "reciprocal inhibition" or rehabilitat* or "relationship therap*" or relaxation or "reminiscence therap*" or rogerian or "role play*" or "self analys*" or "self esteem" or "sensitivity training" or "sex therap*" or "sleep phase chronotherap*" or "social skills education" or "social skills training" or "socioenvironmental therap*" or sociotherap* or "solution focused" or "stress management" or "support group*" or "supportive therap*" or "systematic desensitization" or "systematic desensitisation" or "systemic therap*" or "therapeutic community*" or "transactional analysis" or transference or transtheoretical or "validation therap*" or (dream* Near/3 analys*) or (support Near/3 psycho*))

Indexes=BCI Timespan=All years
 # 11 **152,007** **TOPIC:**(schizo* or psychotic* or psychosis or psychoses)
ORTITLE:(schizo* or psychotic* or psychosis or psychoses)
Indexes=BCI Timespan=All years
 # 10 **383,461** #9 OR #8 OR #7 OR #6 OR #3 OR #2
Indexes=BCI Timespan=All years
 # 9 **39,824** TS=crossover* OR TI=crossover*
Indexes=BCI Timespan=All years
 # 8 **467** TS=(randomi* Near/1 assign*) or TI=(randomi* Near/1 assign*)
Indexes=BCI Timespan=All years
 # 7 **80** TS=(randomi* Near/1 allocate*) or TI=(randomi* Near/1 allocate*)
Indexes=BCI Timespan=All years
 # 6 **122,301** #5 AND #4
Indexes=BCI Timespan=All years
 # 5 **225,151** TS=(mask* OR blind*) OR TI=(mask* OR blind*)
Indexes=BCI Timespan=All years
 # 4 **2,256,036** TS=(singl* OR Doubl* OR Tripl* OR Trebl*) OR
 TI=(singl* OR Doubl* OR Tripl* OR Trebl*)
Indexes=BCI Timespan=All years
 # 3 **316,443** TI=(randomi*) OR TS=(randomi*)
Indexes=BCI Timespan=All years
 # 2 **165,438** TS=(Randomized clinical trial*) OR TI=(Randomized clinical trial*)
Indexes=BCI Timespan=All years
 # 1 **10,515,925** TA=(Hominidae)
Indexes=BCI Timespan=All years

Pubmed Searched 10th January 2018

#12 Search (#10 and #11) 145
 #11 Search ("2017/06/25"[Date - Entrez] : "3000"[Date - Entrez]) 611117
 #10 Search (#4 and #8 and #9) 6852
 #9 Search (((randomized controlled trial[pt]) OR (controlled clinical trial[pt]) OR (randomized[tiab]) OR (placebo[tiab]) OR (drug therapy[sh]) OR (randomly[tiab]) OR (trial[tiab]) OR (groups[tiab])) NOT (animals[mh] NOT humans[mh])) 3607526
 #8 Search (#6 or #7) 979810

#7 Search (abreaction [Title/ Abstract] OR "acceptance [Title/ Abstract] AND commitment therapy" [Title/ Abstract] OR "acting out" [Title/ Abstract] OR adlerian [Title/ Abstract] OR "analytical psychotherapy" [Title/ Abstract] OR "analytical psychotherapies" [Title/ Abstract] OR "anger control" [Title/ Abstract] OR "anger management" [Title/ Abstract] OR "animal therapy" [Title/ Abstract] OR "animal therapies" [Title/ Abstract] OR "art therapy" [Title/ Abstract] OR "art therapies" [Title/ Abstract] OR "assertive training" [Title/ Abstract] OR "assertiveness training" [Title/ Abstract] OR "attention training technique" [Title/ Abstract] OR "autogenic training" [Title/ Abstract] OR autosuggestion [Title/ Abstract] OR "aversion therapy" [Title/ Abstract] OR "aversion therapies" [Title/ Abstract] OR "balint group" [Title/ Abstract] OR befriending [Title/ Abstract] OR "behavior contracting" [Title/ Abstract] OR "behavior modification" [Title/ Abstract] OR "behavior regulation" [Title/ Abstract] OR "behavior therapy" [Title/ Abstract] OR "behavior therapies" [Title/ Abstract] OR "behaviour contracting" [Title/ Abstract] OR "behaviour modification" [Title/ Abstract] OR "behaviour regulation" [Title/ Abstract] OR "behaviour therapy" [Title/ Abstract] OR "behaviour therapies" [Title/ Abstract] OR bibliotherapy [Title/ Abstract] OR bibliotherapies [Title/ Abstract] OR biofeedback [Title/ Abstract] OR "body psychotherapy" [Title/ Abstract] OR "body psychotherapies" [Title/ Abstract] OR "brief psychotherapy" [Title/ Abstract] OR "brief psychotherapies" [Title/ Abstract] OR "caregiver support" [Title/ Abstract] OR cbt [Title/ Abstract] OR "client centre" [Title/ Abstract] OR "client center" [Title/ Abstract] OR "cognitive behavior" [Title/ Abstract] OR "cognitive behavioral" [Title/ Abstract] OR "cognitive intervention" [Title/ Abstract] OR "cognitive interventions" [Title/ Abstract] OR "cognitive rehabilitation" [Title/ Abstract] OR "cognitive remediation" [Title/ Abstract] OR "cognitive technique" [Title/ Abstract] OR "cognitive techniques" [Title/ Abstract] OR "cognitive therapy" [Title/ Abstract] OR "cognitive therapies" [Title/ Abstract] OR "cognitive treatment" [Title/ Abstract] OR "cognitive treatments" [Title/ Abstract] OR "color therapy" [Title/ Abstract] OR "color therapies" [Title/ Abstract] OR "colour therapy" [Title/ Abstract] OR "colour therapies" [Title/ Abstract] OR "compassionate mind training" [Title/ Abstract] OR "conjoint therapy" [Title/ Abstract] OR "conjoint therapies" [Title/ Abstract] OR "contingency management" [Title/ Abstract] OR "conversational therapy" [Title/ Abstract] OR "conversational therapies" [Title/ Abstract] OR "conversion therapy" [Title/ Abstract] OR "conversion therapies" [Title/ Abstract] OR "coping skills" [Title/ Abstract] OR counseling [Title/ Abstract] OR counselling [Title/ Abstract] OR countertransference [Title/ Abstract] OR "couples therapy" [Title/ Abstract] OR "couples therapies" [Title/ Abstract] OR "covert sensitization" [Title/ Abstract]

