Psychological interventions for psychosis

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PSYCHOLOGICAL INTERVENTIONS FOR PSYCHOSIS

Contemporary perspectives on the evidence base from novel approaches

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Contents

Chapter 1

Introduction

Foreword

When reflecting on the broader themes covered in this thesis, one particular experience during my Clinical Psychology Doctoral training was prominent in my thinking. The setting for this experience was a bright, spacious and somewhat old-fashioned National Health Service (NHS) therapy room in a large Scottish town. As this was a Child and Adolescent Mental Health (CAMHS) service all assessments were joint, meaning that I assessed the patient together with a nurse psychological therapist. The sixteen-year-old patient appeared bright, articulate and somewhat alternative in appearance. He was accompanied by his mother, who gave an instant impression as warm, caring and slightly more apprehensive regarding the assessment than her son.

Daniel (anonomised) described having begun to irregularly hear a voice commenting on his actions. The voice had first occurred only a few weeks before the assessment, at which point he discussed it with his mother. She swiftly took him to his General Practitioner, who in turn made an urgent referral to CAMHS. Daniel noted no distress regarding the voice. He described no clear interpretation of what it was, where it came from and why it was occurring; he simply noted that he recognised it was something he should discuss and have checked out professionally. He noted that he had tried cannabis a couple of times with friends roughly one month before the onset of the voice, but informed us that he didn't really enjoy it and had since avoided it. He came across as calm, intelligent, motivated in his studies and quietly social although somewhat isolated circumstantially in an outlying town.

What ensued was from my perspective a highly unfortunate path of hyperbole and negative reinforcement. The nurse therapist concluded from his assessment that Daniel was “floridly psychotic” and quickly communicated this to the team’s Consultant Psychiatrist. She in turn swiftly diagnosed him as experiencing a psychotic episode and prescribed Risperidone (an atypical anti-psychotic). My attempts to temper this approach were met with an unreferenced conviction that failing to medicate was immoral since the psychotic episode was “bad for his brain.” Despite support from my supervisor (the lead Clinical Psychologist in the team) and concerns from Daniel regarding the medication, the Psychiatrist reinforced that medicating the patient was the only acceptable path to follow, albeit with adjunctive cognitive behavioural therapy for psychosis (CBTp) that I myself would deliver. The Psychiatrist also communicated to Daniel and his family that he was experiencing a “dangerous” psychotic episode and that he should expect to be maintained on medication for a considerable time.

Daniel’s presentation quickly worsened. The side effects of the medication left him tired, with great difficulty concentrating and unable to engage in school. He was advised to take time off at a key time before his first exams. The frequency and intensity of his voices increased and he developed paranoid interpretation regarding schoolmates alongside distressing intrusions regarding violence toward his peers. We engaged intensively in formulation-based CBTp in an attempt to counter his interpretation and support his coping. During this time his medication was continually increased despite his pleas regarding debilitating side effects, including heavy drowsiness impairing his ability to study. After a few months engaging in CBTp his presentation improved, although this also coincided with a medication change. The

Psychiatrist attributed the process of deterioration and stablisation to a process of "trial and error" to find the correct medication and dose. The role of CBTp was marginalised, despite communication from the patient and his family that they believed it played a huge role in his improvement.

I chose to begin my thesis with this personal example because I believe that this case is illustrative of many issues pertinent to the clinical application of psychological interventions for psychosis. An apparent theme is the on-going polarity between the medical and psychological models of psychosis; despite great progress in understanding the complex and interwoven factors at play, examples as above demonstrate that reductionist clinical approaches persist from both psychiatric and psychological perspectives. The example also demonstrates a historic power imbalance favouring psychiatry alongside an apparent dismissal of evidence for alternative approaches, such as the ultra-high risk for psychosis paradigm that targets prodromal psychosis using psychological intervention. I believe this case is a great example of one in which an alternative approach may have been more beneficial, or at least worthy of an attempt.

On reflection, this case example also demonstrates my own belief that first attempting a psychological intervention without rushing to medicate would have been the preferred first option. How valid is this belief and what is the true evidence for the merit of psychological interventions for psychosis? This thesis constitutes a body of research I have accumulated with the support of my co-authors over a number of years aiming to investigate the available options for the psychological treatment of psychosis and the current empirical status of these interventions. The questions and

perspectives that the above clinical example bring to the fore are varied and complex therefore this thesis does not purport to address them comprehensively. First and foremost, this thesis attempts to add to the knowledge base on the application of psychological interventions for psychosis and improve the understanding of the point to which evidence in the field has currently developed while considering implications for its future.

Psychological interventions for psychosis

Introduction

Psychological interventions for psychosis have a long and somewhat controversial history. Since as early as psychoanalytic attempts to understand and treat "neuro-psychoses" such as *hysterical psychosis*, psychological intervention for psychosis has been present but rarely mainstream in mental health care. Accumulating evidence over the past two to three decades for cognitive behavioural therapy for psychosis (CBTp) alongside the related development of intricate biopsychosocial explanatory models aiding the understanding of psychosis aetiology has provided a platform from which psychological approaches have challenged the traditional dominance of psychiatric, medical model thinking. This process has been closely related and simultaneous to the advent of evidence-based medicine and empirically-supported treatment. This challenge psychological interventions pose to the established order has produced considerable debate regarding the purported efficacy and widely implementation of CBTp in the United Kingdom.[1,2] The often-polarised debate regarding the efficacy of psychological interventions will provide important context to this thesis.

Historic context and development of medical model

The development of psychological interventions for psychosis has occurred in the context of a historical dominance of psychiatric or "medical model" approaches to severe and enduring mental "illness" or "madness." Early conceptualisations of psychosis in the historical literature are noted as early as the 4th Century in Hippocrates conceptualisation of *melancholia*.[3,4] Throughout the majority of recorded

history, sufferers of psychosis are recognised as having endured various forms of brutality perpetrated by society, the state and the medical profession in the form of medical treatment, incarceration or death including bloodletting, forced imprisonment, torture, lobotomy, capital punishment and burning at the stake for witchcraft.[5–8] As the Middle Ages gave way to the early modern era, citizens in Europe beset with severe mental illness were increasingly detained in the great asylums such as Bethlehem Hospital or "Bedlam" in London, England[9] or the *Asylum de Bicêtre* in Paris, France.[10] Via his work in the latter institution, Phillipe Pinel is noted as central in the development of a humane or 'moral' approach toward severe mental health problems, although in comparison to modern standards his quasi-scientific approach often continued to include methods now unimaginable in mental health care, exemplified by the continuation of bloodletting in severe cases.

In the context of improving medical care and knowledge, Emil Kraepelin (1856-1926) is recognised as the most significant figure in the development of the modern concepts of psychosis and schizophrenia via his *dementia praecox* concept. This new concept attempted to provide a systematic understanding of severe mental illness by linking symptom presentations with patterns of onset, course and outcome to inform nosological categorisation into *syndromes*. Following from Kraeplin's influential approach, Eugen Bleuler (1857-1939) developed the concept of *schizophrenia* influenced by a comparatively psychological approach contrasting the somatic conceptualisation of the earlier dementia praecox concept. The contrast is demonstrated by reports of Bleuler having spent considerable time developing emotional rapport with his patients and his attempts to gain psychological interpretation of their delusions under the influence of Sigmund Freud's methods.

Although psychological rather than narrowly medical conceptualisations of psychosis continued to be in existence, a further shift toward a somatic understanding of severe mental health was influenced by Karl Jasper's distinction between whether delusions and thought disorder were understandable or non-understandable in the context of a patient, with the latter such instances conceptualised as indicative of somatic cause. A medical-model disease-based conceptualisation has since dominated psychiatric treatment while Kraepelin's firmly somatic, diagnostic approach continues to have huge influence worldwide due to its influence in the methods of the *Diagnostic and Statistical Manual of Mental Disorders* and other diagnostic systems.[11,12]

Contemporary understanding of psychosis

Psychosis is widely recognised as a psychiatric symptom that may arise due a variety of underlying causes of biopsychosocial origin.[11] Psychosis in the context of psychological interventions for psychosis typically refers to *psychotic disorders* as specified in diagnostic classification manuals such as the *Diagnostic and Statistical Manual of Mental Disorders Fifth Edition* (DSM-5)[13] or *the International Statistical Classification of Diseases and Related Health Problems 10th Edition* (ICD-10).[14] These diagnoses are currently accommodated in the *Schizophrenia Spectrum and Other Psychotic Disorders* section in DSM-5 which includes schizophrenia, schizoaffective disorder, delusional disorder, schizotypal (personality) disorder, brief psychotic disorder, schizophreniform disorder, substance or medication-induced psychotic disorder, psychotic disorder due to another medical conditions, catatonic disorders, other specified schizophrenia spectrum or psychotic disorders and finally unspecified schizophrenia spectrum and other psychotic disorders. The current

classification represents a reduction in categories with the discontinuation of previous sub-categories of schizophrenia including paranoid schizophrenia alongside the creation of a separate catatonic disorders section. Psychotic experiences have also been shown to exist more widely in the general population, with evidence that only a small proportion of individuals experiencing psychotic-like symptoms are diagnosed with psychotic disorders.[15,16]

Psychotic disorders are characterised by the existence of hallucinations and/or delusions alongside a range of other disturbances in thinking, perceptual and behavioural patterns. The DSM-5 defines schizophreniform and other psychotic disorders as displaying abnormality in one or more of five domains: delusions, hallucinations, disorganised thinking, disorganised or abnormal motor behaviour and negative symptoms (DSM-5). Negative symptoms primarily refer to the absence of or loss of function, specifically in affective blunting, speech, anhedonia/asociality, avolition/apathy and attention.[17] The reduction of positive and negative symptoms is recognised as a primary target in both pharmacological and psychological intervention, while intervention may also target other related outcomes such as social or occupational functioning.[18]

Evidence base for psychosis interventions

Anti-psychotic medication

The dominant form of psychiatric treatment for around 70 years has been pharmacological, following the introduction of first-generation anti-psychotic drugs in the 1950s.[19] Routine psychiatric "care as usual" in Western healthcare systems refers to the maintenance of patients with schizophrenia-spectrum disorders on second-generation "atypical" anti-psychotics, which routinely consists of medication review by a Consultant Psychiatrist and supported administration via Community Psychiatric Nurses. The introduction of reliable anti-psychotics was influential in the process of psychiatric deinsitutionalisation and rise of care-in-the-community from the 1950s.[20] Despite their acknowledged relative success in reducing hallucinations and delusions,[21] anti-psychotic medication has well-documented side effects including extra-pyramidal effects such as dystonic reaction and drug-induced Parkisonism, alongside physical health consequences such as weight gain and increased diabetes risk.[22,23] Recent meta-analytic evidence demonstrates that although anti-psychotic drugs are consistently more effective in reducing symptoms than placebo,[24] effect sizes remain typically in the small to medium range and may be reduced when accounting for publication bias and industry sponsorship of trials.[25] Early evidence for approximately equivalent effects of psychological intervention in psychosis patients not taking medication[26] alongside the complex longitudinal side-effect profile,[27] high relapse-rates[28] and ineffectiveness among a proportion of treatment-resistant patients who often remain hospitalised in resource-heavy settings[29] emphasises the importance of the development of reliable psychological interventions for psychosis.

Early psychological interventions

Psychological intervention (or psychosocial engagement with) psychosis dates back to approximately the turn of the 20th Century. While Bleuler is noted as the first prominent clinician in the modern age to put emphasis on the therapeutic alliance and psychosocial understanding of presenting problems, his work can largely be understood as influenced by Freud's early methods despite Freud's initial scepticism regarding treatability. Therapeutic approaches to psychosis employing psychoanalytic and psychodynamic concepts continued to develop throughout the 20th Century while from the 1950s, systemic approaches combined this influence with knowledge from the diverse fields of cybernetics, systems theory, communication theory, game theory and constructivism to focus more specifically on the impact of family dynamics in the development and maintenance of psychosis.[30]

While the application of psychodynamic approaches to psychosis has dwindled in popularity in the evidence-based era, family therapy remains a relatively widely implemented treatment option. Despite limited evidence for family therapy as a means of reducing the core symptoms of psychosis,[31] those who receive family intervention demonstrate significantly lower relapse rates with moderate strength of evidence.[32] Family therapy continues to be a recommended treatment option in the United Kingdom alongside referral to early intervention psychosis services, anti-psychotic treatment with clozapine and cognitive behavioural therapy.[33]

Cognitive behavioural therapy for psychosis (CBTp)

Cognitive behavioural therapy is a psychological intervention that focuses on the interplay between external circumstances and thoughts (cognitions), emotions,

physical sensations and behaviours. CBT was first developed as an intervention for depression by Aaron T. Beck in the late 1970s[34] concurrent to the development of Rational Emotive Behaviour therapy (REBT)[35] as developed by Albert Ellis, although the former has in recent decades far surpassed the latter in terms of clinical implementation and research. Cognitive behavioural therapy remains the psychological intervention with the most extensive evidence-base and has demonstrated efficacy for a range of psychiatric diagnoses including depression[36] various anxiety disorders,[37–39] post-traumatic stress disorder,[40,41] obsessive-compulsive disorder,[42,43] and eating disorders.[44] Cognitive behavioural therapy for psychosis (CBTp), developed primarily in the UK in the 1990s, applies the key principles of cognitive behavioural therapy with the aim reducing the symptoms of schizophrenia-spectrum disorders. Early approaches such as that by Tarrier and colleagues[45,46] focused primarily on the improvement of coping with symptoms and the reduction of associated distress among psychosis patients while later approaches focused more specifically on the disputation of hallucinatory experiences and delusional beliefs in a *challenging* cognitive–behavioural framework.[47–49]

CBTp evidence base

High-quality scientific evidence for psychological interventions for psychosis has developed incrementally since the 1980s through a number of relatively distinct phases. Early randomised controlled trials examining the efficacy of psychological interventions for psychosis began to accumulate in the 1980s.[50,51] These RCTs were often of limited methodological quality when compared to accepted contemporary standards while the treatment packages assessed were often less clearly defined. The

advent of CBTp in the 1990s resulted in the publication of RCTs examining the aforementioned coping-focused variant of CBTp[45,46,52,53] before roughly around the turn of the millennium a proliferation of primarily UK-based RCTs began to be published focusing on the now 'generic' form of CBTp relying on the disputation of hallucinatory and delusional appraisal.[54,55] These RCTs typically adhered to the appropriate design standards by ensuring sufficient methodological stringency and often assessed CBTp in specific psychosis populations, such as treatment-resistant schizophrenia. In the last decade, a broader range of RCTs have been published investigating the efficacy of new CBTp variants including virtual-reality based CBTp,[56]acceptance-based approaches,[57] mindfulness-based approaches[58] and adaptation of CBTp to non-Western populations.[59]

While well-designed randomised controlled trials continue to represent the best available form of published empirical data, meta-analytic reviews pooling data from these trials to present aggregated effect estimates allow a more compressive estimate of efficacy than individual trials alone can provide. Meta-analysis is particularly important in research fields in which many RCTs exist with sub-optimal statistical power.[60] This circumstance is often valid for RCTs of psychological interventions for psychosis, which require considerable therapeutic resource provision and design complexity in comparison to anti-psychotic RCTs comparing medication to pill placebo. Despite a proliferation of meta-analyses in the previous decade, there remains controversy regarding whether CBTp is effective and truly deserving of recommendation in treatment guidelines, or whether it has instead been "oversold."[1] CBTp has regularly demonstrated small to medium beneficial effect sizes when compared to treatment-as-usual[61–63] but the persistence of null findings in a series of

reviews alongside inconsistency of effects compared to active treatments has facilitated continued scepticism and criticism.[64] Similarly, evidence remains limited on the relative merit of alternative psychological interventions such as social skills training and cognitive remediation alongside specific effects on secondary outcomes including negative symptoms and social functioning.[65]

Common versus specific factors and debate on equivalence of psychological interventions

Our understanding of psychosis outcome research shares a common limitation to the vast majority of psychological therapy outcome research; we know that it *works*, but we are less sure *how* it works. The conventional randomised controlled trial design does not allow the examination of components within interventions therefore RCTs do not allow us to determine which elements of the psychosocial intervention being examined are most effective. Dismantling trials tackling this problem are complex, expensive and to date remain unavailable.[2,66] An influential researcher in this domain is Bruce Wampold, author of *The Great Psychotherapy Debate.*[67] Following large-scale meta-analytical comparison of psychological therapies primarily for depression, Wampold concluded that all bona fide therapies are essentially equivalent and that instances in which significant differences are demonstrated between interventions can usually be explained by various biases, including publication bias and researcher allegiance. Wampold purports that instead of having impact through *specific factors* (for example modifying cognitive appraisal in CBTp or improving social skills in social skills training), the main effects of psychological interventions are achieved via *common factors.* These elements common to all psychological therapies include the core elements of the therapeutic alliance (personal bond, agreement on goals and

agreement about relevant tasks), demonstration of empathy and the expectation of positive outcome via a healing process.[68] While the desired dismantling trials remain currently out of reach, meta-analytic research can provide initial insight into whether the *all therapies are created equal* premise is valid for psychosis by demonstrating reliable differences between interventions.

Cognitive bias and overconfidence in psychosis

The development of efficacious psychological interventions for psychosis is demonstrative of the broadening range of treatment options available for psychosis patients. The fact that this evidence base is developing also brings natural attention to the various potential mechanisms within these treatments. One target of psychological interventions has been cognitive biases, which have been implicated in the development and maintenance of delusional interpretation and impaired decision-making among psychosis patients.[69] Metacognitive training (MCT), is an intervention which integrates cognitive-behavioural principles to specifically target such cognitive biases including the "jumping to conclusions" bias.[70] Psychosis patients have been demonstrated as more likely to demonstrate this bias and have also been shown to have a higher degree of overconfidence in perceptual decision making.[71] In light of the developing range of treatment options and broadening understanding of potential mechanisms, this represents an important evolving area.

Overview of chapters

This thesis has a number of key objectives that will be addressed across five manuscripts published in peer-reviewed international psychiatric journals.
The first objective is to provide a comprehensive and contemporary overview of the efficacy of psychological interventions for psychosis. Included in this objective is a commitment to utilising the best available methods to limit the risk of biased conclusions resulting from limited methodology within the primary research included in the reviews. This objective will be addressed across **Chapters 2 to 5**, each of which provide alternate forms of meta-analytic review investigating the impact of psychological interventions upon psychotic symptoms. These reviews focus primarily on cognitive-behavioural therapy for psychosis (CBTp) as the most widely researched and delivered intervention in the field. **Chapter 2** provides a comparative meta-analysis of contemporary psychological interventions for psychosis, therefore also addressing a sub-objective regarding the *all therapies are created equal* debate. **Chapter 3** presents a network meta-analysis further examining the impact of psychological interventions for psychosis upon psychotic symptoms.

A second objective is to apply more recent developments in meta-analysis methodology that have not yet been utilised in reviewing the evidence base for psychological interventions for psychosis, with aim to providing novel insight into the evidence-base. This objective will be addressed firstly in **chapter 4** by a cumulative meta-analysis investigating whether the evidence base for CBTp in reducing hallucinations and delusions is both *stable* and *sufficient*. This objective will also be addressed in **chapter 5** by an individual-participant data (IPD) meta-analysis, which

provides the opportunity to investigate the impact of moderator variables such as demographic or clinical characteristics on treatment outcome while providing a more precise estimation of the effect on psychotic symptoms.

A third objective is to investigate the possibility that impaired decision making and thinking biases among psychosis patients may be improved by the provision of targeted psychological intervention. This objective will be addressed in **chapter 6** by a randomised controlled trial assessing the efficacy of a brief intervention addressing the "jumping-to-conclusions" reasoning bias on overconfident decision making in psychosis patients.

A final objective is to utilise the evidence from this thesis in a summative manner by providing comment and guidance that is beneficial to the future of the psychosis field from both a clinical and research perspective. This objective is addressed partially by each of the included studies and in particular by the application of cumulative meta-analysis, which provides the opportunity to address the question *what constitutes sufficient evidence for CBTp for psychosis?* This objective will be further addressed in **chapter 7** by critical consideration of the included studies in the general discussion section. This objective aims to capitalise on the somewhat unique opportunity provided by the application of modern and novel meta-analytical techniques to over thirty years of research on psychological interventions for psychosis.

Chapter 2

Psychological interventions for psychosis: A meta-analysis of comparative outcome studies

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Abstract

Objective. Meta-analyses have demonstrated the efficacy of various interventions for psychosis while a small number have compared these interventions. This study aims to provide further insight into the relative efficacy of psychological interventions for psychosis.

Method. 48 outcome trials comparing psychological interventions for psychosis were identified. The comparisons included 3295 participants. Interventions were categorised resulting in 6 interventions being compared against other interventions pooled. Hedges' *g* was calculated for all comparisons. Risk of bias was assessed using 4 items of the Cochrane Risk of Bias tool and sensitivity analyses were conducted. Researcher allegiance was assessed and sensitivity analyses were conducted for robust significant findings.

Results. Cognitive-Behavioural Therapy (CBT) was significantly more efficacious than other interventions pooled in reducing positive symptoms (*g=0.16)*. This finding was robust in all risk of bias sensitivity analyses but lost significance in researcher allegiance sensitivity analyses, which suffered from low power. Social Skills Training (SST) was significantly more efficacious in reducing negative symptoms (*g*=0.27). This finding was robust in sensitivity analyses for risk of bias and researcher allegiance. There were significant findings for CBT, SST and cognitive remediation for overall symptoms which were not robust after sensitivity analyses. CBT was significantly more efficacious when compared directly to befriending for overall symptoms (*g*=0.42) and supportive counselling for positive symptoms (*g*=0.23).

Conclusions. There are small but reliable differences in efficacy between psychological interventions for psychosis which occur in a pattern consistent with the specific factors of particular interventions. This has implications for clinical practise.

Keywords: Schizophrenia, RCT, CBT, SST, psychotherapy, Dodo.

Introduction

It has been suggested that all psychotherapies are roughly equivalent in efficacy, [1-6] although some meta-analyses have suggested differences in relative efficacy between treatments.[7] Previous meta-analyses have demonstrated the absolute efficacy of various psychological interventions for psychosis, [8-16] while others have been suggested as unreliable. [17] Comparatively little is understood about relative efficacy. The most extensive meta-analytic evidence was provided by the UK National Institute for Clinical Excellence (NICE).[18] However, risk of bias was not assessed and many comparisons of psychological interventions against other 'active' treatments were underpowered, including subgroup comparisons for positive and negative symptoms .[19]

Other comparative meta-analyses have not consistently demonstrated superiority of the intervention of interest. Jones *et al* (2012) compared CBT against other interventions pooled and concluded that CBT was not reliably more efficacious.[20] A limitation was that compliance studies were also included in the CBT group.[21] Lynch *et al* (2010) compared CBT to active control conditions and found a statistically significant benefit (g = 0.2) of CBT versus active controls pooled for positive symptoms. [22] However, the authors concluded that CBT was no better than non-specific comparison treatments and that the significant effect size could be explained by lack of blinding.[22] There were some methodological criticisms of Lynch *et al*,[23-25] and there remains controversy over which psychological interventions are most efficacious for psychosis.

Aims of this study

No meta-analysis since NICE[18] has compiled all RCTs in which two psychological interventions for psychosis are compared and pooled these as comparison conditions.[2] The limitations of the NICE meta-analyses plus many new studies having been published since mean that a further comparative meta-analysis is warranted. A tendency of previous meta-analyses has been to examine only CBT versus active treatments while we considered all intervention types with sufficient studies. This study aims to improve understanding of which therapy is most efficacious and for which particular symptoms.

Methods

Search strategy

A systematic literature search conducted in May 2013 identified 5910 potential articles for inclusion. The following databases were included in the search: PubMed (1539 abstracts); Embase (1016); PsychInfo (2128); and Cochrane Central Register of Controlled Trials (1227). Abstracts were identified by entering terms indicative of common psychological interventions for psychosis combined with search terms intended to identify all relevant psychotic disorders. MeSH terms, exploded terms and text words were employed. Reference lists of published meta-analyses were also examined..

Table 1. *Definitions of Psychological and Psychosocial Treatments of Psychosis*

	Definition	N_{st}	N_p
1.	1. *Befriending (BF):* Befriending refers to comparison conditions in which participants were assigned social support to match therapy hours provided in other conditions. Typically this consisted of friendly discussion or social activities with a supportive and empathic individual which were not directly related to symptoms. Discussion instead focused primarily upon neutral topics such as current affairs or hobbies and structured group activities may also have been provided for participants. Befriending has been suggested as an efficacious intervention in reducing symptoms of psychosis. [80,94]	11	400
2.	2. *Cognitive-behavioural therapy (CBT)*: CBT is a talking therapy which aims to promote awareness of the links between thoughts, behaviours and feelings to help implement changes in symptoms and functioning. Therapists focus on the modification of dysfunctional thoughts and self-defeating behaviours which perpetuate symptoms or suffering. CBT targeted specifically at psychosis (CBTp) has been developed primarily since the 1990s and was originally focused on coping with symptoms.[83,84] whereas more recent CBTp has focused on challenging maladaptive cognitions via cognitive restructuring and a formulation-based approach.[64,89,95] We identified these as two main sub-types of CBT for the purposes of this meta-analysis: a) Coping Enhancement and b) Generic CBT.	22	706
3.	3. *Cognitive remediation (CR):* Cognitive deficits have been widely implicated as influential in the development and course of psychosis and cognitive deficits have therefore been suggested as worthy treatment targets.[96] CR refers to those interventions which target basic cognitive processes such as working memory, attention or executive function. This intervention is intended to improve these basic cognitive functions and may also be intended to improve various other aspects of functioning. Computer-based tasks are often the chosen method of implementing CR.	11	475
4.	4. *Psycho-education (PE):* Psycho-education refers to the provision of relevant information to a participant about their diagnosis with the aim of improving understanding and coping with their diagnosis. Various psycho-education methodologies have been developed for psychosis which go further than provision of basic information and therefore may involve development of coping strategies and role-playing. A group format is often utilised and there is often considerable diversity in what may be labelled "psycho-education," with this modality often being used as a comparator intervention for more standardised forms of intervention.	8	249
5.	5. *Social Skills Training (SST):* SST is a behavioural intervention based upon behavioural and social learning traditions in which participant's social functioning is targeted in order to improve their ability to perform in social situations, manage daily life tasks and reduce social distress. Importance is typically placed upon verbal and non-verbal communication alongside learning appropriate perception and responses to social cues. The intervention may also include training in independent living skills.	16	541
6.	*Supportive Counselling (SC):* Supportive counselling refers to non-directive talking therapy which may be based upon the work of Carl Rogers (1951)[97] or may simply be described in studies as a non-directive intervention in which the participant has an open forum to discuss their difficulties which will not be actively led or challenged by the therapist. SC was therefore defined as an intervention in which the common factors of psychotherapy were present without the specific techniques applied in other more directive therapies such as CBT. The opportunity to discuss problems with an empathic therapist in a healing setting may provide relief for the participant without focus on acquiring new skills or challenging cognitive distortions. SC is often used as a means of comparing other interventions against only the common factors of.[1]	17	529

Note. N_{st} = number of studies. N_p = number of participants who received each intervention.

Inclusion and exclusion of studies

We included trials that (a) were randomised; (b) included the comparison of at least two psychological interventions intended as therapeutic and aimed to improve psychiatric symptoms in psychosis; (c) included outcome measures intended to assess psychotic or psychiatric symptoms; (d) primarily included participants diagnosed with a psychotic disorder. Trials including mood disorders with psychotic features were only included when there were a minority of such patients.

Trials were excluded when (a) the comparison condition could not be deemed an active psychological intervention (e.g. attention controls, treatment-as-usual, waiting list); (b) participants were prodromal or ultra-high risk; (c) interventions were primarily aimed at medication adherence or compliance. Only articles in English or German were considered. Interventions were defined as described in Table 1. Two authors (D.T. and M.v.d.G.) categorised interventions into relevant comparisons and disagreements were resolved via discussion.

Quality assessment

To assess the methodological quality of the studies included, we used the first four criteria of the Cochrane Collaboration Risk of Bias Tool (sequence generation; allocation concealment; blinding of assessors; & incomplete outcome data) due to there being no clear indication that items 5 (selective outcome reporting) and 6 (other

sources of bias) influence validity.[19] The 3rd item (blinding of assessors) was adapted to be relevant to psychological intervention trials since it is impossible for these studies to employ a "double blind" design. The item was adapted to include only outcome assessors in masking procedures. Two authors (D.T. and E.K) assessed the risk of bias and disagreements were resolved via discussion.

Data extraction & selection of outcome measures

Data were extracted by the first author (D.T.) and checked for consistency by the 3rd author (E.K.). A spreadsheet piloted in a previous meta-analysis was used for data collection. Attempts were made to contact authors in cases of missing or unusable data and calculations of missing values were carried out in accordance to the Cochrane Handbook.[26]

Table 2 provides study characteristics. Statistical data were extracted for outcome measures relevant to psychotic or psychiatric symptoms.. In studies where multiple relevant outcome measures were used, data from all outcome measures were collected and combined as a mean effect size. Dichotomous outcome data were also considered in cases where symptom measures had been converted into dichotomous outcomes, such as clinical exacerbations.

Meta-analyses

Psychological interventions for psychosis were considered to qualify for inclusion in a separate meta-analysis when there were at least five eligible RCTs comparing that

intervention against another psychological intervention. The comparison group for each separate meta-analysis therefore became the pooled set of comparison interventions from these studies (e.g. CBT versus other interventions pooled). This resulted in meta-analyses for six intervention types. Separate sub-meta-analyses for positive, negative or general symptoms were undertaken when there were sufficient studies (≥5) assessing these outcomes.

The Comprehensive Meta-Analysis (CMA) version 2.2.021 software package was used for all analyses and calculations. For each individual meta-analysis, aggregated effect sizes indicating the pooled difference between the two groups were calculated at post-treatment using Hedges' *g*. Hedges' *g* provides a better effect estimate for small sample sizes than similar measures applied to continuous outcome variables such as Cohen's *d*.[27] This statistic was accompanied by a *p*-value with significance level set at 0.05 and a 95% confidence interval.

Heterogeneity

A chi-squared test provided a *Q* statistic to determine the presence of heterogeneity alongside an I^2 statistic as a description of the percentage of the variance in each meta-analysis that could be explained by heterogeneity between the studies rather than by chance. A value of 0% is indicative of no heterogeneity, while 25% indicates low heterogeneity, 50% moderate heterogeneity and 75% high heterogeneity.[28]

Additional analyses

Publication bias was assessed for primary outcomes in each of the six meta-analyses by examining funnel plots produced by the *CMA* software,[29] alongside using the trim and fill procedure to estimate the effect size after accounting for publication bias.[30] Egger's test of the intercept was conducted to quantify the bias shown by the funnel plots and to determine whether this was significant.

Direct comparisons were made between psychological interventions when there were at least 5 studies available comparing two specific treatments. Sub-group analyses were conducted for the intervention with the highest number of eligible studies (CBT). This included splitting CBT into two relevant sub-types to determine whether these had similar efficacy. Differential effects of group or individual format were investigated by entering intervention format (group or individual) as a moderator variable.

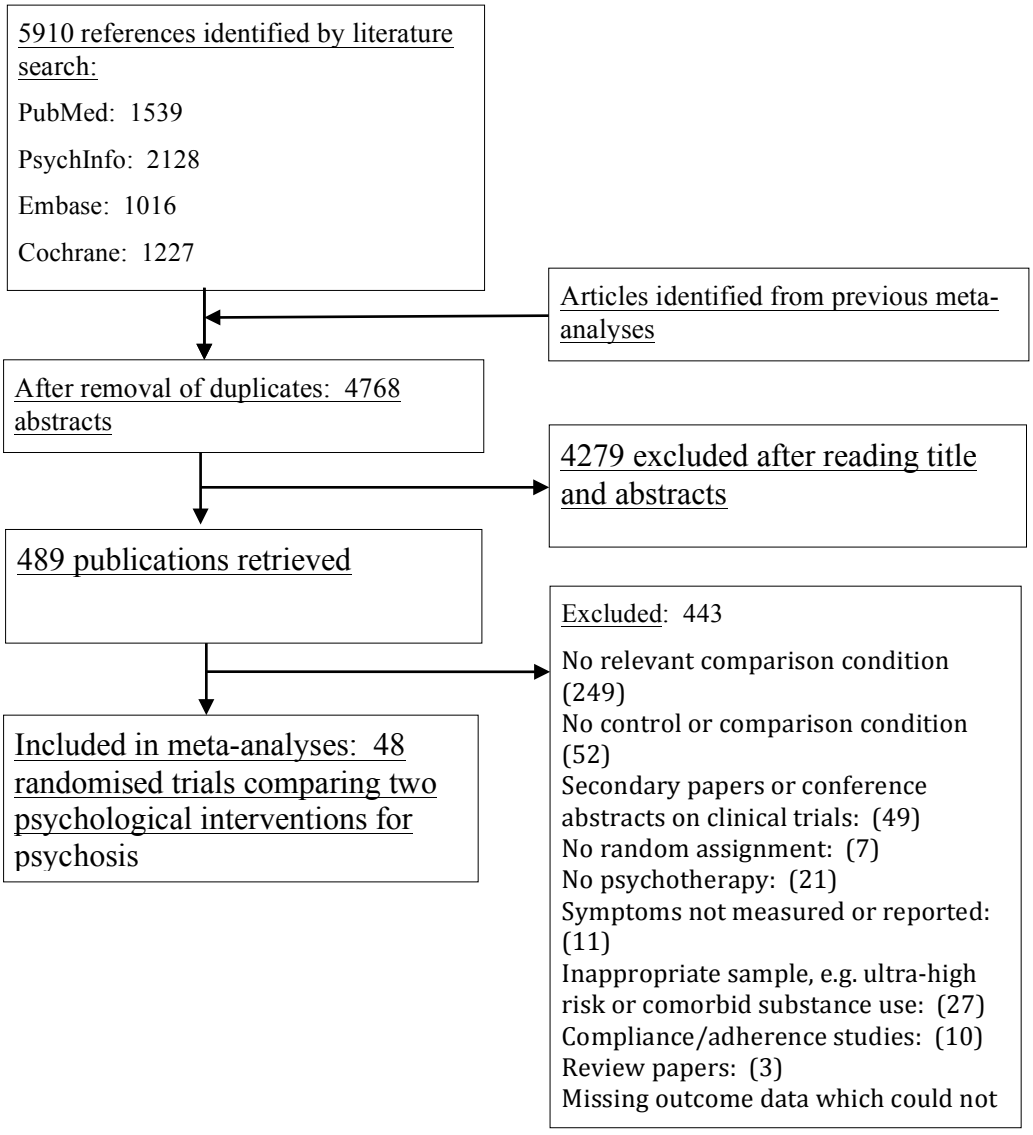
Researcher allegiance (RA) was examined for all studies using a tool adapted from a previous meta-analysis.[31] The tool is included in the supplementary materials. Two researchers independently rated studies and discussed agreement. Subgroup analyses for RA were conducted on robust significant findings which survived the sensitivity analyses for high risk of bias although this was not possible for all such findings due to limited studies being available.

Power calculation

It was expected that a limited number of studies would be available for certain

comparisons. Based upon the recommendations of Borenstein (2009),[32] power calculations were conducted to determine how many studies were required for sufficient statistical power to identify relevant effects. Previous meta-analyses identified small effect sizes (g = 0.1 or g = 0.2) in favour of specific interventions. Conservatively assuming a high-level of between-study variance, τ^2, statistical power of 0.80 and a significance level, α, of 0.05, we estimated that 22 studies with a mean of 30 participants in each intervention arm would be required to detect an effect size of g = 0.2. To detect an effect size of g = 0.1, it was estimated that 88 studies would be required.

Fig. 1. Flowchart of inclusion of studies



Results

Description of included studies

After removal of duplicates, 4768 titles and abstracts were examined resulting in 489 articles being retrieved for possible inclusion. Figure 1 provides the flow chart for

study inclusion. A total of 3295 participants participated in relevant comparisons of psychological interventions in the 48 included studies. Six common psychological intervention modalities were identified.

24 studies utilised group format while 21 studies used individual format. 3 studies used a combination of individual and group sessions. CBT had the highest proportion of studies using only individual format (77%) followed by SC (47%), BF (45%), CR (36%), PE (12.5&) and SST (6%). Length from baseline to post-treatment assessment ranged from 3 weeks to 104 weeks. Risk of bias varied among studies (0-4) and among intervention types. CBT had the highest proportion of studies assessed as having no bias risk (59%) followed by BF (45.5%), SC (41%) CR (36%), SST (12.5%) and PE (12.5%).

Table 2. *Selected characteristics of studies comparing psychological or psychosocial interventions for psychosis*

Study & publications	Country	Sample characteristics	Relevant comparisons & *N*	Symptom outcome measures	Format	Bias Risk (0-4)	Duration (weeks to PT)	Follow-up	Allegiance
Barretto *et al* 2009[33]	Brazil	DSM-IV Schizophrenia, 6 months clozapine treatment-resistant. Outpatients.	CBT (12) vs. BF (10)	CGI, BPRS, PANSS	Individual	2	21	6 months	CBT
Bechdolf *et al* 2004,[34] 2005,[35]	Germany	Schizophrenic or related disorder (ICD-10). Inpatients.	CBT (40) vs. PE (48)	PANSS	Group	0	8	6 months, 24 months	None
Bowie *et al* 2012[36]	Canada & USA	Schizophrenia or schizoaffective disorder. Outpatients.	SST (38) vs. CR (38)	PANSS	Group	1	12	24 weeks	None
Cather *et al* 2005[37]	USA	Schizophrenia or schizoaffective disorder. Outpatients	CBT (15) vs. PE (13)	PANSS, PSYRATS	Individual	1	16	N/A	CBT
Crawford *et al* 2012[38]	UK	Schizophrenia. Outpatients.	BF (140) vs. AT (140)	PANSS	Group	0	12	24 months	AT
Dobson *et al* 1995[39]	Canada	Schizophrenia DSM-III, Outpatients. Severe patients excluded.	SST (15) vs. BF 13)	PANSS	Group	3	11	3 months	None
Drury *et al* 1996,[40] 2000[41]	UK	Current functional psychosis, excluding bipolar, hypomania, organic syndrome, confusional states & drug/alcohol disorders	CBT (20) vs. BF (20)	PAS	Both	3	12	5 years	CBT
Durham *et al* 2003[42]	UK	Schizophrenia, Schizoaffective disorder or delusional disorder suffering positive symptoms. Outpatient & inpatient.	CBT (22) vs. SC (23)	PANSS, PSYRATS, GAS	Individual	0	39	3 months	CBT
Eack *et al* 2009[43]	USA	DSM-IV Schizophrenia or schizoaffective disorder. Early stages of illness. Outpatients.	CR (31) vs. PE (27)	Composite symptoms	Group	2	104	12 months	CR
Falloon *et al* 1982,[44] 1985[45]	UK	DSM-III schizophrenia from high EE families. Inpatients.	SC (18) vs. FI (18)	Symptom exacerbation, remission & target	Individual	3	39	24 months	FI
Farreny *et a*l 2012[46]	Spain	DSM-IV-TR Schizophrenia or Schizoaffective disorder. Over 2 years illness duration. Outpatients.	CR (34) vs. BF (28)	PANSS	Group	2	16	40 weeks	CR
Fries *et al* 2004[47]	Germany	ICD-10 Schizophrenia and schizoaffective, at least twice hospitalised. At least partial remission at baseline.	PE (23) vs. SC (17)	BPRS, SANS	Group	4	25	12 months	None
Garety *et al* 2008[48]	UK	Recently relapsed non-affective psychosis (ICD 10 F2 & DSM-IV), with carers. Positive symptoms.	CBT (27) vs. FI (28)	PANSS, PSYRATS, BDI, BAI	Individual	0	52	24 months	None
Haddock *et al* 1999[49]	UK	DSM-IV schizophrenia or schizoaffective disorder (< 5 years). Current acute ward admission for positive symptoms.	CBT (9) vs. SC (10)	BPRS	Individual	1	5	N/A	CBT
Haddock *et al* 2009[50]	UK	DSM-IV schizophrenia or schizoaffective disorder. History of violence. Current anti-psychotic medication & positive symptoms.	CBT (38) vs. BF (39)	PANSS, PSYRATS	Individual	0	26	12 months	CBT
Hayes *et al* 1995[51]	Australia	DSM-III-R schizophrenia. Non-current positive symptoms. From a range of services.	SST (23) vs. SC (22)	BPRS, SANS	Group	4	18	6 months	SST
Hogarty *et al*, 1986,[52] 1991[53]	USA	RDC schizophrenia or schizoaffective disorder. High EE family. Inpatients.	SST (23) vs. FI (23)	Symptom relapse	Individual	4	104	N/A	None
Hogarty *et al* 2004,[54] 2006[55]	USA	DSM-III-R or DSM-V schizophrenia or schizoaffective disorder. Outpatients	CR (67) vs. PE (54)	Composite symptoms	Group	3	52	24 months	CR

Table 2. *Continued*

Study & publications	Country	Sample characteristics	Relevant comparisons & *N*	Symptom outcome measures	Format	Bias Risk (0-4)	Duration (weeks to PT)	Follow-up	Allegiance
Horan *et al* 2009[56]	USA	DSM-IV schizophrenia or schizoaffective disorder. Clinically stable outpatients.	SST (17) vs. PE (17)	BPRS	Group	2	6	N/A	SST
Horan *et al* 2011[57]	USA	DSM-IV schizophrenia, schizoaffective disorder, delusional disorder or psychosis NOS (not secondary to substance disorder). Clinically stable outpatients.	SST (19) vs. CR (24)	BPRS	Group	2	12	N/A	SST
Jackson *et al* 2007[58]	Australia	First episode psychosis including schizophrenia, schizophreniform, schizoaffective, bipolar, delusional disorder & psychosis NOS. Inpatient & outpatient.	CBT (31) vs. BF (31)	BPRS, SANS	Individual	2	12	12 months	CBT
Keefe *et al* 2012[59]	USA	Chronic DSM-IV schizophrenia, moderate severity	CR (27) vs. BF (26)	PANSS	Group	1	12	N/A	CR
Klingberg *et al* 2011,[60] 2012[61]	Germany	DSM-IV schizophrenia. At least one negative symptom. Positive symptoms excluded. Outpatients.	CBT (99) vs. CR (99)	PANSS, SANS, CDSS, CGI, SCL-90	Individual	0	52	N/A	CBT
Lecomte *et al* 2008,[62] 2012[63]	Canada	Early psychosis (< 2 years). Current psychotic symptoms. Stabilized outpatients.	CBT (48) vs. SST (54)	BPRS	Group	0	13	6 months, 12 months	None
Lewis *et al* 2002[64]	UK	1st or 2nd admission DSM-IV schizophrenia, schizophreniform, schizoaffective or delusional disorder. Inpatients & outpatients.	CBT (101) vs. SC (106)	PANSS, PSYRATS	Individual	0	5	18 months	CBT
Liberman *et al* 1998[65]	USA	Persistent & unremitting schizophrenia. Outpatients.	SST (42) vs. OT (42)	BSI, GAS, BPRS	Both	3	26	24 months	None
Lukoff *et al* 1986[66]	USA	DSM-III schizophrenia. Inpatients.	SST (14) vs. PE (14)	PAS	Group	2	10	N/A	None
Marder *et al* 1996[67]	USA	DSM-III schizophrenia. At least 2 acute episodes or 2 years psychotic symptoms. Male outpatients.	SST (13) vs. SC (14)	BPRS Exacerbations	Group	3	104	N/A	None
Moritz *et al* 2011[68]	Germany	Broad psychotic inpatients who met criteria for schizophrenifom disorder.	CBT (24) vs. CR (24)	PANSS, PSYRATS	Both	0	4	N/A	CBT
Ng *et al* 2007[69]	Hong Kong	DSM-IV schizophrenia. Inpatients.	SST (18) vs. SC (18)	BPRS, SANS	Group	0	8	6 months	SST
O'Connor *et al* 2007[70]	Canada	DSM-IV delusional disorder. Stabilised medication.	CBT (12) vs. SC (12)	MADS, BAI, BDI	Individual	3	24	N/A	CBT
Ojeda *et al* 2012[71]	Spain	DSM-IV schizophrenia. Treatment resistant inpatients.	CR (47) vs. OT (46)	PANSS	Individual	2	13	N/A	CR
Patterson *et al* 2005[72]	USA	DSM-IV schizophrenia or schizophreniform. Older chronic Latino inpatients.	SST (21) vs. SC (8)	PANSS	Group	3	26	12 months	SST
Patterson *et al* 2006[73]	USA	DSM-IV schizophrenia or schizophreniform. Older chronic inpatients.	SST (124) vs. SC (116)	PANSS, HAM-D	Group	2	26	N/A	SST
Penades *et al* 2006,[74] 2010[75]	Spain	DSM-IV schizophrenia. Chronic. Prevalence of negative symptoms & cognitive impairment.	CBT (20) vs. CR (20)	PANSS	Individual	0	17	6 months	CR
Penn *et al* 2009[76]	USA	Schizophrenia or schizoaffective disorder & current auditory hallucinations. Outpatients.	CBT (32) vs. SC (33)	PANNS, BAVQ, PSYRATS	Group	0	12	3 months, 12 months	CBT