stract] OR "covert sensitisation" [Title/ Abstract] OR "crisis intervention" [Title/ Abstract] OR "dance therapy" [Title/ Abstract] OR "dance therapies" [Title/ Abstract] OR dialectic [Title/ Abstract] OR dialectical [Title/ Abstract] OR "dream analysis" [Title/ Abstract] OR eclectic [Title/ Abstract] OR "emotion focused" [Title/ Abstract] OR "emotionally focused" [Title/ Abstract] OR "emotional freedom technique" [Title/ Abstract] OR "encounter group therapy" [Title/ Abstract] OR "encounter group therapies" [Title/ Abstract] OR "existential therapy" [Title/ Abstract] OR "existential therapies" [Title/ Abstract] OR "experiential psychotherapy" [Title/ Abstract] OR "experiential psychotherapies" [Title/ Abstract] OR "exposure therapy" [Title/ Abstract] OR "exposure therapies" [Title/ Abstract] OR "expressive psychotherapy" [Title/ Abstract] OR "expressive psychotherapies" [Title/ Abstract] OR "eye movement desensitization" [Title/ Abstract] OR "eye movement desensitisation" [Title/ Abstract] OR "family intervention" [Title/ Abstract] OR "family interventions" [Title/ Abstract] OR "family therapy" [Title/ Abstract] OR "family therapies" [Title/ Abstract] OR "feminist therapy" [Title/ Abstract] OR "feminist therapies" [Title/ Abstract] OR "free association" [Title/ Abstract] OR freudian [Title/ Abstract] OR "geriatric psychotherapy" [Title/ Abstract] OR "geriatric psychotherapies" [Title/ Abstract] OR "gestalt therapy" [Title/ Abstract] OR "gestalt therapies" [Title/ Abstract] OR griefwork [Title/ Abstract] OR "group intervention" [Title/ Abstract] OR "group interventions" [Title/ Abstract] OR "group psychotherapy" [Title/ Abstract] OR "group psychotherapies" [Title/ Abstract] OR "group therapy" [Title/ Abstract] OR "group therapies" [Title/ Abstract] OR "guided imagery" [Title/ Abstract] OR "holistic psychotherapy" [Title/ Abstract] OR "holistic psychotherapies" [Title/ Abstract] OR "humanistic psychotherapy" [Title/ Abstract] OR "humanistic psychotherapies" [Title/ Abstract] OR hypnosis [Title/ Abstract] OR hypnotherapy [Title/ Abstract] OR hypnotherapies [Title/ Abstract] OR hypnotizability [Title/ Abstract] OR hypnotisability [Title/ Abstract] OR imagery [Title/ Abstract] OR "implosive therapy" [Title/ Abstract] OR "implosive therapies" [Title/ Abstract] OR "individual psychotherapy" [Title/ Abstract] OR "individual psychotherapies" [Title/ Abstract] OR "insight therapy" [Title/ Abstract] OR "insight therapies" [Title/ Abstract] OR "integrated psychological therapy" [Title/ Abstract] OR "integrative psychotherapy" [Title/ Abstract] OR "integrative psychotherapies" [Title/ Abstract] OR "integrative therapy" [Title/ Abstract] OR "integrative therapies" [Title/ Abstract] OR interpersonal [Title/ Abstract] OR jungian [Title/ Abstract] OR kleinian [Title/ Abstract] OR logotherapy [Title/ Abstract] OR logotherapies [Title/ Abstract] OR "marathon group therapy" [Title/ Abstract] OR "marathon group therapies" [Title/ Abstract] OR "marital therapy" [Title/ Abstract]

OR "marital therapies" [Title/ Abstract] OR meditation [Title/ Abstract]
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 bilitating [Title/ Abstract] OR "relationship therapy" [Title/ Abstract] OR
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 tle/ Abstract] OR rogerian [Title/ Abstract] OR "role play" [Title/ Abstract]
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 Random /Intervention =
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WHO ICTRP Trial registry 26th June to present

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psycho* and random* = 174

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