Table 2. *Continued*

Study & publications	Country	Sample characteristics	Relevant comparisons & *N*	Symptom outcome measures	Format	Bias Risk (0-4)	Duration (weeks to PT)	Follow-up	Allegiance
Pinto *et al* 1999[77]	Italy	DSM-IV schizophrenia. Treatment-refractory outpatients.	CBT (19) vs. SC (18)	BPRS, SAPS, SANS	Individual	3	26	N/A	CBT
Rodewald *et al* 2011[78]	Switzerland	DSM schizophrenia or schizoaffective disorder. Inpatients.	CR (44) vs. PST (45)	PANSS	Group	3	3	N/A	PST
Rohricht *et al* 2006[79]	UK	DSM-IV schizophrenia. At least 2 episodes. Outpatients.	SC (21) vs. BP (24)	PANSS	Group	0	10	4 months	BP
Sensky *et al* 2000[80] & Turkington *et al* 2008[81]	UK	DSM-IV & ICD-10 schizophrenia. Treatment resistant. Outpatients.	CBT (46) vs. BF (44)	CPRS, SANS, MADRS	Individual	0	39	9 months, 5 years	CBT
Shawyer *et al* 2012[82]	Australia	DSM-IV schizophrenia or related condition including command hallucinations in previous 6 months. Outpatients.	CBT (21) vs. BF (22)	PANSS, PSYRATS, CH	Individual	0	15	6 months	CBT
Tarrier *et al* 1993[83]	UK	DSM-III-R schizophrenia. Treatment resistant.	CBT (15) vs. PST (12)	BPRS, PSE	Individual	3	6	6 months	CBT
Tarrier *et al* 1998,[84] 1999,[85] 2000,[86] 2001[87]	UK	Schizophrenia via PSE. Acute-ward inpatients.	CBT (19) vs. SC (19)	BPRS, SANS	Individual	0	13	12 months	CBT
Tas *et al* 2012[88]	Turkey/Germany	DSM-IV schizophrenia. Clinically stable outpatients.	SST (22) vs. BF (27)	PANSS	Group	0	16	N/A	SST
Valmaggia *et al* 2005[89]	UK/ Netherlands	DSM-IV schizophrenia including residual delusions or auditory hallucinations. Medication resistant.	CBT (36) vs. SC (26)	PANSS, PSYRATS	Individual	0	22	6 months	CBT
Wykes *et al* 1999,[90] 2003[91]	UK	DSM-IV schizophrenia, over 2 years contact with services. Outpatients & inpatients	CR (20) vs. OT (16)	BPRS	Individual	0	13	6 months	CR
Xiang *et al* 2006[92]	China	DSM-IV schizophrenia. Clinically stable outpatients.	SST (48) vs. SC (48)	PANSS	Group	1	9	6 months	SST
Xiang *et al* 2007[93]	China	DSM-IV schizophrenia. Clinically stable inpatients & outpatients.	SST (50) vs. PE (53)	PANSS	Group	2	4	6 months, 12 months	SST

AT, Art Therapy; BAI, Beck Anxiety Inventory; BAVQ, Beliefs About Voices Questionnaire; BDI, Beck Depression Inventory. BF, Befriending; BPRS, Brief Psychiatric Rating Scale; CBT, Cognitive-Behavioural Therapy; CDSS, Calgary Depression Scale for Schizophrenia; CGI, Clinical Global Impression; CH, Command Hallucinations; CPRS, Comprehensive Psychopathological Rating Scale; CR, Cognitive Remediation; FI, Family Intervention; GAS, Global Assessment Scale; Ham-D, Hamilton Depression Rating Scale; MADRS, Montgomery-Asberg Depression Rating Scale; MADS, Maudsley Assessment of Delusions Schedule; *N,* Number of participants in each treatment group; OT, Occupational Therapy; PANSS, Positive and Negative Symptoms Scale; PE, Psycho-education; PSE, Present State Examination; PSYRATS, Psychotic Symptom Rating Scale; PT, Post-treatment; SCL-90, PST, Problem Solving Therapy; SANS, Scale for Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms; SC, Supportive Counselling; Symptom Checklist 90; SST, Social Skills Training;

Differences Between Psychological Interventions versus Other Interventions Pooled at Post-treatment

The results of the six meta-analyses comparing psychological interventions against other interventions pooled are presented in Table 3. Separate meta-analyses were conducted for psychosis symptom groupings. Within each symptom grouping, sensitivity analyses were conducted for varying levels of bias risk. Sensitivity analyses were only conducted when a minimum of 4 studies were available for that comparison.

Befriending was less efficacious for all symptom outcomes measures pooled compared to other therapies pooled (g = -0.366, p < .05*)*. This effect was robust when removing studies with high risk of bias (g = -0.279, p < .05*),* but lost significance when excluding studies with low risk and no risk of bias. Removing the low risk and no risk of bias studies also limited power of this comparison. 7 comparisons of befriending against other interventions pooled showed moderate heterogeneity while 2 comparisons showed low heterogeneity.

Cognitive behavioural therapy was more efficacious compared to other interventions pooled for all symptom outcomes measures pooled (g = 0.161, p < .05). This effect was robust when removing studies with a high risk of bias (g = 0.118, p < .05) but lost significance when excluding studies with low risk and no risk of bias. For positive symptoms outcome measures, CBT was more efficacious (g = 0.162, p < .05). This effect was robust in all 3 sensitivity analyses when sequentially removing studies with

high risk (g = 0.144, p < .05), low risk (g = 0.149, p < .05) and no risk of bias (g = 0.137, p < .05). All comparisons of CBT versus other interventions pooled showed no heterogeneity or low heterogeneity.

Social skills training was more efficacious compared to other interventions pooled for negative symptoms (g = 0.267, p < .05). This finding was robust when removing studies with high risk of bias (g = 0.317, p < .05) and low risk of bias (g = 0.563, p < .05). Only one SST study suggested no risk of bias therefore it was not possible to run a sensitivity analysis for no risk of bias. SST was more efficacious for all symptom measures pooled when excluding studies with high risk of bias (g = 0.187, p < .05) but this comparison lost significance when including all studies or when excluding studies with low bias risk. Again there were not enough studies available for a comparison including only studies with no bias risk. Heterogeneity among comparisons of SST to other interventions pooled varied with 4 comparisons showing moderate heterogeneity.

Cognitive remediation was more efficacious than other interventions pooled for all symptoms in the excluding high risk of bias sensitivity analysis (g = 0.202, p < .05), but was not shown as significantly more efficacious in any other comparisons. Heterogeneity varied among comparisons for CR with 2 comparisons showing moderate heterogeneity.

Table 3. *Effect sizes of psychological interventions vs. other interventions pooled*

	N	*g*	95% CI	*Z*	Q-value	I^2 (%)
Befriending vs. all other therapies						
All symptoms						
all eligible studies	11	-0.37*	-0.60, -1.33	-3.08	21.24*	52.93
excluding high risk of bias (≥3)	9	-0.28*	-0.51, -0.05	-2.39	14.84	46.08
excluding low risk of bias (≥2)	6	-0.22	-0.50, 0.06	-1.56	10.78	53.61
excluding any risk of bias (≥1)	5	-0.20	-0.52, 0.11	-1.27	10.04*	60.17
Positive symptoms						
all eligible studies/excluding high risk (≥3)	6	-0.14	-0.41, 0.13	-0.10	8.81	43.23
excluding any risk of bias (≥1)	4	-0.17	-0.56, 0.22	-0.86	8.50*	64.72
Negative symptoms						
including all eligible studies	9	-0.22	-0.41, 0.04	-1.69	18.12*	55.85
excluding high risk of bias (≥3)	8	-0.18	-0.45, 0.80	-1.37	15.93*	56.67
excluding low (≥2) & any risk of bias (≥1)	5	-0.10	-0.44, 0.24	-0.56	11.94*	66.49
General Symptoms (PANSS)	5	-0.24	-0.61, 0.13	-1.26	10.42*	61.61
Cognitive behavioural therapy vs. all other therapies						
All symptoms						
all eligible studies	22	0.16*	0.04, 0.28	2.64	23.91	12.18
excluding high risk of bias (≥3)	18	0.12*	0.00, 0.23	2.01	14.98	0.00
excluding low risk of bias (≥2)	15	0.10	-0.03, 0.22	1.53	11.30	0.00
excluding any risk of bias (≥1)	13	0.11	-0.02, 0.24	1.72	9.16	0.00
Positive symptoms						
all eligible studies	17	0.16*	0.04, 0.28	2.67	11.17	0.00
excluding high risk of bias (≥3)	15	0.14*	0.02, 0.27	2.32	9.42	0.00
excluding low risk of bias (≥2)	12	0.15*	0.02, 0.28	2.18	9.19	0.00
excluding any risk of bias (≥1)	11	0.14*	0.00, 0.27	1.97	7.44	0.00
Negative symptoms						
all eligible studies	15	0.04	-0.09, 0.16	0.55	13.94	0.00
excluding high risk of bias (≥3)	14	0.02	-0.10, 0.15	0.36	13.04	0.34
excluding low risk of bias (≥2)	11	-0.00	-0.15, 0.14	-0.06	8.13	0.00
excluding any risk of bias (≥1)	10	-0.01	-0.15, 0.14	-0.06	8.14	0.00
General Symptoms (PANSS)						
all eligible studies/low bias risk (≥2)	8	0.10	-0.13, 0.32	0.86	12.103	42.16
excluding any risk of bias (≥1)	7	0.05	-0.14, 0.24	0.54	7.60	21.06
Cognitive remediation vs. all other therapies						
All symptoms						
all eligible studies	11	0.13	-0.05, 0.31	1.46	14.63	31.69
excluding high risk of bias (≥3)	10	0.20*	0.01, 0.39	2.06	11.34	20.65
excluding low risk of bias (≥2)	6	0.14	-0.05, 0.33	1.41	3.21	0.00
excluding any risk of bias (≥1)	4	0.12	-0.11, 0.34	1.02	2.49	0.00
Positive symptoms						
all eligible studies	6	0.16	-0.17, 0.49	0.97	14.11*	64.56
excluding low risk of bias (≥2)	4	0.29	-0.06, 0.64	1.63	6.61	54.59
Negative symptoms						
all eligible studies	6	-0.14	-0.39, 0.06	-1.12	8.47	40.99
excluding high (≥3) & low (≥2) risk of bias	4	-0.08	-0.38, 0.22	-0.50	5.23	42.59
Psycho-education vs. all other therapies						
All symptoms						
all eligible studies	8	0.10	-0.27, 0.11	-0.80	8.02	12.66
excluding high risk of bias (≥3)	6	-0.13	-0.41, 0.14	0.94	7.43	32.67
Positive symptoms						
all eligible studies/excluding high risk (≥3)	4	0.19	-0.06, 0.44	1.50	1.70	0.00
Negative symptoms						
all eligible studies	5	0.02	-0.22, 0.25	0.13	3.06	0.00
excluding high risk of bias (≥3)	4	0.03	-0.22, 0.28	0.23	2.97	0.00

Table 3. *Continued*

	N	*g*	95% CI	*Z*	Q-value	I^2 (%)
Social skills training vs. all other therapies						
All symptoms						
all eligible studies	16	0.06	-0.17, 0.28	0.49	45.33*	66.91
excluding high risk of bias (≥3)	10	0.19*	0.02, 0.36	2.15	8.72	0.00
excluding low risk of bias (≥2)	4	0.34	-0.02, 0.70	1.87	5.47	45.13
Positive symptoms						
including all eligible studies	7	0.09	-0.23, 0.41	0.56	16.44*	63.51
excluding high risk of bias (≥3)	6	0.09	-0.26, 0.45	0.50	16.41*	69.53
Negative symptoms						
including all eligible studies	9	0.27*	0.01, 0.53	2.01	17.33*	53.83
excluding high risk of bias (≥3)	7	0.32*	0.07, 0.56	2.55	10.25	41.47
excluding low risk of bias (≥2)	4	0.56*	0.31, 0.82	4.29	1.99	0.00
Supportive counselling vs. all other therapies						
All symptoms						
all eligible studies	17	0.00	-0.21, 0.22	0.04	40.31*	60.31
excluding high risk of bias (≥3)	10	0.01	-0.30, 0.32	0.06	32.97	72.70
excluding low risk of bias (≥2)	9	-0.12	-0.30, 0.05	-1.37	6.18	0.00
excluding any risk of bias (≥1)	7	-0.08	-0.28, 0.11	-0.83	1.74	0.00
Positive symptoms						
all eligible studies	8	-0.14	-0.36 , 0.09	-1.12	10.28	31.90
excluding high (≥3) & low (≥2) risk of bias	6	-0.05	-0.25, 0.15	-0.51	5.33	6.27
excluding any risk of bias (≥1)	5	-0.02	-0.27, 0.23	-0.17	5.00	19.98
Negative symptoms						
all eligible studies	9	-0.12	-0.41, 0.17	-0.83	18.55*	56.87
excluding high (≥3) & low (≥2) risk of bias	6	-0.21	-0.57, 0.15	-1.13	13.34*	62.52
excluding any risk of bias (≥1)	5	-0.09	-0.45, 0.27	-0.50	7.74	48.30

Note. All comparisons were using random model. Risk of bias analyses were only included in instances where at least 4 studies were available. *p<0.05.

Direct comparisons of Two Types of Psychological Intervention for Psychosis

The results of direct comparisons between interventions are presented in Table 4. Limited comparisons were possible since few studies were available. CBT was more efficacious than befriending for all symptom measures pooled (g = 0.419, p < .05). CBT was also more efficacious than SC for positive symptoms (g = 0.226, p < .05).

Meta-analyses for Cognitive-Behavioural Therapy subtypes: Coping enhancement vs. Generic CBT & Group vs. Individual

To examine whether there were differences between CBT subtypes (coping enhancement and generic CBT), subgroup analyses were conducted. Results included in Table 4 suggested that subtype B (generic CBT) was more efficacious for all symptom measures pooled and for positive symptoms. The between-group comparisons for group versus individual format were not significant but this comparison was hampered by low power. No subgroup analyses showed significant heterogeneity.

Researcher allegiance

Sensitivity analyses for researcher allegiance were conducted for the robust findings of CBT on positive symptoms and SST on negative symptoms. The effect of CBT on positive symptoms became non-significant in both sensitivity analyses although only 3 studies could be included in the *No allegiance* group resulting in low power. The

effect of SST on negative symptoms remained significant in the sensitivity analyses although comparison was not possible for the stricter risk of bias categories due to limited studies being available.

Publication bias

Funnel plots and the trim and fill procedure suggested the presence of publication bias in some comparisons of the CR and SST meta-analyses. The funnel plot for all symptoms pooled in the CR meta-analysis suggested 3 studies with negative findings remained unpublished. Using the trim and fill procedure to investigate the significant effect shown for overall symptoms without high risk of bias studies (g = 0.20), 2 studies were trimmed meaning the effect size was reduced to g = 0.10 (-0.12, 0.32). For the SST overall symptoms meta-analyses, the funnel plot suggested 7 studies had not been published when all studies were included. However, when examining the funnel plot and trim and fill procedure for the only significant finding within this meta-analysis there was no suggestion of publication bias. Similarly, there was no suggestion of publication bias for the significant effects of SST found for negative symptoms.

Table 4: *Direct comparisons of interventions, segregation of CBT subtypes, subgroup analyses for therapy format and subgroup analyses for researcher allegiance in robust significant findings*

	N	*g*	95% CI	*Z*	Q-value	I^2 *(%)*	p^a
Direct comparisons of two interventions							
Cognitive-behavioural therapy vs. befriending							
All symptoms (R)	6	0.42*	0.15, 0.69	3.02	7.00	28.61	
Cognitive-behavioural therapy vs. supportive counselling							
All symptoms (F/R)	8	0.10	-0.10, 0.30	0.99	6.09	0.00	
Positive symptoms (F/R)	6	0.23*	0.01, 0.44	2.07	5.00	0.04	
Social skills training vs. supportive counselling							
All symptoms (R)	6	-0.07	-0.54, 0.40	-0.29	26.27	80.96	
Cognitive behavioural therapy sub-types vs. other interventions pooled							
Subtype A: Coping							
All symptoms (F/R)	6	-0.01	-0.19, 0.18	-0.08	1.83	0.00	
Negative Symptoms (F/R)	5	-0.04	-0.23, 0.15	-0.41	2.45	0.00	
Subtype B: Challenging							
All symptoms (R)	16	0.22*	0.08, 0.37	2.97	16.96	11.58	
Positive symptoms (F/R)	13	0.17*	0.03, 0.32	2.28	10.66	0.00	
Negative symptoms (R)	10	0.01	-0.08, 0.28	1.07	10.44	13.76	
Subgroup analyses of cognitive-behavioural therapy: group vs. individual format †[1]							
All symptoms							
Individual (R)	18	0.18*	0.05, 0.32	2.66	19.93	14.9	
Group (R)	3	0.00	-0.26, 0.27	0.03	1.08	0.00	
Overall (R)	21	0.13	-0.02, 0.29	1.64	22.45	10.93	0.24
Positive symptoms							
Individual (F/R)	13	0.16*	0.02, 0.30	2.17	9.04	0.00	
Group (F/R)	3	0.12	-0.13, 0.36	0.93	0.39	0.00	
Overall (F/R)	16	0.15*	0.01, 0.34	2.04	9.50	0.00	0.80
Negative Symptoms							
Individual (F/R)	12	0.09	-0.06, 0.23	1.15	12.05	8.68	
Group (F/R)	3	-0.11	-0.35, 0.14	-0.85	0.16	0.00	
Overall (F/R)	15	0.02	-0.17, 0.20	0.17	13.939	0.00	0.19
Subgroup analyses of researcher allegiance for comparisons with robust significant effects							

CBT vs. all other therapies †[2]							
Positive symptoms (F/M)							
excluding high risk of bias (≥3)							
No allegiance	3	0.10	-0.15, 0.35	0.80	0.24	0.00	0.42
Allegiance for CBT	11	0.17	0.01, 0.32	2.40	5.35	0.00	
excluding low risk of bias (≥2)							
No allegiance	2	0.08	-0.25, 0.40	0.50	0.21	0.00	0.60
Allegiance for CBT	9	0.18	0.03, 0.33	2.33	5.07	0.00	
excluding any risk of bias (≥1)							
No allegiance	2	0.08	-0.25, 0.40	0.50	0.21	0.00	0.58
Allegiance for CBT	8	0.19	0.03, 0.34	2.36	4.96	0.00	
SST vs. all other therapies							
Negative symptoms (M)							
including all eligible studies							
No allegiance	3	0.37	0.04, 0.7	2.20	2.30	13.27	0.55
Allegiance for SST	6	0.21	-0.21, 0.62	0.98	15.50	67.7	
excluding high risk of bias (≥3)							
No allegiance	2	0.30	-0.10, 0.71	1.48	1.51	33.82	0.83
Allegiance for SST	6	0.36	0.04, 0.69	2.19	8.97	44.25	

(R): Random effects model. (M): Mixed effects model (F/M): Mixed model and fixed model identical (F/R): Fixed and random effects model identical. *g*: Hedges' *g*. *N*: Number of comparisons. Z: Z-score. P^a: *P*-values of the difference between effect size of the subgroups

†[1] Excluding one study which used both group and individual format

†[2] Excluding one study with alliance against CBT

Discussion

This series of meta-analyses comparing psychological interventions for psychosis found significant differences in their relative efficacy for the reduction of psychotic symptoms. While some of these differences lost significance when sensitivity analyses were conducted for risk of bias, others were more robust. CBT showed a small but robust superiority in reducing positive symptoms while SST showed a small but relatively robust superiority in reducing negative symptoms. Befriending was shown as less efficacious than other interventions in reducing overall symptoms, however this was not robust when the more stringent sensitivity analyses for risk of bias were conducted. Similarly, significant effects suggesting benefits of CBT, SST and CR for all symptom measures pooled were not significant after risk of bias sensitivity analyses. It should be noted that the more robust sensitivity analyses resulted in statistical power dropping well below 0.80. Heterogeneity did not appear as a significant problem in the CBT meta-analyses while some comparisons for the other intervention modalities did show moderate to high heterogeneity, including SST. Sensitivity analyses for researcher allegiance resulted in the effect of CBT on positive symptoms losing significance while this was not the case for the effect of SST on negative symptoms. Researcher allegiance comparisons were hampered by very low power and it should also be noted that no significant differences in effect sizes were found when comparing studies for CBT and SST with allegiance against those with no allegiance.

CBT also showed superiority when compared directly to befriending for all symptoms and when compared to supportive counselling for positive symptoms. The *generic CBT*

subtype appeared more efficacious in reducing overall symptoms and positive symptoms.

With respect to the much discussed "Dodo Bird Verdict,"[1] this study provides evidence which could both support and contradict the statement. The differences shown between interventions are small in terms of clinical significance. This may suggest that the major therapeutic effects of interventions occur via common factors. However, the pattern of differences in efficacy are consistent with the specific aims of the interventions. CBT appears most successful in reducing positive symptoms, consistent with the rationale of challenging positive symptoms via a formulation-based approach and cognitive restructuring.[89,98] Similarly, SST appeared most suitable for reducing negative symptoms.[51,99] These findings provide potential evidence for the role of specific factors as at least partially influential in determining treatment outcome. When we consider that the effects of common factors are already accounted for in the treatment comparisons and that a high proportion of the participants also receive pharmacotherapy, findings suggesting that specific factors influence their targeted symptoms are of interest. The design of this study does not however allow us to control completely for other potential influences on outcome which may explain the effect we are attributing to specific factors. An attempt was made to control for researcher allegiance but only limited comparisons were possible due primarily to few studies showing no allegiance.

We are aware that CBT is uniform in its assumption that negative emotions and behavioural problems are the result of the appraisal and interpretation of antecedent

events. By changing appraisal and interpretation of events and stimuli, the emotions and the behaviour will change. However, there are variants within CBT that differ via more stress on cognitions or on behavioural experiments. We have the impression that variants in CBT are not typically reflected in results, although the meta-analysis by Wykes *et al* (2008)[11] found a trend for larger effect-sizes in more behavioural CBT. Comparisons could be made to antipsychotic medication where almost all brands target dopamine D2 receptors. Although the compounds are slightly different from each other, they have about the same efficacy.[100] A recent development is that CBT using the same technique is becoming more focused. For example, there are protocols in development for command hallucinations[101] and negative symptoms.[102, 103] Preliminary results show larger effect-sizes for more focused applications compared to generic CBT for psychosis.

There are various limitations of this study which impact the extent to which robust conclusions can be drawn from results. The majority of comparisons had low statistical power (<0.80)). Without satisfactory power there is a high risk of Type II errors. A further limitation of any meta-analysis categorising RCTs into groups by intervention type is that such decisions involve a degree of subjectivity. Attempts were made to address this by having two researchers agree on categorisation. There was controversy following the Lynch *et al* (2009) CBT meta-analysis regarding study selection.[22-24, 99] The risk of bias procedure applied in our meta-analysis addresses the issues raised about inclusion since all studies other than one excluded in the Lynch meta-analysis were excluded in the most stringent sensitivity analysis. For the aims of this meta-analysis there did not appear to be any reason to exclude this study.[73]

Another limitation concerns our focus on positive, negative and general symptoms. While CBT, SC and BF are targeted for symptom reduction, PE, SST and CR only indirectly target symptoms. PE often intends improve medication adherence with secondary symptom improvement and although the effects on symptoms were not significantly different from all other interventions, this does not mean that PE was not able to improve adherence. Similarly, CR targets the improvement of cognitive functioning and the absence of an effect on symptoms does not mean that there was no improvement in cognitive functioning. Those effects are beyond the scope of the meta-analyses we present and are not reported. It was also beyond the scope of this study to consider the possibility of patients with better prognosis being channelled into a particular treatment, interaction with pharmacotherapies and diagnostic heterogeneity among samples since information on these domains was not reliably available.

There was considerable variety in the quality of studies as assessed by the risk of bias procedure and there were marked differences in quality between specific intervention types. CBT had the highest proportion of studies assessed as having no risk of bias. SST had the lowest proportion. It is important that future studies on the relative efficacy of SST address these issues. Research should continue to compare psychological interventions for psychosis in order that power can improve in meta-analyses. It is essential that comparative RCTs minimise bias risk and that the issue of researcher allegiance is addressed. Meta-analytic studies must also answer related questions about psychosis interventions, such as predictors of treatment outcome and dropout. This includes individual participant data (IPD) meta-analyses in which the

authors of this paper are currently involved. Future research may also focus upon dismantling studies, which provide insight into the influence of common and specific factors. Future development of treatment plans may take into account the effects of specific factors on the specific symptom areas and integrate these to optimise both positive and negative symptom reduction. In conclusion, although the differences shown between interventions for psychosis by this meta-analysis are small, the relatively robust nature of these differences and the pattern by which differences occur has implications for the continued clinical implementation, design and improvement of psychosocial therapies for psychosis.

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Chapter 3

A network meta-analysis of psychological interventions for schizophrenia and psychosis: impact on symptoms

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Abstract

Background: Evidence for the effectiveness of psychological interventions for schizophrenia/psychosis is growing, however there is no consensus on the psychological intervention most likely to reduce symptoms.

Methods: A network meta-analysis was conducted to identify all randomised controlled trials (RCTs) of psychological interventions for adults with schizophrenia/psychosis. A systematic review of the literature using MEDLINE, PsycINFO, EMBASE and CENTRAL led to an analysis of 90 RCTs with 8,440 randomised participants across 24 psychological intervention, and control groups. Psychological interventions were categorised and rated for treatment fidelity and risk of bias. Data for total symptoms were extracted and network meta-analysis, using a frequentist approach, was undertaken using Stata SE v15 to compare the direct and indirect evidence for the effectiveness of each psychological intervention.

Findings: Psychological interventions were more likely to reduce symptoms than control groups, and one intervention, mindfulness-based psychoeducation, was consistently ranked as most likely to reduce total symptoms. Subgroup analyses identified differential effectiveness in different settings and for different subgroups.

Interpretation: Mindfulness-based psychoeducation was consistently ranked as most likely to reduce symptoms; however all studies were based in China. More RCTs in a

variety of cultural contexts would help to elucidate whether these findings generalise internationally. A number of psychological interventions could potentially be more effective than interventions recommended by NICE guidelines, such as CBT and family therapy, and additional RCTs and meta-analyses are needed to generate more conclusive evidence in this regard. Cognitive remediation and social skills training were differentially effective in different subgroup analyses.

Keywords; psychological intervention, network meta-analysis, treatment, psychotherapy

Introduction

Schizophrenia is a major psychiatric syndrome with a diverse array of potential symptoms. Antipsychotic medication has been the primary treatment option however this carries the risk of adverse effects which require extensive, and expensive, monitoring. Patient choice, whether for or against medication, has been recognised as crucial in clinical decision-making, as it impacts both adherence to, and efficacy of, interventions.[1] Evidence based information is essential to support this.[2]

There is evidence to support psychological models of the mechanisms that contribute to the emergence and maintenance of distress and disability associated with schizophrenia. These include the mediating impacts of attachment style and negative cognitive schema on the likelihood of developing psychotic symptoms after experiencing childhood trauma[3,4] as well as emerging evidence supporting cognitive and emotion based models of schizophrenia.[5] UK National Institute for Clinical Excellence (NICE)[6] guidelines indicate that psychological intervention should be included at all stages of intervention for schizophrenia or psychosis as follows: family intervention and cognitive behaviour therapy (CBT) alongside antipsychotic medication as part of early intervention for first episode psychosis, for acute exacerbation, or reoccurrence. Art therapy is recommended for people with primarily negative symptoms, whereas counselling, supportive psychotherapy and social skills training are contraindicated.[6] However, it has been

recognised that social skills training may be beneficial for negative symptoms.[7] Psychoanalytic and psychodynamic principles are cited as useful in understanding experiences in the early post-acute period, while CBT and family therapy are both recommended for people with active symptoms, persistent symptoms, and when people are 'in remission.'[6]

Intervention-specific meta-analyses are available (for example[8]) and a few direct comparisons have been carried out.[9,10] Since registration of the protocol of this review, a network meta-analysis of psychological interventions has been published that identifies that CBT may be effective in reducing positive symptoms.[11] A comprehensive statistical analysis of all available evidence is needed however to identify the interventions that are most likely to be effective for total symptoms- and this is not currently available. Network meta-analysis allows for comparison across a whole network of psychological interventions that have not been compared in real-life, using both direct and indirect evidence from randomised controlled trials (RCTs).[12]

In a resource-scarce environment, it is essential that evidence about the most appropriate and effective interventions be available to guide service-provision and clinical decision-making. This study aimed to provide this evidence synthesis, starting with total symptoms. It is acknowledged however that symptom reduction is often not the primary aim of psychological interventions. Interventions include those considered beneficial by NICE[6] and British Psychological Society (BPS) guidelines.[13] This network meta-analysis aimed to address two questions: "What is the effect of psychological interventions on total symptoms scores in psychosis?" and "Which psychological interventions are most likely to reduce symptoms?"

Materials and methods

A systematic review of the literature was followed by a network meta-analysis of psychological interventions for schizophrenia/psychosis. The protocol was initially based on Leucht et al's complementary network meta-analysis for antipsychotics,[14] and adjusted where necessary.

Study Pre-registration

This project was pre-registered in 2016 on Prospero (see Appendix 1 or https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=32806). Changes made subsequent to protocol registration are identified in Appendix 2.

Search and Selection

Searches of MEDLINE, PsycINFO, EMBASE and CENTRAL were conducted using search terms presented in Appendix 3, and briefly summarised below. Initial title screening was completed by one author (EMG) using EndNote Web. Two authors (EMG & GD) independently completed the abstract and full text screening using Covidence software, and discrepancies were resolved through discussion with arbitration performed by a 3rd author (PH). There were no language or time period restrictions for the initial search as per the protocol; however only RCTs published in English up to the end of 2016 were included in this analysis.

Network meta-analysis depends on an assumption of transitivity- all participants could in theory have been randomised to any of the intervention arms, and potential effect modifiers, such as differences in participant samples, are balanced across the range of psychological interventions.[12,15] The pre-specified systematic review protocol therefore included a caveat that any RCT that contained a highly specified population, unlikely to be generalisable to the whole, would be deemed ineligible. Full details of adaptations to, and clarifications of, the initial protocol are included in Appendix 2.

The systematic review focused on adults with schizophrenia, psychosis or related disorder (schizophreniform disorder, schizoaffective disorder, delusional disorder). Exclusion criteria were: co-morbid serious medical illness or psychiatric disorder (except anxiety or depression), 'at-risk' populations or prodromal symptoms, and primary negative symptoms. The registered protocol specified 'stable at baseline' as an exclusion criteria to replicate Leucht et al,[14] however early in the systematic review it became apparent that a large proportion of otherwise relevant RCTs specified 'stable medication' or ‘clinically stable’. The criteria were updated and a sensitivity analysis was planned to identify whether this decision impacted the results.

Psychological intervention was defined as theory-driven, goal-oriented intervention designed to reduce symptoms of psychosis and/or improve psychological wellbeing and functioning. Psychological therapies of specific interest included, but were not limited to, CBTpsychosis, social skills training, family therapy, and cognitive remediation. All control groups were acceptable including treatment as usual, befriending, and supportive counselling. Treatment as usual (TAU) was categorised according to the standard of care; medication only, medication with ongoing case management, access to

a multi-disciplinary team and/or receipt of a range of multi-disciplinary interventions including psychological interventions. Where information about TAU was not provided, the country and year of the RCT was used to categorise the likely TAU (see Appendix 2 for further details). Psychological interventions and control groups were defined according to an adapted definition list from Turner et al (10) (see Appendix 4 for full details). Psychological interventions were aggregated into theoretically similar categories after data extraction was complete, but before analysis (see Table 2). This sorting was completed by three authors including two Clinical Psychologists (PH and WP) who were blind to the results of the RCTs. Combined interventions, such as cognitive remediation with social skills training, were considered as discrete interventions because the mechanism of change is assumed to be an interaction between the interventions.

Total symptom data were extracted from the Positive and Negative Syndrome Scale (PANSS) if available; scores from the Brief Psychiatric Rating Scale (BPRS) were considered next. If neither scale was used, the clinician-identified total symptoms outcome was extracted.

Data Extraction

Similar to Leucht et al[14] the total symptom outcome data extracted were within-group mean change score with standard deviation, or if unavailable, post intervention mean score with standard deviation. Unreported standard deviations were calculated from other information or requested from authors, as were missing data for total symptom outcomes. Unreported total PANSS scores were calculated if PANSS positive, negative, and general scales were available, using the correlations reported in Kay et al.[16] Data

from two meta-analyses that had previously been extracted by study authors were included where appropriate. This data had been double-entered and checked for consistency. All remaining study characteristics and data were extracted by one author (EMG) with a random 10% sample of the full dataset independently extracted by another author (GD) and checked for consistency. There was 100% match for mean and standard deviation extractions.

Quality Assessment

Bias 'due to deviation from intended interventions' is of specific importance to RCTs of psychological interventions.[17,18] This is arguably more important to account for in a network meta-analysis, as inconsistent treatment implementation across different RCTs in the same treatment category could undermine its validity.[15] Nine factors adapted from the Clinical Trial Assessment Measure (CTAM)[19] and the treatment fidelity framework reported by Borrelli et al[20] were used to assess implementation issues in this network meta-analysis (see Appendix 5 for definition and results). This included intervention integrity, fidelity (adherence to the therapeutic model within the RCT), and dose.

The Cochrane Risk of Bias (RoB) tool was used to assess study quality.[17] All data were rated by one author (EMG) and compared with ratings from previously collected data. A random sample of 10% of all included RCTs was also rated independently and discrepancies were discussed. Full results are provided in Appendix 6. Sensitivity analyses were completed in two stages; first, the RoB 2.0 cut off for high/low risk was adapted.[17] Performance bias was likely to be rated as high in all RCTs of psychological interventions and so all RCTs were expected to fail the RoB 2.0 criteria. Thus RCTs were considered high risk if one *other* RoB item was rated as high risk, or if more than

one other item was rated as unclear risk.[17] Few studies met this adapted criteria, and so a second sensitivity (post hoc) analysis was completed based on the Leucht et al definition;[14] studies that reported high risk of bias for randomisation or allocation concealment were considered high risk and excluded. A third sensitivity analysis was also planned post hoc; excluding RCT with samples described as 'clinically stable', to account for the change in protocol.

Statistical Analysis

Network meta-analysis was carried out using Stata SE v15. A random effects model was conducted using a frequentist approach to pool direct and indirect evidence while preserving randomisation, using the Stata "mvmeta", "mvmeta-make" and "network" packages. Direct evidence refers to the pooled effect based on RCTs (similar to traditional meta-analysis), whereas indirect is calculated from the network, for example, difference between B and C, as extrapolated from A -v- B and A -v- C. The protocol followed the method from the University of Bristol manual,[21] summarised in Appendix 7. The analysis plan below was repeated for the three sensitivity and eight subgroup analyses.

A map of the network was generated for each network. Network meta-analysis provides between-group standardised mean difference (SMD) effect sizes based on direct and indirect evidence between each intervention, as well as confidence intervals and p values (calculated as 95% confidence intervals that exclude 0). Cohen's d interpretations were used to describe the effect sizes; small 0.2, medium 0.5 and large 0.8.

Consistency checks (providing statistical evidence about the transitivity assumption) were then completed using three methods: the chi-squared statistic of the complete model, p values from a comparison of the direct and indirect SMD for each connecting 'arm' of the network, and visual inspection of the diamond plot. Where evidence of inconsistency was identified the source was explored in sequence; 1. investigation of errors in data entry and intervention categorisation, 2. inconsistencies in population/study quality that could explain the discrepancy, and 3. reassessing the intervention categorisation.

The analysis also generated information about the probability of each intervention being 'most effective' using SUCRA (surface under the cumulative rankings curve) values for each intervention. This SUCRA value compares each intervention against a hypothetical 'best' intervention (with a score of 100%), and so a score lower than 50 indicates approximately half of the effectiveness.

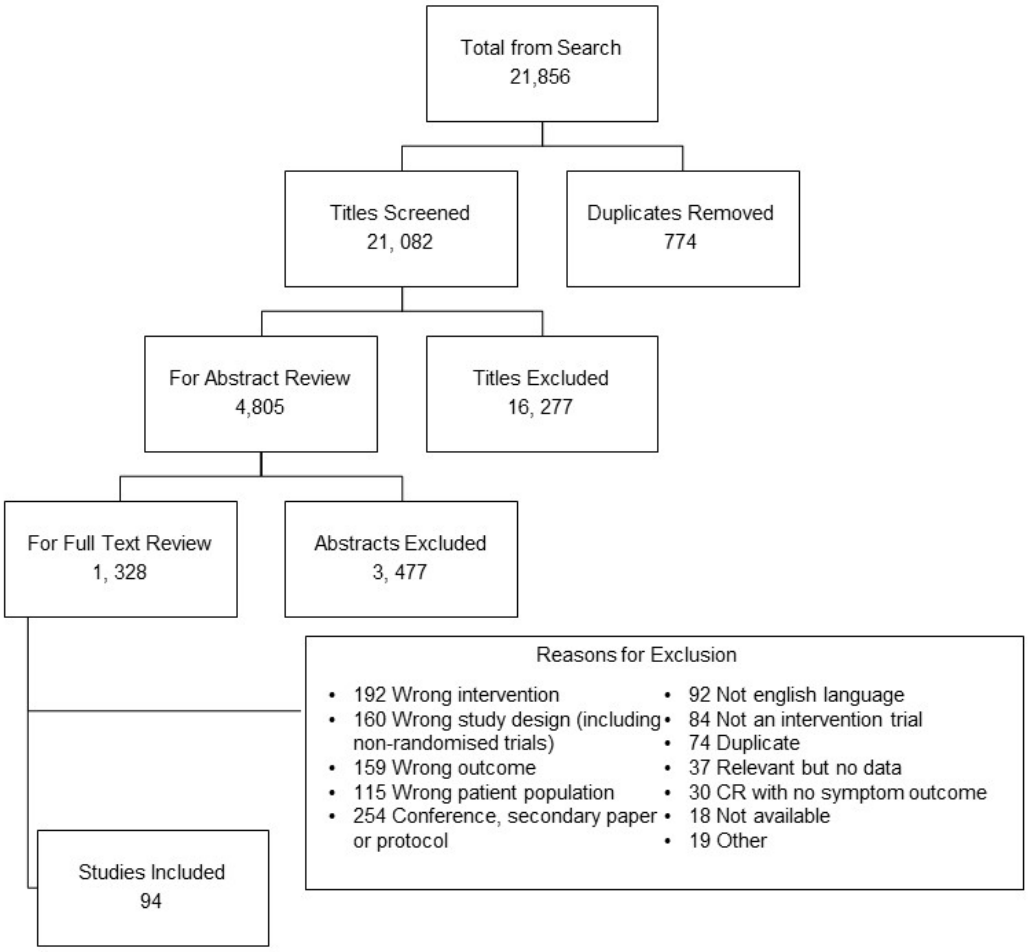

Figure 1: PRISMA diagram of systematic review

Results

Description of Included RCTs

The systematic review identified 94 relevant RCTs with available total symptom outcome data. There were 42 psychological interventions, control groups, and 'combined' interventions which were grouped into 24 categories for analysis, with 10 psychological interventions, 6 control groups (3 active, 4 treatment as usual), and 7 'combined' interventions (see Table 2). Two RCTs had interventions that were

subsumed in the same category (family therapy) and could not be included in the analysis as the interventions were not unique. Two published studies (were identified as containing data from the same trial and just one was included. Lastly, one study was removed due to evidence of inconsistency (see Appendix 8 for rationale). Ninety studies remained, with 195 trial arms (see Appendix 9 for a table detailing the characteristics of the included RCTs).

The 90 RCTs included 8,440 randomised participants, (approximately 39% of whom were female, n = 3,320), with data for 7,410 participants (87%). The median year of publication was 2011 (range 1986-2017- articles dated 2017 were published online in 2016). The RCTs took place in various countries, including the UK (20: 22%), the US (14: 15%) and China (13: 14%).

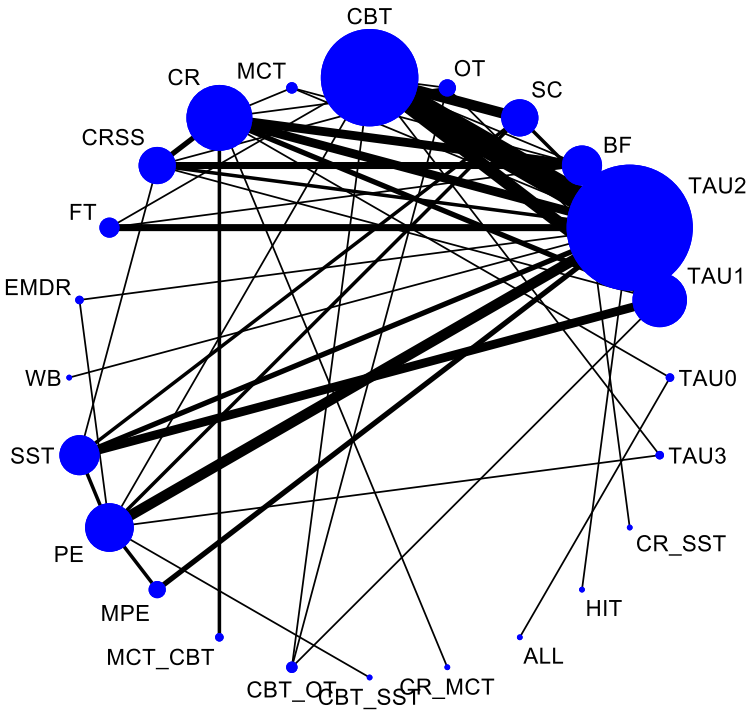

Figure 2: Network of psychological interventions

Note: The circles represent intervention arms in an RCT- larger circles represent presence in more RCTS. The lines connect interventions that were compared in an RCT and thicker connecting lines indicate more direct RCT comparisons. Intervention

Abbreviations: ALL - Protocol with 4 psychotherapies combined; BF – Befriending; CBT -Cognitive behaviour therapy**;** CR - Cognitive remediation; CRSS - Cognitive remediation focussed on social cognition; EMDR - Eye movement desensitisation and reprocessing; FT - Family therapy**;** HIT - Hallucinations focused integrative therapy; MCT - Metacognitive therapy; MPE - Mindfulness-based psychoeducation; OT - Occupational therapy; PE – Psychoeducation**;** SC - Supportive counselling; SST - Social skills training; TAU - Treatment as usual (levels 0-3); WB – Wellbeing. Combined interventions (that included two therapies) are indicated by Intervention_Intervention.

Fifty-six (62%) RCTs were based in outpatient settings, 15 (16%) were inpatient settings, and 10 (11%) recruited participants from both settings. Regarding the interventions, 65 (intervention or control) arms from 29 RCTs were delivered individually, whereas 91 arms across 43 RCTs were delivered in a group format. Thirteen arms across 11 studies were computer-based. The average intervention length was 20 sessions (median 16, range 4-52). Seventeen RCTs included people with 'recent onset' schizophrenia, defined as <5 years since diagnosis. Few RCTs reported specific adverse effects; some reported aspects of patient satisfaction, or serious adverse events, and none reported measuring adverse effects using a standardised measure. Intervention integrity was rated on a scale of 0 to 6, with 0 being high integrity; 92% of intervention arms scored 0. There was more variance for fidelity, with 35% scoring in middle of a scale from -1 to 8, with -1 being high likelihood of adherence to the therapy model (full results are reported in Appendix 5). Fourteen RCTs (15%) met the adapted Cochrane RoB 2.0 criteria for low risk of bias (see Appendix 6 for full results). Six RCTs met the post hoc RoB criteria for high risk of bias. Thirty-three RCTs (36%) specified their sample as clinically stable, and/or on stable medication and 4 specified acute, or post-acute symptoms. Five RCTs specified a treatment resistant sample.

Total Symptom Analysis

A detailed map of the network was created which depicts the 189 treatment RCT arms from 90 RCTs (see Figure 2). Table 2 describes the characteristics of the intervention categories. There was no evidence of inconsistency in the model $\chi 2$ (27, N = 90) = 22.86, p = .583 and there was no evidence of loop inconsistency, that is, when the effect sizes for the direct and in a pairwise comparison do not align.[21]

The results of the network meta-analysis comparisons (that is, SMD effect sizes, confidence intervals and statistical significance) can be seen in Table 3 and are briefly summarised here. Table 1 clarifies all intervention abbreviations. Most interventions were found to be statistically significantly more likely to reduce symptoms compared to control groups. Two interventions, CBT with social skills training, and mindfulness-based psychoeducation were also found to be statistically significantly different to other psychological interventions, with medium and large effect sizes respectively, and large confidence intervals. These interventions were also ranked as having the highest probability of being most effective according to the SUCRA values (see Table 4 for scores and Appendix 7 for more detail on SUCRA values). Psychoeducation, family therapy, social skills training and cognitive remediation with social skills training were statistically significantly different compared with TAU2 and had a SUCRA score above the 50 level- indicating that they are likely to provide approximately 50% of the level of effectiveness of a hypothetical best intervention. CBT was ranked below befriending and most intervention categories (with a SUCRA of 39.7), however it was identified as statistically significant, with a small effect size and narrow confidence intervals.

Table 1: List of psychological intervention abbreviations

ALL	Protocol with 4 psychotherapies combined
BF	Befriending
BFT	Behavioural family therapy
CAT	Cognitive adaptation therapy (an OT intervention)
CBT	Cognitive behaviour therapy
CBTp	Cognitive behaviour therapy; psychosis
CC	Computerised control group
CCBF	Computerised control with befriending
CPS	Coping skills training
CR	Cognitive remediation
CR_meta	Cognitive remediation targeting metacognitive processes
CRSS	Cognitive remediation focussed on social cognition
EMDR	Eye movement desensitisation and reprocessing
FPE	Family psychoeducation
FSG	Family support groups
FSIT	Family assisted social cognition training
FT	Family therapy
HIT	Hallucinations focused integrative therapy
MCT	Metacognitive therapy
MPE	Mindfulness-based psychoeducation

OT	Occupational therapy
PE	Psychoeducation
PESC	Psychoeducation with supportive counselling
PMR	Progressive muscle relaxation
PST	Problem solving training
SC	Supportive counselling
SE	Self esteem training
SST	Social skills training
SST_FPE	Social skills training with family psychoeducation
TAU	Treatment as usual
WB	Wellbeing

			years) n/%	n /%									
TAU0	2	380	1	1	0	1 FGA only	0	1	0				
TAU1	16	634	3	8	0	1 Treatment resistant 1 Insomnia	2	13	1				
TAU2	35	1336	7	11	3	1 No med 1 Suicide attempt 2 Auditory hallucinations 1 Relapse prone	3	28	6				
BF	11	410	2	8	0	1 Treatment resistant	3	9	0	2	8	2	0
SC	9	464	3	2	1	1 Auditory Hallucination 1 Treatment resistant	4	4	2	6	4	0	0
OT	3	103	0	1	0	1 Treatment resistant	1	2	0	2	1	0	0
CBT	25	1477	4	6	2	3 Treatment Resistant 1 No med 1 Suicide attempt 1 Persecutory delusions 1 Insomnia 1 Relapse prone 1 Auditory hallucinations	2	18	8	23	5	0	0
MCT	3	100	1	0	0		2	0	1	0	3	0	0

and Group

CRSS	11	263	3	6	0	1 Treatment resistant	3	7	1	0	9	0	2		
FT	4	312	0	1	1		0	9	0	3	6	0	0		
EMDR	1	15	1	0	1		1	0	0	1	0	0	0		
WB	1	47	0	0	0		0	0	1	0	1	0	0		
SST	13	638	2	8	0		2	12	0	1	13	0	0		
PE	13	482	7	0	2		3	9	2	6	8	0	0		
MPE	3	130	3	0	0		0	3	0	0	3	0	0		
MCT_CBT	1	70	0	0	0		1	0	1	1	1	0	0		

HIT	1	37	0	0	0	0	1	0	1	0	0	0	
CR_SST	1	27	0	1	0	0	1	0	0	1	0	0	
TAU3	1	52	1	0	0	0	1	1					

Intervention Abbreviations: ALL - Protocol with 4 psychotherapies combined; BF – Befriending; CBT -Cognitive behaviour therapy; CR - Cognitive remediation; CRSS - Cognitive remediation focussed on social cogn integrative therapy; MCT - Metacognitive therapy; MPE - Mindfulness-based psychoeducation; OT - Occupational therapy; PE – Psychoeducation; SC - Supportive counselling; SST - Social skills training; TAU - Trea Intervention_Intervention.

Table 3: Total symptoms SMD effect sizes and confidence intervervals between each category

	TAU0	TAU1	TAU2	BF	SC	OT	**CBT**	**MCT**	**CR**	**CRSS**	**FT**	**EMDR**	**WB**	**S**
TAU1	0.29 (-0.42 to 1.00)													
TAU2	0.15 (-0.54 to 0.85)	-0.14 (-0.37 to 0.09)												
BF	0.16 (-0.53 to 0.86)	-0.13 (-0.45 to 0.20)	0.01 (-0.28 to 0.30)											
SC	-0.03 (-0.76 to 0.70)	**-0.32 (-0.61 to -0.03)**	-0.19 (-0.43 to 0.06)	0.20 (-0.56 to 0.17)										
OT	-0.35 (-1.14 to 0.44)	**-0.64 (-1.09 to -0.19)**	**-0.50 (-0.95 to -0.05)**	**-0.51 (-0.98 to -0.04)**	-0.32 (-0.81 to 0.18)									

MCT	(-0.89 to 0.70)	-0.38 (-0.90 to 0.13)	-0.25 (-0.74 to 0.25)	-0.26 (-0.74 to 0.23)	-0.06 (-0.60 to 0.48)	0.26 (-0.37 to 0.88)	0.07 (-0.43 to 0.58)							
CR	-0.07 (-0.72 to 0.59)	**-0.36 (-0.63 to -0.08)**	-0.22 (-0.46 to 0.02)	-0.23 (-0.48 to 0.02)	-0.03 (-0.36 to 0.29)	0.28 (-0.16 to 0.73)	0.10 (-0.16 to 0.36)	0.03 (-0.43 to 0.49)						
CRSS	-0.24 (-0.95 to 0.47)	**-0.53 (-0.86 to -0.19)**	**-0.39 (-0.70 to -0.08)**	**-0.40 (-0.69 to -0.11)**	-0.20 (-0.58 to 0.17)	0.11 (-0.33 to 0.56)	-0.07 (-0.39 to 0.25)	-0.14 (-0.66 to 0.37)	-0.17 (-0.45 to 0.11)					
FT	-0.19 (-0.95 to 0.56)	**-0.48 (-0.86 to -0.10)**	**-0.35 (-0.66 to -0.03)**	-0.36 (-0.75 to 0.04)	-0.16 (-0.55 to 0.24)	0.16 (-0.38 to 0.70)	-0.03 (-0.37 to 0.32)	-0.10 (-0.67 to 0.47)	-0.13 (-0.51 to 0.26)	-0.04 (-0.38 to 0.47)				
EMDR	-0.25 (-1.30 to 0.81)	-0.53 (-1.36 to 0.29)	-0.40 (-1.20 to 0.40)	-0.41 (-1.26 to 0.44)	-0.21 (-1.04 to 0.61)	0.10 (-0.81 to 1.02)	-0.08 (-0.89 to 0.73)	-0.15 (-1.09 to 0.78)	-0.18 (-1.01 to 0.65)	0.01 (-0.86 to 0.85)	-0.05 (-0.91 to 0.81)			
WB	-0.30 (-1.26 to 0.66)	-0.59 (-1.29 to 0.11)	-0.45 (-1.11 to 0.21)	-0.46 (-1.18 to 0.26)	-0.26 (-0.97 to 0.44)	0.05 (-0.75 to 0.85)	-0.13 (-0.81 to 0.55)	-0.20 (-1.03 to 0.62)	-0.23 (-0.94 to 0.47)	-0.06 (-0.79 to 0.67)	-0.10 (-0.84 to 0.63)	-0.05 (-1.09 to 0.99)		
SST	-0.17 (-0.89 to 0.55)	**-0.46 (-0.68 to -0.23)**	**-0.32 (-0.56 to -0.08)**	-0.33 (-0.68 to 0.01)	-0.14 (-0.43 to 0.16)	0.18 (-0.30 to 0.66)	0.00 (-0.25 to 0.24)	-0.08 (-0.60 to 0.45)	-0.10 (-0.41 to 0.20)	0.07 (-0.28 to 0.42)	0.02 (-0.37 to 0.41)	0.08 (-0.75 to 0.90)	0.13 (-0.58 to 0.83)	
PE	-0.41 (-1.13 to 0.32)	**-0.70 (-0.99 to -0.41)**	**-0.56 (-0.79 to -0.34)**	**-0.57 (-0.93 to -0.22)**	**-0.38 (-0.66 to -0.10)**	-0.06 (-0.55 to 0.43)	**-0.24 (-0.48 to 0.00)**	-0.32 (-0.85 to 0.22)	-0.34 (-0.66 to 0.03)	-0.17 (-0.54 to 0.20)	-0.22 (-0.60 to 0.17)	-0.16 (-0.96 to 0.64)	-0.11 (-0.81 to 0.59)	- (- 0
	-0.70	**-0.98**	**-0.85**	**-0.86**	**-0.66**	-0.35	**-0.53**	**-0.60**	**-0.63**	-0.46	**-0.50**	-0.45	-0.40	-

MCT_CBT	to 0.44)	**to -0.10)**	to 0.02)	to 0.01)	to 0.25)	to 0.64)	to 0.35)	to 0.39)	to 0.18)	to 0.43)	to 0.44)	to 0.84)	to 0.78)	(
CBT_OT	0.08 (-0.84 to 0.99)	0.21 (-0.83 to 0.41)	-0.08 (-0.71 to 0.55)	-0.09 (-0.75 to 0.58)	0.11 (-0.55 to 0.77)	0.42 (-0.25 to 1.09)	0.24 (-0.38 to 0.86)	0.17 (-0.61 to 0.95)	0.14 (-0.50 to 0.79)	0.31 (-0.35 to 0.98)	0.27 (-0.43 to 0.97)	0.32 (-0.69 to 1.34)	0.37 (-0.54 to 1.29)	(((
CBT_SST	**-1.13 (-2.23 to -0.02)**	**-1.42 (-2.30 to -0.53)**	**-1.28 (-2.14 to -0.42)**	**-1.29 (-2.20 to -0.38)**	**-1.09 (-1.97 to -0.21)**	-0.78 (-1.75 to 0.19)	**-0.96 (-1.83 to -0.09)**	**-1.03 (-2.02 to -0.04)**	**-1.06 (-1.95 to -0.17)**	-0.89 (-1.80 to 0.02)	**-0.93 (-1.85 to -0.02)**	-0.88 (-2.04 to 0.27)	-0.83 (-1.92 to 0.26)	- (-(
CR_MCT	-0.16 (-1.15 to 0.84)	-0.45 (-1.24 to 0.35)	-0.31 (-1.10 to 0.48)	-0.32 (-1.11 to 0.47)	-0.12 (-0.94 to 0.70)	0.19 (-0.68 to 1.06)	0.01 (-0.78 to 0.80)	-0.06 (-0.94 to 0.82)	-0.09 (-0.84 to 0.66)	0.08 (-0.72 to 0.88)	0.04 (-0.81 to 0.88)	0.09 (-1.03 to 1.21)	0.14 (-0.89 to 1.17)	(((
ALL	-0.29 (-0.81 to 0.23)	-0.58 (-1.46 to 0.30)	-0.45 (-1.31 to 0.42)	-0.46 (-1.33 to 0.41)	-0.26 (-1.16 to 0.64)	0.06 (-0.89 to 1.00)	-0.13 (-1.00 to 0.75)	-0.20 (-1.15 to 0.75)	-0.23 (-1.06 to 0.61)	-0.06 (-0.94 to 0.82)	-0.10 (-1.02 to 0.82)	-0.05 (-1.23 to 1.13)	0.00 (-1.09 to 1.10)	- ((
HIT	-0.49 (-1.47 to 0.50)	-0.77 (-1.51 to -0.04)	-0.64 (-1.34 to 0.06)	-0.65 (-1.41 to 0.11)	-0.45 (-1.19 to 0.29)	-0.14 (-0.97 to 0.69)	-0.32 (-1.03 to 0.39)	-0.39 (-1.25 to 0.46)	-0.42 (-1.16 to 0.32)	-0.25 (-1.01 to 0.51)	-0.29 (-1.06 to 0.47)	-0.24 (-1.30 to 0.82)	-0.19 (-1.15 to 0.77)	- ((
CR_SST	0.09 (-0.94 to 1.12)	-0.20 (-1.03 to 0.63)	-0.06 (-0.88 to 0.75)	-0.07 (-0.84 to 0.69)	0.12 (-0.72 to 0.97)	0.44 (-0.46 to 1.33)	0.26 (-0.56 to 1.07)	0.18 (-0.72 to 1.08)	0.16 (-0.64 to 0.96)	0.33 (-0.49 to 1.14)	0.28 (-0.58 to 1.14)	0.33 (-0.81 to 1.48)	0.39 (-0.66 to 1.44)	((1
TAU3	0.25 (-0.64 to 1.14)	-0.04 (-0.63 to 0.55)	0.10 (-0.47 to 0.66)	0.08 (-0.54 to 0.71)	0.28 (-0.31 to 0.87)	0.60 (-0.11 to 1.31)	0.42 (-0.14 to 0.97)	0.34 (-0.40 to 1.08)	0.34 (-0.29 to 0.92)	0.49 (-0.15 to 1.12)	0.44 (-0.20 to 1.08)	0.49 (-0.47 to 1.46)	0.55 (-0.32 to 1.41)	((1

Table 3 notes: Vertical compared to the horizontal- minus score indicates greater reduction in symptoms; such that compared to TAU1, CBT reported a redu
reduction in symptoms, such that compared to MPE, CBT_OT reported 0.77 less of a reduction in score. Statistically significant differences highlighted in bo
Intervention Abbreviations: ALL - Protocol with 4 psychotherapies combined; BF – Befriending; CBT -Cognitive behaviour therapy; CR - Cognitive remediatio
reprocessing; FT - Family therapy; HIT - Hallucinations focused integrative therapy; MCT - Metacognitive therapy; MPE - Mindfulness-based psychoeducatio

Table 4: SUCRA values, probability of being best in rank order and SMD (CI) compared to TAU2 (see Table 1 for abbreviations)

	SUCRA	Prob. Best	SMD (CI)*
MPE	91.8	26.4	**-0.85 (-1.21 to -0.49)**
CBT_SST	86.3	42	**-1.28 (-2.14 to -0.42)**
HIT	73.4	5.3	-0.64 (-1.34 to 0.06)
MCT_CBT	68.3	1	-0.53 (-1.08 to 0.02)
WB	61.8	1.9	-0.45 (-1.11 to 0.21)
ALL	59.9	3.8	-0.45 (-1.31 to 0.42)
MCT	57.2	5.1	-0.25 (-0.74 to 0.25)
PE	56.6	0.1	**-0.56 (-0.79 to -0.34)**
FT	56.2	0	**-0.35 (-0.66 to -0.03)**
SST	54.9	0.3	**-0.32 (-0.56 to -0.08)**
CRSS	54.5	9.3	**-0.39 (-0.70 to -0.08)**
EMDR	51.1	1.1	-0.40 (-1.20 to 0.40)
CR_MCT	50.7	1.2	-0.31 (-1.10 to 0.48)
CR_SST	46.4	1.7	-0.06 (-0.88 to 0.75)
CR	44.4	0	-0.22 (-0.46 to 0.02)
BF	41.1	0	0.01 (-0.28 to 0.30)
CBT	39.7	0	**-0.32 (-0.48 to -**

			0.16)
TAU0	39.4	0.2	.
SC	38.7	0.3	-0.19 (-0.43 to 0.06)
OT	33.1	0.2	**-0.50 (-0.95 to -0.05)**
CBT_OT	33	0.1	-0.08 (-0.71 to 0.55)
TAU2	28.9	0	.
TAU1	22.5	0	.
TAU3	10.2	0	.

*Compared with TAU2

Intervention Abbreviations: ALL - Protocol with 4 psychotherapies combined; BF – Befriending; CBT -Cognitive behaviour therapy; CR - Cognitive remediation; CRSS - Cognitive remediation focussed on social cognition; EMDR - Eye movement desensitisation and reprocessing; FT - Family therapy; HIT - Hallucinations focused integrative therapy; MCT - Metacognitive therapy; MPE - Mindfulness-based psychoeducation; OT - Occupational therapy; PE – Psychoeducation; SC - Supportive counselling; SST - Social skills training; TAU - Treatment as usual (levels 0-3); WB – Wellbeing. Combined interventions (that included two therapies) are indicated by Intervention_Intervention.

Sensitivity Analyses

A sensitivity analysis was carried out with the 14 RCTs that met the stringent criteria for low risk of bias RoB 2.0 (17) (see Appendix 6 for full results) to investigate whether study quality affected the results. Eleven intervention types remained across 33 arms (see Figure 3 and Table 5). There was no evidence of inconsistency in the model $\chi 2$ (2, N = 14) = 0.61, p = .736 and no statistically significant differences between the direct and indirect evidence indicating that the model was coherent. As seen in Table 5, the results were similar to the total analysis; mindfulness-based psychoeducation remained highest ranked according to SUCRA values, with psychoeducation also ranked highly

and with statistical significance. In contrast to the full analysis befriending had the lowest SUCRA and family therapies were ranked lower.

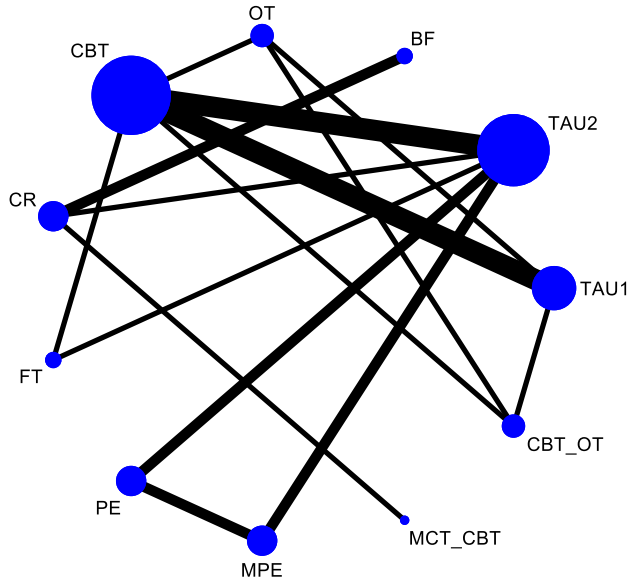

Figure 3: Network of psychological interventions for sensitivity analysis (Cochrane RoB).

Note: The circles represent intervention arms in an RCT- larger circles represent presence in more RCTS. The lines connect interventions that were compared in an RCT and thicker connecting lines indicate more direct RCT comparisons. Intervention Abbreviations: BF – Befriending; CBT -Cognitive behaviour therapy**;** CR -Cognitive remediation; FT - Family therapy**;** MPE - Mindfulness-based psychoeducation; OT - Occupational therapy; PE – Psychoeducation**;** TAU - Treatment as usual (levels 0-3). Combined interventions (that included two therapies) are indicated by Intervention_Intervention.

The post hoc RoB sensitivity analysis based on the Leucht et al[14] criteria excluded six studies which had a high risk of allocation concealment and/or randomisation bias. Eighty-four RCTs remained, with 177 arms. All intervention types were included, and there was no evidence of inconsistency in the model $\chi 2$ (25, N = 84) = 20.74, p = .706 and no statistically significant differences between the direct and indirect evidence. Again, the SUCRA hierarchy was similar, with mindfulness-based psychoeducation and CBT with social skills training, reporting the highest SUCRA values. As in the original analysis, the majority of control groups were ranked lower than the intervention groups.

The sensitivity analysis removing RCTs that specified a clinically stable sample involved 48 RCTs with 102 arms across 20 interventions. The results were largely consistent with the full analysis (see Table 6), with most interventions ranked in similar positions in the SUCRA hierarchy compared to the full analysis, except cognitive remediation had a lower SUCRA score, while befriending and meta-cognitive training had a higher SUCRA score than in the full analysis. Figure 4 details the number of RCTs that met the criteria for each level of risk of bias, RCT level details can be found in Appendix 9.

Table 5: Sensitivity analysis (Cochrane RoB): SUCRA values and probability of being best in rank order

	SUCRA	Prob. Best	SMD (CI)*
MPE	97.7	81.7	**-1.02 (-1.42 to -0.62)**
PE	74.7	0.1	**-0.50 (-0.89 to -0.11)**
MCT_CBT	68.2	11.5	-0.43 (-1.29 to 0.43)
OT	61.4	4.6	-0.23 (-0.87 to 0.41)
CBT	54.2	0	-0.23 (-0.50 to 0.05)
CBT_OT	37.3	0.9	0.07 (-0.55 to 0.69)
FT	35.7	0.6	-0.03 (-0.62 to 0.56)
CR	32.7	0	0.02 (-0.54 to 0.57)
TAU1	31.4	0.6	.
TAU2	31.4	0	.
BF	25.4	0	0.11 (-0.60 to 0.82)

*Compared with TAU2

Intervention Abbreviations: BF – Befriending; CBT -Cognitive behaviour therapy; CR -Cognitive remediation; FT - Family therapy; MPE - Mindfulness-based psychoeducation; OT - Occupational therapy; PE – Psychoeducation; TAU - Treatment as usual (levels 0-3). Combined interventions (that included two therapies) are indicated by Intervention_Intervention.

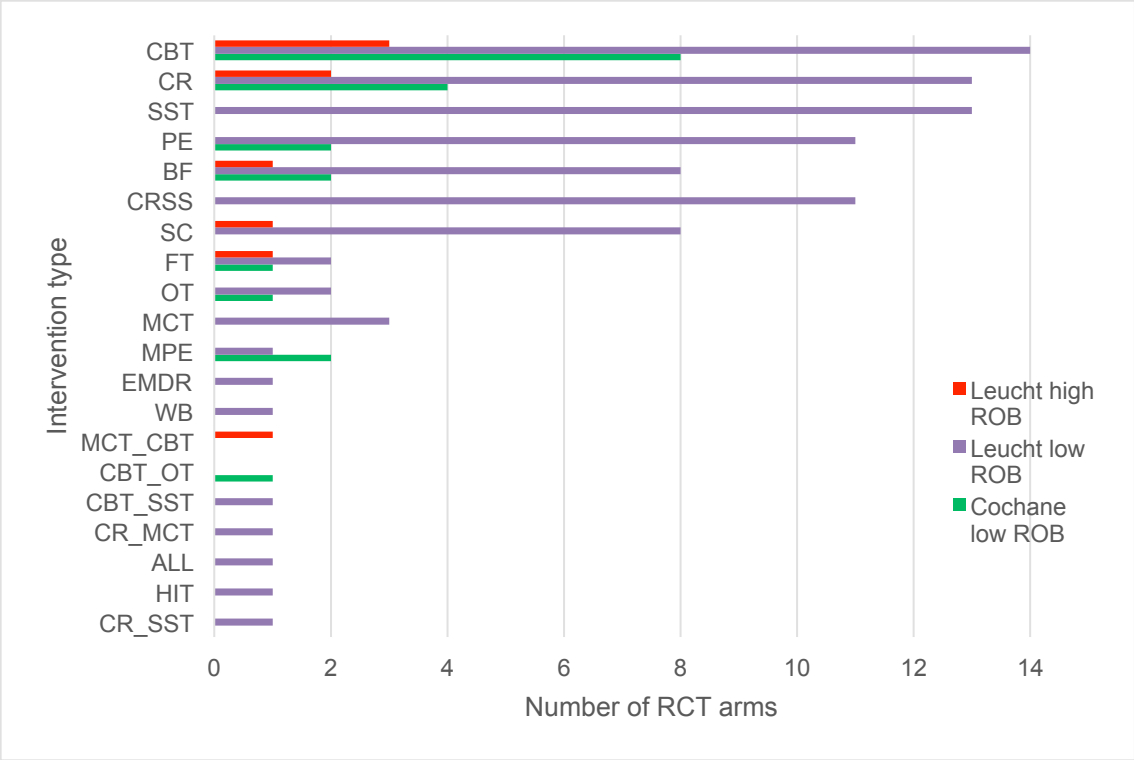

Figure 4: Risk of bias by intervention category

Note Intervention Abbreviations: ALL - Protocol with 4 psychotherapies combined; BF – Befriending; CBT -Cognitive behaviour therapy; CR - Cognitive remediation; CRSS - Cognitive remediation focussed on social cognition; EMDR - Eye movement desensitisation and reprocessing; FT - Family therapy; HIT - Hallucinations focused integrative therapy; MCT - Metacognitive therapy; MPE - Mindfulness-based psychoeducation; OT - Occupational therapy; PE – Psychoeducation; SC - Supportive counselling; SST - Social skills training; TAU - Treatment as usual (levels 0-3); WB – Wellbeing. Combined interventions (that included two therapies) are indicated by Intervention_Intervention.

Subgroup Analyses

Eight subgroup analyses were completed with the 84 studies meeting the post hoc RoB sensitivity analysis criteria. The SMD and CI for each, compared with TAU2 is presented in Table 6. Evidence of inconsistency was not found for any of the models except Chronic. Similarly, there was no evidence of inconsistency between the direct and indirect evidence in any analysis, except as detailed for the Chronic analysis- details can be found in Appendix 8.

RCTs that specified treatment resistant symptoms or a sample not taking medication were excluded to identify if these characteristics impacted the results. Seventy-seven RCTs across 22 intervention types remained. Similar to the full analysis, the highest ranked intervention was mindfulness-based psychoeducation and cognitive remediation focussed on social cognition was ranked second. OT (occupational therapy) and TAU1 had the lowest SUCRA values. Fifteen RCTs were in the inpatient setting across 13 intervention types. OT had the highest SUCRA value, and CBT had the lowest for this setting. Fifty-six RCTs were described as outpatient, with 119 study arms across 17 interventions. Mindfulness-based psychoeducation was ranked highest followed by psychoeducation. Ten RCTs across seven intervention types took place across both in- and outpatient settings CBT with social skills training was ranked highest.

Seventeen RCTs were classified as 'recent onset', with 38 arms. Cognitive remediation focussed on social cognition, mindfulness-based psychoeducation, and cognitive remediation were ranked highest; social skills training and TAU1 ranked lowest. Sixty-six RCTs were classified as 'chronic', however inconsistency was identified between the direct and indirect evidence for OT and CRSS. In this analysis CBT with social skills training and HIT were ranked highest, with TAU1 lowest.

Interventions in 29 RCTs were delivered on an individual basis. Fourteen intervention types were included in the analyses of 65 arms. CBT with social skills training, psychoeducation, and HIT were ranked highest using SUCRA scores, with family therapy and TAU1 lowest. Interventions were delivered in a group format for 15 different intervention types across 91 arms in 43 RCTs. OT, mindfulness-based

psychoeducation, and metacognitive therapy with CBT were ranked highest, with befriending ranked lowest.

Table 6: Subgroup analyses: network details and SMD with CI for each intervention compared with TAU2

	Number of studies	Total (Post hoc RoB) SMD (CI)	Without Clinically Stable SMD (CI)	Treatment resistant removed SMD (CI)	Inpatient SMD (CI)	Outpatient SMD (CI)	Both	Chronic SMD (CI)
Number of RCTs		84	48	77	15	56	10	66
Number of study arms		177	102	163	31	119	19	137
Model consistency: Chi^2 (d.f.) p value		20.74 (25) p = .706	10.42 (17) p = .885	17.10 (23) p = .804	0.67 (3) p = .881	14.08 (19) p = .779	0.61 (2) p = .737	27.94 (20) p = .111
Intervention types		24	20	22	13	17	7	20
TAU0	2	.	.	.	.	.	.	.
TAU1	16	.	.	.	.	.	.	.
TAU2	35	.	.	.	.	.	.	.
BF	11	-0.01 (-0.33 to 0.30)	-0.16 (-0.64 to 0.32)	-0.02 (-0.37 to 0.34)	-0.17 (-0.73 to 0.39)	0.02 (-0.36 to 0.41)	.	0.03 (-0.26 to 0.32)
SC	9	-0.16 (-0.41 to 0.10)	-0.08 (-0.40 to 0.23)	-0.14 (-0.40 to 0.12)	-0.14 (-0.96 to 0.67)	0.09 (-0.32 to 0.50)	-0.21 (-0.46 to 0.04)	0.01 (-0.27 to 0.29)
OT	3	**-0.49 (-0.94 to -0.04)**	-0.10 (-0.66 to 0.46)	-0.17 (-0.72 to 0.38)	-0.64 (-1.41 to 0.13)	-0.20 (-0.78 to 0.38)	.	**-0.43 (-0.83 to -0.02)**
CBT	25	**-0.29 (-0.45 to -0.13)**	**-0.24 (-0.47 to -0.02)**	**-0.27 (-0.45 to -0.10)**	0.42 (-0.79 to 1.64)	**-0.31 (-0.53 to -0.10)**	**-0.21 (-0.40 to -0.02)**	**-0.25 (-0.40 to -0.10)**
MCT	3	-0.24 (-0.74 to 0.25)	-0.22 (-0.74 to 0.31)	-0.24 (-0.74 to 0.27)	-0.45 (-1.14 to 0.25)	.	.	-0.18 (-0.65 to 0.30)
CR	19	-0.20 (-0.46 to 0.05)	-0.11 (-0.50 to 0.29)	-0.19 (-0.46 to 0.07)	0.00 (-0.47 to 0.47)	-0.26 (-0.59 to 0.07)	.	-0.15 (-0.38 to 0.08)
CRSS	11	**-0.39 (-0.71 to -0.07)**	-0.21 (-0.68 to 0.27)	**-0.46 (-0.81 to -0.12)**	-0.05 (-0.68 to 0.58)	**-0.66 (-1.07 to -0.25)**	.	-0.24 (-0.57 to 0.09)
FT	4	-0.26 (-0.60 to 0.08)	-0.33 (-0.71 to 0.05)	-0.26 (-0.60 to 0.09)	.	-0.26 (-0.62 to 0.10)	.	-0.26 (-0.55 to 0.04)
EMDR	1	-0.41 (-1.21 to 0.39)	.	-0.41 (-1.21 to 0.39)	-0.29 (-1.07 to 0.48)	.	.	.
WB	1	-0.45 (-1.11 to 0.21)	-0.45 (-1.08 to 0.18)	-0.45 (-1.11 to 0.21)	.	.	**-0.45 (-0.88 to -0.02)**	-0.45 (-1.01 to 0.11)
SST	13	**-0.31 (-0.55 to -0.07)**	-0.25 (-0.64 to 0.14)	**-0.29 (-0.54 to -0.05)**	-0.34 (-1.27 to 0.59)	-0.27 (-0.55 to 0.01)	.	**-0.34 (-0.57 to -0.11)**
PE	13	**-0.58 (-0.81 to -0.36)**	**-0.61 (-0.86 to -0.37)**	**-0.58 (-0.81 to -0.35)**	-0.36 (-1.12 to 0.40)	**-0.63 (-0.92 to -0.35)**	-0.47 (-0.93 to 0.00)	**-0.63 (-0.95 to -0.30)**
MPE	3	**-0.86 (-1.21 to -0.50)**	**-0.87 (-1.21 to -0.52)**	**-0.85 (-1.21 to -0.50)**	.	**-0.88 (-1.26 to -0.49)**	.	.

MCT_CBT		1	-0.65 (-1.45 to 0.15)	-0.55 (-1.39 to 0.28)	-0.64 (-1.45 to 0.16)	-0.45 (-1.19 to 0.30)	.	.	-0.59 (-1.30 to 0.12)
CBT_OT		1	-0.06 (-0.69 to 0.57)	0.12 (-0.52 to 0.76)	0.06 (-0.58 to 0.70)	.	0.04 (-0.64 to 0.72)	.	-0.01 (-0.57 to 0.54)
CBT_SST		1	**-1.30 (-2.16 to -0.44)**	**-1.33 (-2.18 to -0.49)**	.	.	.	**-1.18 (-2.00 to -0.37)**	**-1.34 (-2.16 to -0.52)**
CR_MCT		1	-0.29 (-1.08 to 0.50)	.	-0.29 (-1.08 to 0.51)	.	-0.35 (-1.20 to 0.50)	.	-0.24 (-0.94 to 0.46)
ALL		1	-0.43 (-1.30 to 0.44)	.	.	.	.	.	.
HIT		1	-0.64 (-1.33 to 0.06)	-0.64 (-1.30 to 0.03)	-0.64 (-1.34 to 0.06)	.	-0.64 (-1.37 to 0.10)	.	**-0.64 (-1.24 to -0.04)**
CR_SST		1	-0.09 (-0.91 to 0.73)	.	-0.09 (-0.93 to 0.75)	.	-0.05 (-0.94 to 0.83)	.	-0.04 (-0.77 to 0.69)
TAU3		1	.	.	.	.	.	.	.

SMD (standardised mean difference) and CI (confidence interval) results that are statistically significant are in bold and underlined.
Intervention Abbreviations: ALL - Protocol with 4 psychotherapies combined; BF – Befriending; CBT -Cognitive behaviour therapy; CR - Cognitive rem
focussed on social cognition; EMDR - Eye movement desensitisation and reprocessing; FT - Family therapy; HIT - Hallucinations focused integrative t
MPE - Mindfulness-based psychoeducation; OT - Occupational therapy; PE – Psychoeducation; SC - Supportive counselling; SST - Social skills traini
WB – Wellbeing. Combined interventions (that included two therapies) are indicated by Intervention_Intervention.

Discussion

This network meta-analysis is the first to synthesise the evidence base for psychological interventions impact on total symptoms for schizophrenia and psychosis. The systematic review identified 42 distinct interventions, analysed within 24 categories. Of these, two were consistently identified as being most likely to be most effective at reducing total symptoms; mindfulness-based psychoeducation and CBT with social skills training. Mindfulness-based psychoeducation had the first or second highest SUCRA value in every analysis it was included in, including sensitivity analyses and subgroup analyses. It is important to note that the three RCTs of mindfulness-based psychoeducation were conducted in China. Replication of these RCTs in Western settings is prudent, given the cultural relevance of mindfulness in Buddhist traditions, which are more prevalent in Asia, compared to the West. It is unclear whether cultural familiarity with mindfulness may have contributed to the large effect sizes for mindfulness-based psychoeducation and further RCTs are required. Similarly, more RCTs of CBT with social skills training are required as it was present in just one RCT, which may inflate its effect size, and this study did not meet the stringent Cochrane low risk of bias criteria.

There is a lack of direct comparisons of the interventions currently recommended[6,13] against the available alternatives, and this network meta-analysis allows these comparisons to be inferred. Specifically, CBT alone and family therapy consistently had SUCRA values in the mid-range or bottom compared to all other interventions, including in the stringent RoB analysis. CBT was ranked as least likely intervention to reduce symptoms for inpatient settings. Despite the comparatively low ranking, CBT was consistently identified as having a statistically significant reduction in total symptoms. This may in be due to a function of the greater number of studies with CBT- as the evidence base is more robust, and inversely, there is the potential for an inflation of effects for interventions with few RCTs. A third of the CBT

interventions included other specific criteria such as insomnia and suicide attempts (see Table 2). Similarly, there was a wide variety of family therapy interventions.

Social skills training and cognitive remediation had differential ranking depending on setting, and both had differential rankings depending on stage of illness. Social skills training had a higher SUCRA score (that is, greater than 50) for group delivered interventions, and for samples with >5 years with schizophrenia, and lowest for recent onset. Cognitive remediation had a low SUCRA score for most analyses; however it was ranked highly for recent onset and group delivered interventions. It is important to note that most RCTs of cognitive remediation do not target, or measure, clinical symptoms, and the bulk of evidence is not represented in this analysis. Indeed, total symptoms is often not the primary goal and/or outcome for psychological interventions for psychosis- distress and quality of life are more common treatment targets. RCTs that included total symptoms as a secondary outcome were designed with other outcomes in mind which may have affected participant sampling and be underpowered to detect a change in total symptoms. While meta-analysis addresses the issue of underpowered studies, it is acknowledged that consideration of other outcomes may be more appropriate to understanding the effectiveness of psychological interventions. As per the pre-registered protocol, these outcomes will be considered in later analyses.

Supportive counselling, included as a control group, was ranked in the mid and bottom ranges for most analyses. Similarly, befriending was ranked in the mid to low range- it was last in the analysis of group interventions. Its ranking above TAU1 in most analyses provides some support to the argument that manualised befriending merits investigation as an intervention (23). Occupational therapy as a control group was ranked highest for inpatient settings and group delivered interventions, but second to last in the analysis that excluded treatment resistant samples, indicating that the large effects may be associated with this group in particular. Art therapy was not included in the definition of psychological intervention for

this network meta-analysis, and no RCTs were found for psychoanalytic and/or psychodynamic interventions, and thus no inferences can be made about their inclusion in NICE guidelines.

Overall, three interventions were consistently identified as being most likely to reduce total symptoms across analyses: mindfulness-based psychoeducation, CBT with social skills training, and cognitive remediation focussed on social cognition. However not all of these were included in the stringent RoB analysis and high quality RCTs are required to confirm/refute these findings. The categorisation of cognitive remediation focussed on social cognition also provides insight into the differential effects compared with traditional cognitive remediation. TAU0, unsurprisingly was in the bottom third for all analyses.

Limitations

This analysis did not include non-English articles, and while the grey literature was retained in the systematic review, it was not possible to investigate whether there were unpublished RCTs associated with conference proceedings or search clinical trial registries. This may lead to publication bias especially for intervention categories with few RCTs. Similarly, there are a number of psychological interventions currently under investigation which, as of December 2016 had not been included in a complete evaluation using a randomised design and were not included in this analysis.[24]

This network meta-analysis was based on the initial design of Leucht et al[15] which excluded RCTs from China, citing concerns about study quality; however, no evidence was found to assume this concern also applied to RCTs of psychological interventions. All three RCTs of mindfulness-based psychoeducation, conducted in China and ranked as having a low RoB using the stringent Cochrane criteria, were conducted in medically affiliated university

hospitals, and published in prestigious peer reviewed journals- meeting the criteria suggested by Wu et al.[25]

A random effects model was chosen in the first instance to account for heterogeneity across RCTs.[22] The subgroup analyses overall suggest differential effectiveness in different settings and with different samples however this is in part due to the lack of RCTs across multiple settings, for example, mindfulness-based psychoeducation was not delivered in an inpatient setting and therefore effectiveness cannot be assumed in this setting. As there were differences in potential confounding variables, such as location, sample and delivery, across intervention types (see Table 2) it is possible that overall findings may be impacted by such confounders, however it is important to note that there was little evidence of loop inconsistency.[22] Future analyses, including meta-regression, may identify the impact of potential confounding variables. It recommended that the subgroup results be given precedence in clinical decision-making and could support research strategies.

This network meta-analysis excluded people with substance-induced psychosis or substance abuse, bipolar disorder, veterans, and RCTs conducted in forensic settings, and is therefore not generalisable to these populations. First episode psychosis (FEP) is included in the recent onset subgroup analysis, however RCTs that had an age restriction of less than 40 years old were excluded, therefore the majority of evidence relevant to FEP is missing from this analysis.

This analysis focused on total symptoms however symptom reduction is not always the goal of psychological therapy. Alternative measures of recovery, and patient identified outcomes are increasingly being used in RCTs (e.g. Choice of outcome in CBT for psychoses.[26] Indeed, many psychological interventions are recovery focused, an outcome which encapsulates aspects of subjective improvement which are not correlated with symptom change.[30] Further analysis of the effectiveness for different outcomes is required, particularly as some

interventions target specific outcomes[7]- effectiveness may be obscured within the total symptoms analysis.

There is no consensus on the number of RCTs required in each intervention type (aka node) for network meta-analysis[27] however it is important to note that intervention nodes containing single RCTs are arguably less accurate as they do not represent a robust evidence base, and may be susceptible to overestimation of effects.[28] This issue may be compounded by the inclusion of single RCTs that did not meet the Cochrane low risk of bias criteria. In this review, this is of particular relevance to CBT with social skills training. In contrast, nodes with numerous RCTs are likely to have a lower effect size but also more likely to report statistical significance.[29] This pattern may be observed with CBT.

Conclusions

This analysis indicates that several treatments not currently included in NICE guidelines (for example, mindfulness-based psychoeducation and CBT with social skills training) could potentially be more effective than currently included treatments, though this finding is based on few studies and additional RCTs and meta-analyses are needed to generate more conclusive evidence in this regard.

This analysis also highlights the importance of including evidence from combined interventions which may have different mechanisms of change and efficacy, compared with either intervention alone. As seen in the subgroup analysis, recommendations should take treatment setting and time since onset into account- this analysis may inform hypothesis generation about the effectiveness of different interventions across different settings and samples. More high quality RCTs based on these results would be prudent, particularly as many intervention categories in this study contained just one RCT. Meta-analysis of

recovery-based outcomes would also provide further evidence to support personalised patient and clinician decision-making about psychological interventions for psychosis and schizophrenia.

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Funding body

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Contributors

EMG and PH designed the study. EMG registered the protocol and managed the literature search, analysis and writing of the draft. GD contributed to the systematic review of the literature, categorisation of interventions, and data extraction. DT and CW provided pre-collected data. PH, ND, PM, WP and HS provided ongoing supervision and advice, and in-depth feedback on drafts of the article.

Declaration of interest: None.

Appendices for
A network meta-analysis of psychological interventions for schizophrenia and psychosis

NMA Appendix 1- Prospero registered protocol
-as copied from Prospero: International prospective register of systematic reviews- last update June 2017.

A network meta-analysis of psychological interventions for schizophrenia and psychosis

Edel Mc Glanaghy, Paul Hutton, David Turner, Georgina Davis

Citation

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Review question

What is the effect of psychological interventions for psychosis?
Which psychological interventions are most effective?
For which outcomes are psychological interventions most effective?

Searches

Searches of MEDLINE, PsycINFO, EMBASE and CENTRAL will be conducted using search terms for 'psychosis and schizophrenia' from relevant Cochrane Reviews, psychological interventions as listed in Turner et al 2014, and RCT filters where available. Unpublished trials will be identified through contacting investigators listed in grey literature (such as conference abstracts) and a search of clinicaltrials.gov.
Abstracts and full text will be screened by 2 authors using Covidence software and discrepancies will be resolved through discussion.
There will be no language or time period restrictions, however trials published after 31st December 2017 will not be included.
Reference:
Turner, D. T., van der Gaag, M., Karyotaki, E., & Cuijpers, P. (2014). Psychological interventions for psychosis: a meta-analysis of comparative outcome studies. American Journal of Psychiatry.

Types of study to be included

Ideally blinded randomised controlled trials will be included, however, due to the nature of psychological intervention it is anticipated that there will be minimal blinded trials. Thus 'open label' randomised trials will be included. Single intervention within group studies and case studies will be excluded. So too will studies that allow for switching of treatments between groups (crossover trials).

Condition or domain being studied

People with schizophrenia, psychosis or related disorder (schizophreniform disorder, schizoaffective disorder, delusional disorder) as defined by diagnostic or clinical criteria.

Participants/population

People aged 18-65 years old of both sexes with schizophrenia, psychosis or related disorder (schizophreniform disorder, schizoaffective disorder, delusional disorder) as defined by diagnostic or clinical criteria.
This includes first episode psychosis, people with drug-resistant symptoms, people receiving concurrent treatment as usual and/or pharmacological intervention.
Exclusion criteria are as follows: Trials that specify a co morbid serious medical illness or other psychiatric disorder (except anxiety or depression), trials of people deemed to be 'at-risk' or who have not yet developed symptoms, trials that specify primary negative symptoms or in which all participants were stable at baseline. Exclusion criteria also include trials that focus on conditions such as bipolar disorder, substance-induced psychosis, post-partum psychosis specifically or dementia.
To protect the assumption of transitivity, it is important that all participants in all trials could, theoretically, be recruited into all trials. Thus any trial that meets the inclusion criteria yet has further rigid inclusion criteria may be excluded.

Intervention(s), exposure(s)
Psychological intervention is defined as theory driven, goal oriented intervention designed to reduce symptoms and improve functioning, taking place in the community or inpatient setting. Therapies of specific interest include, but are not limited to, CBTp, social skills training, family therapy and cognitive remediation- however cognitive remediation trials must include a clinical outcome, such as PANNS, to be included. Group and individual trials will be included.
Art, music and exercise therapy will be excluded, along with occupational therapy and interventions targeting physical health (such as weight gain), or adherence to medication schedules. Self help, online and trials of environmental interventions (such as community versus inpatient setting) will be excluded, as will trials that are drug only or preventative.
Comparator(s)/control
All psychological interventions will be compared against each other, and against the 'non- interventions', that is, the treatment as usual, waitlist, befriending and psychological placebo groups. Alternative groups may be included to facilitate loops in the Network Meta Analysis network if required. This will be stated explicitly.
Primary outcome(s)
Overall efficacy will be primarily measured as the mean change in total score of the Positive and Negative Syndrome Scale (PANNS) from baseline to endpoint. If PANNS results are not available, the scores from the Brief Psychiatric Rating Scale (BPRS) will be used. If neither scale is used, the clinician identified primary outcome will be used and noted.
Timing and effect measures
All pre and post data will be gathered along with follow up data for up to 12 months post trial, where available.
Secondary outcome(s)
1. Positive Symptoms (derived from PANNS, BPRS or author defined).
2. Negative Symptoms (derived from PANNS, BPRS or author defined).
3. Relapse (as measured by authors)
4. Hospital (re) admission rates
5. General Functioning (General Assessment Functioning preferred then as measured)
6. Quality of Life (as measured by authors).

Finally, data on stakeholder defined improvement/recovery (outcomes defined by person receiving intervention, such as QPR (Questionnaire about the Process of Recovery) or as described by authors) and adverse outcomes will be collected where available however it is anticipated that there will be insufficient studies to allow for analysis.
Timing and effect measures
All pre- and post data will be gathered along with follow up data for up to 12 months post trial, where available.
Data extraction (selection and coding)
Independent data extraction will be completed by EMG and GD and discrepancies will be resolved by discussion. Previously extracted data for comparative outcome studies included in Turner et al (2014) will be included in the dataset, updated with extra outcomes where relevant.
Reference: Turner, D. T., van der Gaag, M., Karyotaki, E., & Cuijpers, P. (2014). Psychological interventions for psychosis: a meta-analysis of comparative outcome studies. American Journal of Psychiatry
Risk of bias (quality) assessment
Risk of bias assessed by Cochrane Risk of Bias tool.
Strategy for data synthesis
Aggregate trial data will be collected and a Network Meta-Analysis will be carried out using STATA 14. A detailed diagram of the network will be presented with a brief narrative table to describe the trials and categorisation of interventions. Similar to Leucht et al (2013) the primary outcome will be based on mean scores, using LOCF for dropouts where possible. Unreported standard deviations will be calculated from other information or requested from authors. Standardised mean difference will be calculated with a 95% CI, with a random effects model in the first instance. Dichotomous outcomes will be based on ITT, and odds ratio will be calculated with a 95% CI. Statistical heterogeneity will be investigated through visual inspection of the forest plots, the I-squared statistic and p value from a standard test for heterogeneity.
A mutli-treatment meta-analysis will be carried out, following the statistical protocol of Leucht et al (2013). To ensure the validity of the underlying assumptions of the analysis the network will be assessed for coherence. Incoherence within a closed loop will be investigated for material cause, that is clinical and methodological variables that may explain the incoherence, such as differences in therapy, participants, chronicity etc, rather than the nature of the intervention.
Reference: Leucht, S., Cipriani, A., Spineli, L., Mavridis, D., Örey, D., Richter, F., ... & Kissling, W. (2013). Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. The Lancet,382(9896), 951-962.
Analysis of subgroups or subsets

A number of exploratory sensitivity analyses will be carried out if there are adequate numbers of studies:
1. Trials that specify first episode/early stage compared with non-specified,
2. Drug resistant psychosis compared with non-specified,
3. Group -v- individual format interventions.
Sensitivity analysis will include:
1. Blinded -v- non-blinded RCTs and
2. High quality trials -v- low quality (as assessed by Cochrane Risk of Bias tool).

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Anticipated or actual start date

31 May 2016

Anticipated completion date

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EMG is a Trainee clinical psychologist, funded by NHS Education for Scotland, via NHS Forth Valley and University of Edinburgh.

Conflicts of interest

None known

Language

English

Country

Scotland

Stage of review

Review_Ongoing

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

Humans; Psychotic Disorders; Schizophrenia

Date of registration in PROSPERO

22 May 2016

Date of publication of this version

27 June 2017

Revision note for this version

After recent training on Network Meta Analysis the population criteria has been specified more clearly; for example, older adults will be excluded. Similarly, the interventions of interest have been identified with a more concise definition of a psychological therapy. The Systematic review is not complete and will be updated to reflect these criteria moving forwards.

Details of any existing review of the same topic by the same authors

While a full search will be carried out, it is anticipated that there will be some overlap in trials from Turner et al, 2014, and data already extracted will be incorporated into this analysis.
Reference: Turner, D. T., van der Gaag, M., Karyotaki, E., & Cuijpers, P. (2014). Psychological interventions for psychosis: a meta-analysis of comparative outcome studies. American Journal of Psychiatry.

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	Yes

Stage	Started	Completed
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

----- End-----

NMA Appendix 2- Clarifications of, and adaptations to, registered protocol.

General RCT characteristics

- Only RCTs that were randomised were included- and this was conservatively judged. Cluster randomisation and crossover trials were excluded.
- Cochrane RoB 2.0 (17) was used in first instance, however was too stringent, so a post hoc analysis was completed using Leucht criteria which considered RCTs to be at high risk of bias if there was high risk of randomisation or allocation concealment bias.
- There was only one double-blind RCT (involving computerised intervention), and so the blind -v- non-blind subgroup was not possible.
- RCTs published up to end of 2016 were included. Some RCTs, dated 2017 were included if the article was published online in 2016.
- RCTs that specified 'clinically stable' or 'on stable medication' were included, as a large proportion of RCTs included this in their inclusion criteria. A sensitivity analysis was carried out to account for the impact of this.

Participant Characteristics

- RCTs that included people with characteristics cited as exclusion criteria for this protocol (that is, people with bipolar disorder, substance-induced psychosis, post-partum psychosis specifically or dementia) were considered for inclusion if the number meeting that criteria was 10% or less of the RCT total sample. Where RCTs included people from specific populations not listed as exclusion criteria in the protocol, such as veterans and people in forensic settings; these were included if no more than 50% of the RCT sample met the specific criteria.
- RCTs that took place in forensic and VA (Veteran's Administration health centres in the US) settings only were excluded.
- RCTs that included extra inclusion criteria that were unlikely to be commonly present in other samples, for example, history of violence, or history of compliance with command hallucinations, were excluded. Clinical judgements were made about other criteria such as PTSD, worry, and auditory hallucinations, and these were considered symptoms likely to be commonly present in non-specified samples.
- RCTs that specified primarily, or predominantly, negative symptoms as inclusion criteria were excluded. In contrast, RCTs that involved an intervention targeting negative symptoms, but did not specify negative symptoms as inclusion criteria, were included.
- Age 18 and above was specified in the protocol, however a number of RCTs included people age 16 and 17 up to age 60, and the criteria was adapted as follows; RCTs targeting young

people or older people specifically were excluded, such that RCTs with an upper age limit of less than age 40, or RCTs with a lower age limit of more than 40 years old were excluded.

Intervention/Control Characteristics

- Interventions lasting longer than 12 months were not included in the analysis.
- Psychoeducation interventions were only included if they were judged by both reviewers (EMG & GD) to have psychological aspects beyond medication adherence, except as a control group for other relevant interventions.
- Family based interventions were only included if the person with psychosis was included in the intervention sessions as standard; RCTs targeted at family members alone were not included, except as a control group for other relevant interventions.
- RCTs that included 2 variations of the same psychological intervention were excluded as they could not be included in the analysis; for example, psychotherapy administered in group and individual format, or two forms of cognitive remediation targeting broad and specific functions respectively.
- RCTs that included medication were included unless medication dose was an element under investigation. Similarly, RCTs with an uncommon medication under investigation were excluded.
- RCTs of psychological intervention alongside vocational programmes were excluded, as were psychological intervention that were provided within a service wide intervention- for example, CBT included as part of a global early intervention service which included enhanced case management, psychoeducation etc. compared with a TAU service. The exception to this rule was if both randomised groups received the enhanced service (TAU3) and the specific psychological interventions were the only difference.
- Treatment as usual was categorised according to the level of standard treatment; medication only (TAU0), medication with ongoing case management (TAU1), access to a multi-disciplinary team (TAU2) and receipt of a range of multi-disciplinary interventions including psychological interventions (TAU3). Where information about TAU was not provided, the country and year of the RCT was used to categorise the likely TAU as follows.
    - Country of RCT was used to identify the number of psychiatrists per 100,000 for that population (according to WHO global health observatory data; http://www.who.int/gho/mental_health/human_resources/en/)
        - If the country had 10+ psychiatrists per 100,000 AND was published in the past 10 years it was assigned TAU2.
        - If the country had 10+ psychiatrists per 100,000 AND was published in more than 10 years ago it was assigned TAU1.

- Countries with between 4-10 psychiatrists per 100,000 were assigned TAU1.
- Countries with less than 4 psychiatrists per 100,000, were assigned TAU0.

- Behavioural interventions which would now be considered unethical (such as self-shock) were excluded.

Outcome Measure Characteristics

- A range of outcomes were listed in the protocol; this study reports on total symptoms outcome only.

NMA Appendix 3- Search terms

Simultaneous search of Medline R, Embase and Pychinfo using Ovid

1. psychotherapy.mp OR exp Psychotherapy, Rational-Emotive/ or exp Psychotherapy/ or exp Psychotherapy, Multiple/ or exp Psychotherapy, Group/ or exp Psychotherapy, Brief/ or exp Psychotherapy, Psychodynamic/ OR psychological intervention.mp OR exp Cognitive Therapy/ OR exp Behavior Therapy/ OR behavio*r therapy.mp OR cognitive therapy.mp Or CBT.mp OR exp Family Therapy/ OR family therapy.mp OR cognitive remediation.mp OR social skills training.mp OR sensory art therapies.mp OR exp sensory art therapies/ OR art therapy.mp OR exp Art therapy/ OR psychoeducation*.mp OR exp Patient Education as Topic/ OR psychoanalytic therapy.mp OR exp Psychoanalytic Therapy/ OR counse*ling.mp OR Directive Counselling OR exp Counselling/ OR Distance Counselling/ OR supportive therapy.mp Or befriending.mp or psychosocial intervention.mp
2. exp SCHIZOPHRENIA/ or exp SCHIZOPHRENIA, CATATONIC/ or exp SCHIZOPHRENIA, CHILDHOOD/ or exp SCHIZOPHRENIA, DISORGANIZED/ or exp SCHIZOPHRENIA, PARANOID/ or Disorders with Psychotic Features/ or exp Psychotic Disorders/ or exp Paranoid Disorders/ or schizo*.mp or psychotic*.mp or psychos*.mp or psychoses.mp
3. randomi$ed controlled trial.pt OR controlled clinical trial .pt OR randomi$ed.tw OR randomly.tw OR trial.tw OR groups.tw
4. animals/ NOT humans/
5. 3 NOT 4
6. 1 AND 2 AND 5

CENTRAL database

1. Psychotherapy OR psychological intervention OR behavio*r therapy OR cognitive therapy Or CBT OR family therapy OR cognitive remediation OR social skills training OR sensory art therapies OR art therapy OR psychoeducation* OR psychoanalytic therapy OR counse*ling OR Directive Counselling OR Distance Counselling OR supportive therapy Or befriending or psychosocial intervention
2. MeSH descriptor: [Psychotherapy] explode all trees
3. #1 or #2
4. MeSH descriptor: [Schizophrenia] explode all trees
5. Schizo* or Psychotic or psychos* or psychoses
6. #4 or #5
7. #3 and #6 Publication Year from 1860 to 2016, in Trials

NMA Appendix 4- Classification of psychological interventions
-See Table 1 in main text for list of abbreviations

Category & Code	Description	Intervention Code
Control Groups		

Treatment as Usual TAU0 TAUA TAUB	Treatment as usual is a control condition where participants continue to receive routine services and/or interventions. This includes wait list control groups that continued to receive TAU. As standard intervention may vary across time and geography, a number of distinct categories were listed as follows; • TAU0- Minimal contact and/or intervention- for example, medication only with no follow up. • TAU1- Medication with routine check-up appointments/follow up. • TAU2: Case management and/or access to MDT services such as social work, OT and psychosocial interventions. • TAU3- TAU2 plus specified delivered psychological interventions, for example, CBT or motivational interviewing. • Details on classification of TAU that was not specified can be found in Appendix 1.	TAU0 TAU TAU1 TAU2 TAU3
Befriending BF	Often included as a control group. Intervention contact time and format is matched, but the content involves leisure activities and/or socialising with peers and supportive 'therapist'. Content is not related to mental health difficulty. This category also included computerised controls- control groups for computerised interventions to match contact time and format.	BF CCBF CC
Supportive counselling SC	Supportive counselling is often included as a control condition to account for contact time and the non-specific factors of a face-to-face talking therapy, without specific techniques or agenda. This usually involves an empathetic, person-centred approach focused on mental health difficulty but there is no focus on developing new skills or perspective.	SC
Occupational Therapy OT	Occupational therapy is often included as a control group. It included guided activities to develop daily living skills and cognitive adaptive therapy, which involved adaptation to the home environment to support daily functioning.	OT CAT
Intervention Groups		
Cognitive behaviour therapy CBT	CBT is a goal focused intervention based on the links between thoughts, feelings, behaviours and bodily sensations. CBT typically includes formulation, psychoeducation about the CBT model, thought challenging, progressive muscle relaxation and relaxation strategies, regular 'homework' and behavioural experiments. In this systematic review CBT has also been used to target insomnia and worry specifically. CBTp specifically focused on theoretical models of psychosis.	CBT CBTp
Metacognitive therapy MCT	A form of CBT, metacognitive therapy focuses on meta-cognitions specifically. It aims to bring cognitive distortions to awareness of patient, and highlight alternative responses (Agothor et al, 2010). It is commonly delivered in a group using power-point presentation.	MCT
Cognitive remediation	Cognitive remediation targets the cognitive difficulties	CR CR_BF

CR	associated with psychosis, and typically involves strategies to promote basic cognitive processes, such as working memory, attention, and executive function. The intervention may be delivered in group or in a one-to-one setting, may be computerised or include pen and paper tasks. Therapist/trainer involvement is common. Some CR interventions focus primarily on attention or auditory hallucinations. Only included if a trainer/therapist was involved- so no self help.	CR_meta
Cognitive remediation; social cognition CRSS	Interventions classed as CRSS are similar to CR but specifically target social cognitive difficulties, such as theory of mind and emotional processing.	CRSS CR_CRSS
Family therapy FT	Family therapy includes all interventions that aimed to improve functioning by involving and supporting family members. To meet the systematic review criteria family based interventions had to include the person with psychosis, and not only target carer needs. Behavioural family therapy, family psychoeducation, family social groups (which may involve psychoeducation, but not only psychoeducation), family therapy and family assisted social cognitive training were all included in this category.	BFT FPE FSG FT FSIT
Eye Movement Desensitisation and Reprocessing EMDR	EMDR is a one-to-one therapy that targets traumatic memories and aims to ameliorate these using eye movements and/or other bilateral stimulation.	EMDR
Wellbeing WB	WELLFOCUS (Schrank, 2016), a wellbeing intervention, focuses on positive psychology and uses exercises to promote positive experiences and self-narrative.	WB
Social skills training SST	Behavioural intervention based on social learning theory in which participants' social functioning is targeted in order to improve their ability to perform in social situations, manage daily life tasks, and reduce social distress. Importance is typically placed on verbal and nonverbal communication alongside learning appropriate perception and responses to social cues. The intervention may also include training in independent living skills and is often provided in a group setting.	SST SST_FPE
Psychoeducation& Coping PE	Psychoeducation interventions are diverse yet most aim to share information about psychosis and/or helpful coping strategies. Psychoeducation for medication adherence alone did not meet the systematic review criteria. This category included coping skills sessions, progressive muscle relaxation, problem-solving therapy and a self-esteem intervention (Lecomte, 1999).	PE CPS PMR PST PESC SE
Mindfulness-based psychoeducation MPE	Mindfulness-based psychoeducation aims to enhance understanding of schizophrenia, and to increase awareness, acceptance and management of symptoms such as hallucinations and delusions.	MPE

Combined Others		
MCT_CBT CBT_OT CBT_SST CR_MCT CR_SST	Combined interventions are identified as X_Y; Intervention X combined with intervention Y.	
ALL	ALL refers to an intervention protocol which included 4 distinct therapies delivered simultaneously (Guo, 2010); psychoeducation, family intervention, skills training and CBT.	ALL
HIT	HIT included cognitive behavioural interventions, coping training, family therapy and rehabilitative efforts- case management was not mentioned and so HIT was included, whereas other MDT based interventions are not.	HIT
This table is adapted from the descriptive table in Turner et al (2014)		

NMA Appendix 5- Evaluation of Intervention Implementation

	Rating item	Scoring system
1	Is the treatment described?	0 In Detail/Yes 2 No
2	Is the treatment manualised/protocol referenced?	0 Yes includes adapted/developed for this intervention 1 Unclear/flexible 2 No
3	Was the theoretical model articulated/appropriate?	0 Yes 1 Unclear. 2 No
	Integrity of Intervention total	**0 High Integrity- 6 Low Integrity**
4	Was therapy practice supervised?	0 Yes, with detail. 1 Unclear/not mentioned 2 No
5	Was adherence to manual assessed?	0 Yes 1 Not mentioned/unclear/using therapist's own notes 2 No
6	Was the training received by therapists described?	0 Yes with some detail 1 Unclear/not mentioned/'was trained' 2 No
7	What was the qualification of therapist?	-1 Clinical Psychologist, Psychiatrist, other therapist above MSc level 0 Other mental health professional (includes nurses, therapists, OTs) 1 Unspecified 2 Inappropriate
	Reported fidelity total	**-1 to 0 High likelihood of fidelity- 8 Low likelihood of fidelity**
8	Was dose captured?	0 Yes with enough detail to calculate total contact time 1 Unclear 2 Not mentioned
9	Was attendance captured?	0 Yes 1 Unclear 2 No
	Dose total	**0 Dose well reported- 4 Dose not reported**

Ratings of intervention arms of RCTs

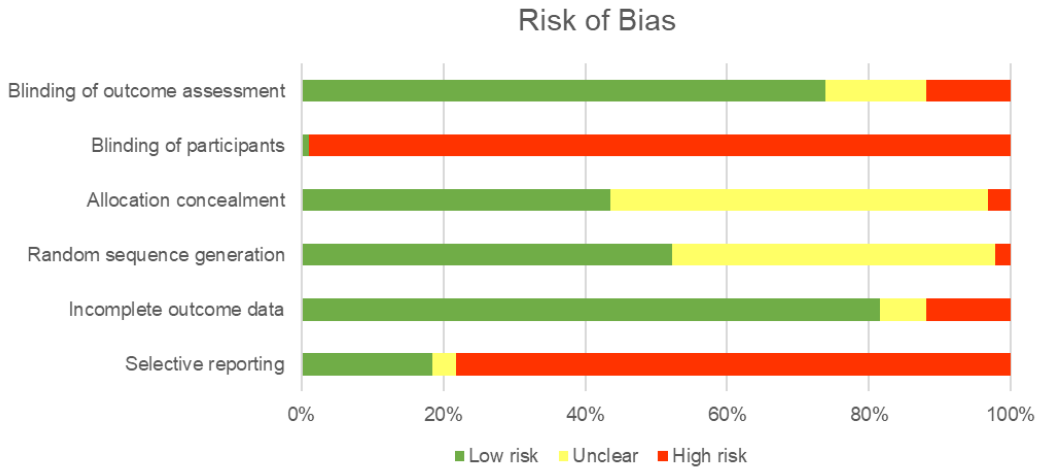
	Rating	Intervention arms N (%)	Score interpretation
Integrity of intervention	0	92 (81%)	0 High Integrity
	1	15 (13%)	6 Low Integrity
	2	5 (4%)	
	3	2 (2%)	
	4	0 (0%)	
	5	0 (0%)	
	6	0 (0%)	
Fidelity to intervention	-1	15 (13%)	-1 to 0 High likelihood of adherence
	0	20 (18%)	
	1	16 (14%)	8 Low likelihood of adherence
	2	23 (20%)	
	3	12 (11%)	
	4	27 (24%)	
	5	1 (1%)	
	6	0 (0%)	
	7	0 (0%)	
	8	0 (0%)	
All 20 (18%) arms where the fidelity rating outcome was reported it was at least 'good' or distinct from control			
Dose	0	2 (2%)	0 Dose well reported
	1	31 (27%)	4 Dose not reported
	2	57 (50%)	
	3	24 (21%)	
	4	0 (0%)	
Dose 83 (73% arms)			
Session length		Mean: 77 minutes Median: 60 (range: 25-210)	
Number of sessions		Mean: 20 sessions Median: 16 sessions (range: 1-52)	
Total contact time		Mean: 24 hours Median: 20 hours (range: 3.5- 65)	
Results based on 114 of 197 intervention arms. Excluded: TAU (58), BF (12), SC (10) and OT (3).			

NMA Appendix 6- Risk of bias assessment

Author year	Selection bias; random sequence generation	Selection bias; allocation concealment	Reporting bias; selective reporting	Attrition bias; incomplete outcome data	Performance bias; blinding of ppts and personnel	Detection bias; blinding of outcome assessment
Aghotor 2010	+	?	-	+	-	+
Andreou 2017	?	+	-	+	-	+
Bark 2003	?	?	-	?	-	+
Barrowclough 2006	+	+	-	+	-	+
Bechdolf 2004	+	?	-	+	-	?
Bradley 2006	+	+	-	+	-	+
Buonocore 2015	+	?	-	+	-	?
Byrne 2013	+	+	-	-	-	-
Cai 2015	+	+	-	+	-	+
Chan 2009	+	+	-	+	-	+
Chien 2013a	?	?	-	+	-	+
Chien 2013b	+	?	-	+	-	+
Chien 2014	+	+	+	+	-	+
d'Amato 2011	?	?	-	+	-	+
Dickinson 2010	?	+	-	+	+	+
Durham 2003	+	+	-	+	-	+
England 2007	+	?	-	+	-	+
Fardig 2011	+	?	-	+	-	+
Farreny 2012	+	?	+	+	-	+
Fernandez-Gonzalo 2015	+	+	-	+	-	+
Fiszdon 2016	?	?	-	+	-	-
Freeman 2015a	+	+	+	+	-	+
Freeman 2015b	+	+	+	+	-	+
Garcia 2003	?	?	-	-	-	?
Garety 2008 (i)	?	+	+	+	-	+
Garety 2008 (ii)	?	+	+	+	-	+
GilSanz 2009	?	?	-	?	-	?
Gohar 2013	?	?	-	+	-	-
Gumley 2003	-	-	-	+	-	-
Guo 2010	?	?	-	-	-	+

Author year	Selection bias; random sequence generation	Selection bias; allocation concealment	Reporting bias; selective reporting	Attrition bias; incomplete outcome data	Performance bias; blinding of ppts and personnel	Detection bias; blinding of outcome assessment
Haddock 1999	?	?	-	+	-	+
Hayes 1995	?	?	-	-	-	+
Jenner 2004	?	+	-	+	-	-
Jorgensen 2015	+	+	+	+	-	-
Kang 2016	+	+	-	+	-	+
Kantrowitz 2016	+	+	+	-	-	+
Keefe 2012	?	?	-	+	-	+
Kim 2010	?	?	-	+	-	+
Kuipers 1997	+	+	-	+	-	?
Kumar 2010	?	?	-	?	-	?
Leclerc 2000	?	?	-	+	-	+
Lee 2013	+	?	-	+	-	+
Lewis 2002	?	+	?	+	-	+
Li 2015	+	+	+	+	-	-
Liberman 2009	?	?	-	+	-	+
Lincoln 2012	+	+	+	+	-	+
Lindenmayer 2013	?	?	-	+	-	-
Lopez-Luengo 2016	+	+	-	-	-	+
Lukoff 1986	?	?	-	+	-	?
Moritz 2011	+	+	+	+	-	+
Mortiz 2013	?	+	?	+	-	+
Morrison 2014	+	+	+	-	-	+
Naeem 2015	+	+	+	+	-	+
Naeem 2016	+	+	-	+	-	+
Ng 2006	+	+	-	+	-	+
Ojeda 2012	?	?	-	+	-	+
Omiya 2016	-	?	-	+	-	?
Penn 2009	+	+	-	+	-	+
Penn 2011	+	?	-	+	-	+
Peters 2010	+	?	-	-	-	+

Author year	Selection bias; random sequence generation	Selection bias; allocation concealment	Reporting bias; selective reporting	Attrition bias; incomplete outcome data	Performance bias; blinding of ppts and personnel	Detection bias; blinding of outcome assessment
Pinto 1999	?	?	✗	✓	✗	?
Rakitzi 2016	?	✓	✗	✓	✗	✓
Rathod 2013	✓	✓	✓	✓	✗	✓
Rector 2003	?	?	✗	✓	✗	✓
Roberts 2014	?	?	✗	✓	✗	✓
Rus-Calafell 2013	?	?	✗	✓	✗	?
Sanchez 2014	✓	?	✗	✓	✗	✓
Schaub 2016	✓	?	✗	✓	✗	✓
Schrank 2016	✓	✓	✓	✓	✗	✗
Sensky 2000	?	?	✗	✓	✗	✓
Shin 2002	?	?	✗	✓	✗	✓
Startup 2004	✓	✗	✗	✗	✗	✗
Tan 2016	✓	?	✗	✓	✗	✓
Tao 2015	?	?	✗	?	✗	?
Tarrier 2014	✓	✓	✗	✗	✗	✓
Tas 2012	✓	✗	✗	✓	✗	✓
Turkington 2002	✓	✓	✗	✓	✗	✓
Valencia 2007	?	?	✗	✓	✗	✓
Valencia 2010	?	?	✗	✓	✗	✓
Valencia 2012	?	?	✗	✓	✗	✓
Valencia 2013	?	?	✗	✓	✗	✓
Valmaggia 2005	✓	?	✗	✓	✗	✓
Velligan 2015	✓	✓	?	✓	✗	✓
Veltro 2011	✓	✓	✗	?	✗	?
Vita 2011b	?	?	✗	✓	✗	✓
Vita 2011a	✓	✓	✗	✓	✗	✓
Wang 2016	✓	✓	✓	✓	✗	✓
Wolwer 2011	?	?	✗	✓	✗	✓
Wykes 1999	?	?	✗	✓	✗	✓
Wykes 2007	✓	✓	✓	✓	✗	✓


Risk of Bias
Blinding of outcome assessment
Blinding of participants
Allocation concealment
Random sequence generation
Incomplete outcome data
Selective reporting
0%
20%
40%
60%
80%
100%
Low risk
Unclear
High risk

NMA Appendix 7- Statistical method

This study applied a frequentist approach to network meta-analysis using a random effects model, in Stata SE v15. The first author attended training with the University of Bristol and applied the method as indicated in the course manual (21). The summary below is based on this manual and training, and the accessible review provided by Tonin et al (2017) (12). The mvmeta package in Stata applies multivariate meta-analytical models, similar to regression where estimates of multiple studies are combined while accounting for their correlation (Gasparrini, 2018; White, 2009).

Network meta-analysis is an evidence synthesis method similar to traditional meta-analysis, and it shares many of the same statistical and epistemological assumptions. Where meta-analysis synthesises the evidence for A -v- B using pooled effect sizes, network meta-analysis synthesises the evidence for A -v- B, A -v-C, B -v- D etc, by creating a network of all interventions and calculating the direct and indirect effects. The indirect effect is calculated from the network, for example, difference between B and C, as extrapolated from A -v- B and A -v- C. Direct evidence, the pooled effect based on RCTs (similar to traditional meta-analysis) is therefore not necessarily available for all comparisons within the network; indeed the ability of network meta-analysis to compare interventions which have not been compared in real life RCTs is one of the key attractive features of the analysis. It can support clinical decision-making across a wider range of intervention types.

The principle assumption, transitivity (known as consistency in the statistical analysis) assumes that every participant in every RCT could, *in theory,* have been randomised to any study arm. Again, this is similar to traditional meta-analysis however in network meta-analysis it is important to consider across intervention types as well as across RCTs. Clear inclusion criteria, and a well-defined systematic review protocol can support the preservation of transitivity in the sample (15). Consistency checks statistically compare the indirect and direct evidence (where available) to provide evidence about the consistency of the model as a whole using a chi^2 statistic. P values are reported for comparisons of the direct and indirect SMDs for each connecting 'arm' of the network, and the diamond plot provides a visual depiction of this evidence. Where evidence of inconsistency was identified the

source was explored in sequence; 1. investigation of errors in data entry and intervention categorisation, 2. inconsistencies in population/study quality that could explain the discrepancy, and 3. reassessing the intervention categorisation. Decisions about the exclusion of RCTs which contribute to inconsistency are reported in Appendix 8 to preserve transparency of analysis decision-making. Higgins et al (22) indicate that loop inconsistency across RCTs is usually caused by differences between; participants, intervention delivery and/or setting, context or time period.

Along with direct and indirect effect sizes, network meta-analysis also generates information about the probability of each intervention being 'best' using SUCRAs (surface under the cumulative rankings curve) for each intervention. This SUCRA value compares each intervention against a hypothetical 'best' intervention which permits easy comparison across all interventions- by providing a hierarchy of effectiveness. A score of 100 would indicate 100% effectiveness of the hypothetical 'best'- a score lower than 50 indicates approximately half of the effectiveness.

References specific to Appendix 7:

Gasparrini A, Multivariate and univariate meta-analysis and meta-regression [Package 'mvmeta']. March 7, 2018. Retrieved from https://cran.r-project.org/web/packages/mvmeta/mvmeta.pdf.

White, I R. Multivariate random-effects meta-analysis. The Stata Journal, 2009; 9, 1. 40-56.

Total Symptom Analysis

Original model; 91 RCTs with 191 arms. There was no evidence of inconsistency for the model $\chi 2$ (27, N = 91) = 32.45, p = .216 however there was a statistically significant difference between direct and indirect evidence for OT -CRSS (direct 0.58, indirect -0.43, p = .032), and CRSS-SST (direct 1.71, indirect 0.01, p = .001). Review of the diamond plot (see Figure 8.1) identified Study 564 (Mazza, 2010) as the potential source of the inconsistency. Data was checked, and no obvious RCT characteristic was identified as the source of the inconsistency. Mazza (2010) was excluded and the analysis was re-run; no evidence of inconsistency found $\chi 2$ (27, N = 90) = 22.86, p = .583 with no differences between direct and indirect evidence. The full results are presented in the main article.

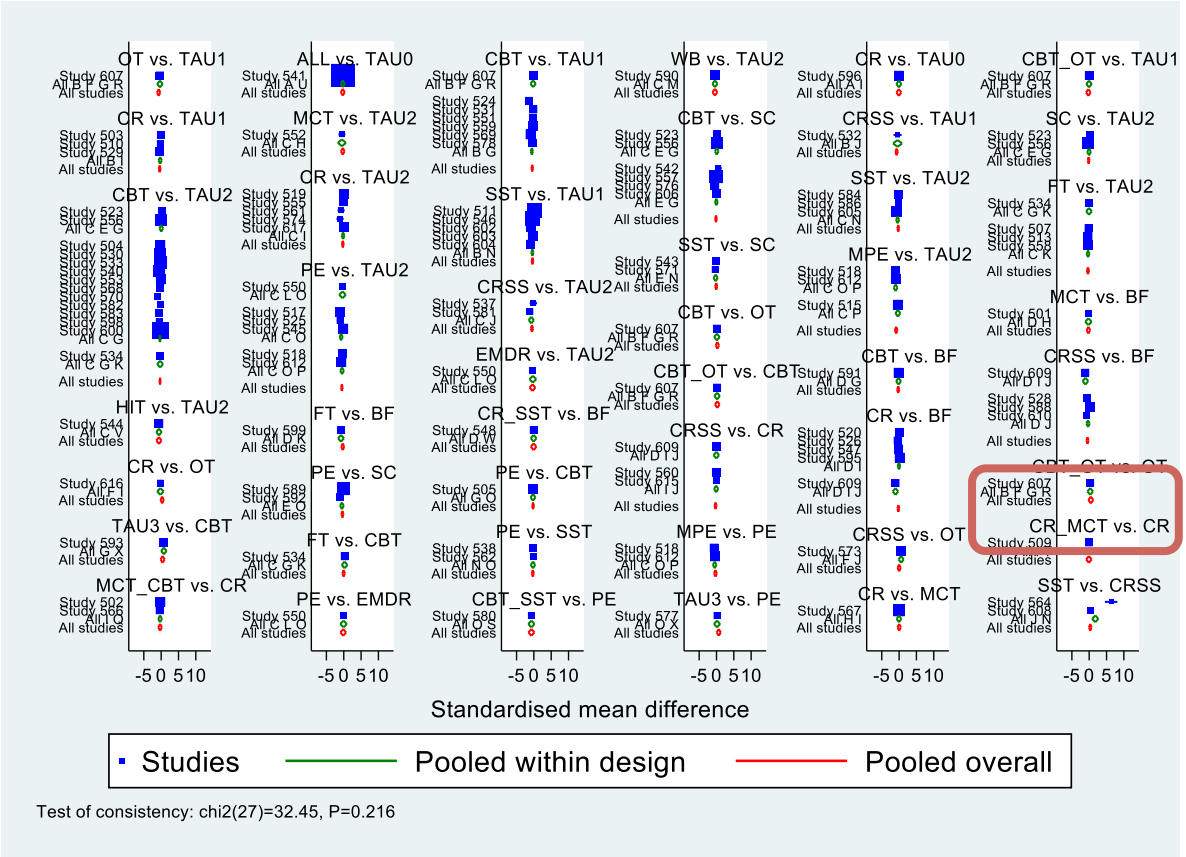


Figure 8.1: Original Analysis diamond plot. Note; blue indicates direct evidence from RCTs, green diamond is combined direct evidence, and red is indirect evidence. Inconsistency can be identified if green and red diamonds are different. Table 1 in the main text contains the full list of abbreviations.

Sub group analysis: Chronic

Original model for chronic included 66 RCTs with 139 arms. There was no evidence of inconsistency $\chi 2$ (20, N = 66) = 27.94.86, p = .111 however comparison of direct and indirect evidence identified one comparisons as being statistically significantly different OT v cognitive remediation focussed on social cognition (see Figure 8.2); Study 609, Vita 2011a (3 arms; cognitive remediation- befriending - cognitive remediation focussed on social cognition) was visibly inconsistent and the analysis was run again without this RCT, however this did not change the results. As the model was not found to be inconsistent the decision was made to keep this RCT in the full analysis, however the discrepancy with direct and indirect evidence indicates that the results should be interpreted with caution.

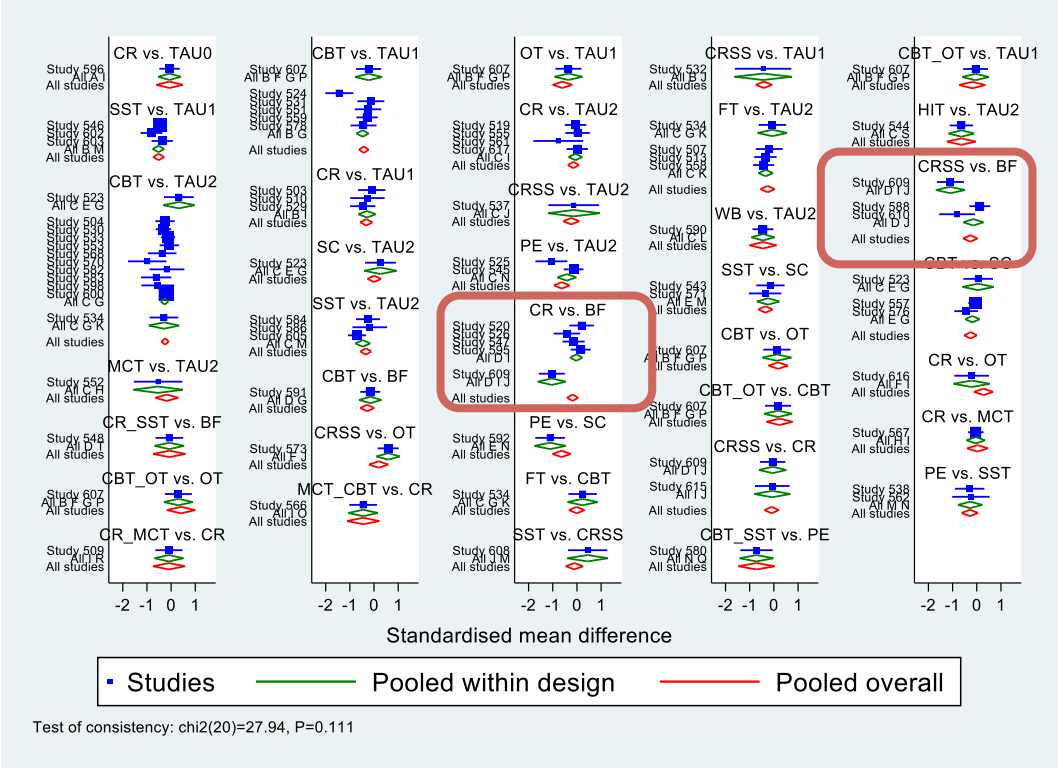


Figure 8.2: Original Chronic sub group analysis diamond plot

NMA Appendix 9- Description of included studies
Reference list is in Appendix 10.

Study, year	Mean Duration of illness (years)	Setting	Mean Age (x.x sd; x-x range)	Stage			Intervention and Control Groups			
				Early (<5 years duration)	Clinically Stable/ Acute	Other	Group	n	Intervention format	Tria leng (weel
Aghotor 2010	3.75	Inpatient	28.9 (18-48)	Early			MCT	16	Group	4
Aghotor 2010			32.6 (22-62)	Early			BF	14	Group	4
Andreou 2017	.	Both	36.91 (12.5)			Delusional disorder	MCT_CBT	46	Individual	6
Andreou 2017	.		35.59 (13.1)				CR	46	Computer	6
Bark 2003	.	Inpatient	35 (7.07)				CR	36	Computer	10
Bark 2003			38.55				TAU1	18		10
Barrowclough 2006	13.67 (7.99)	Outpatient	38.83 (8.6)		Stable		CBT	57	Group	26
Barrowclough 2006					Stable		TAU2	56		26
Bechdolf 2004	4.72 (5.45)	Both	32.2 (9.9)	Early			CBT	40	Group	8
Bechdolf 2004	4.17 (4.89)		31.4 (10.6)	Early			PE	48	Group	8
Bradley 2006	n/a	Outpatient	33.6 (6.68)				FSG	25	Group	52
Bradley 2006			34.0 (9.6)				TAU2	25		52
Buonocore 2015	13	Outpatient	34.4 (9.9)		Stable		CR_MCT	30	Group & Indiv	16
Buonocore 2015			38.4 (9.2)		Stable		CR_BF	27	Group & Indiv	16
Byrne 2013	19.44 (10.04)	Inpatient	45.15 (9.81)		Stable		CR	27	Computer	6
Byrne 2013	24.92 (8.82)		46.04 (8.68)		Stable		TAU1	24		6
Cai 2015	3.95 (0.72)	Outpatient	33.92 (9.03)	Early	Stable		SST_FPE	133	Group	10
Cai 2015	3.69 (1.37)		34.49 (8.92)	Early	Stable		TAU1	123		10
Chan 2009	10.2 (7.6)	Outpatient	34.2 (10.1)				FPE	36	Group	13
Chan 2009	10.5 (9.5)		36.3 (13.10)				TAU2	37		13
Chien 2013a	3.1	Outpatient	25.8 (8.5)	Early			MPE	48	Group	13
Chien 2013a				Early			TAU2	48		13
Chien 2013b	0.1	Outpatient	25.7 (6.9)	Early			PE	48	Individual	13
Chien 2013b	0.1			Early			TAU2	48		13
Chien 2014	2.6 (1.7)	Outpatient	25.1 (6.8)	Early			MPE	36	Group	24
Chien 2014	2.5 (1.8)		25.8 (7.9)	Early			PE	36	Group	24
Chien 2014	2.7 (1.8)		26.0 (8.5)	Early			TAU2	35		24
d'Amato 2011	8.7	Outpatient	33.4 (6.9)		Stable		CR	39	Computer	7
d'Amato 2011	8.1		32.2 (6.0)		Stable		TAU2	38		7
Dickinson 2010	0	Outpatient	46.9 (6.6)		Stable		CR	35	Computer	15
Dickinson 2010	0		48.5 (8.8)		Stable		CC	32		15
Durham 2003	15 (2-31)	Outpatient	36 (10)		Stable		CBT	22	Individual	39
Durham 2003	14 (2-30)		37 (11.2)		Stable		SC	23	Individual	39
Durham 2003	10 (2-27)		36 (10.2)		Stable		TAU2	21		39
England 2007		Outpatient	41				CBT	44	Individual	18

England 2007							TAU1	21		18
Fardig 2011		Outpatient	40.38 (6.76)				PE	21	Group	39
Fardig 2011			40.45 (6.44)				TAU2	20		39
Farreny 2012	17.5 (8.9)	Outpatient	40.6 (7.6)		Stable		CRmeta	34	Group	16
Farreny 2012					Stable		BF	28	Group	
Fernandez-Gonzalo 2015	2.3 (1.7)	Outpatient	30.9 (5.9)	Early	Stable		CR_CRSS	28	Computer	17
Fernandez-Gonzalo 2015	3.01 (1.8)		30.02 (7.4)	Early	Stable		CC	25	Computer	17
Fiszdon 2016	.	Outpatient	47.22 (9.17)		Stable		CR	50	Individual	8
Fiszdon 2016			49.00 (9.68)		Stable		TAU1	25		8
Freeman 2015a	Median; >20 years	Both	40.9 (10.5)			Persecutory delusions	CBT	73	Individual	8
Freeman 2015a	Median: 11-20 years		42.1 (12.2)				TAU2	77		
Freeman 2015b	.	Outpatient	39.6 (11.6)			Insomnia	CBT	24	Individual	12
Freeman 2015b			42.2(13.5)				TAU1	26		
Garcia 2003	21	Outpatient	40.45 (7.1)				CRSS	13	Group	13
Garcia 2003	14.77		36.88 (8.1)				TAU1	10		13
Garety 2008 (i)	10.9 (8.1)	Outpatient	39.1 (10.3)		Acute		CBTp	106	Individual	52
Garety 2008 (i)	9.9 (8.7)		37.1 (10.9)		Acute		TAU2	112		52
Garety 2008 (ii)	10.9 (9.7)	Outpatient	38.6 (12.2)		Acute		CBTp	27	Individual	52
Garety 2008 (ii)	13.3 (11.8)		35 (12.3)		Acute		FT	28	Individual	52
Garety 2008 (ii)	10.5 (8.6)		35.6 (11.2)		Acute		TAU2	28		52
GilSanz 2009	13.43	Outpatient	33.29 (8.36)				CRSS	7	Group	10
GilSanz 2009	20.57		41.43 (9.03)				TAU2	7		
Gohar 2013	11.77 (10.6)	Outpatient	32.95 (10.86)				SST	22	Group	8
Gohar 2013	8.40 (7.02)		30.75 (10.58)				PE	20	Group	8
Gumley 2003	9.42 (6.75)	Outpatient	35.8 (9.6)			Relapse prone	CBT	72	Individual	52
Gumley 2003	9.5 (7)		36.7 (10.1)				TAU2	72		52
Guo 2010	.	Outpatient	26.1 (25.5-26.8)	Early	Stable		ALL	633	Group	52
Guo 2010			26.4 (25.7-27)	Early	Stable		TAU0	635		52
Haddock 1999	.	Inpatient	28.1 (7.24)	Early			CBT	10	Individual	5
Haddock 1999	.		30 (7.9)	Early			SC	11	Individual	5
Hayes 1995	11	Outpatient	36 (10)		Stable		SST	32	Group	18
Hayes 1995					Stable		SC	31	Group	
Jenner 2004	13.4 (12.3)	Outpatient	36.7 (11.4)			Auditory hallucinations	HIT	37	Individual	39
Jenner 2004	10.3 (8.1)		36 (11.6)				TAU2	39		39
Jorgensen 2015	7.9 (8.4)	Outpatient	35.4 (12.2)				PST	50	Individual	26

Jorgensen 2015	11.7 (9.3)		39.6 (12.7)				TAU2	51		26
Kang 2016	21.3 (11.7)	Outpatient	46.4 (11.9)		Stable		SST	118	Group	52
Kang 2016	19.8 (12.1)		45.4 (12.3)		Stable		TAU1	126		52
Kantrowitz 2016	.	Outpatient	37.7 (10.1)		Stable		CR	56	Group	26 (4 mont
Kantrowitz 2016					Stable		CC	64	Group	
Keefe 2012	.	Outpatient	37 (10.27)		Stable		CR_SST	27	Group	12
Keefe 2012					Stable		CCBF	26	Group	
Kim 2010	2.81 (2.91)	Inpatient	29.9 (7.4)	Early	Acute		EMDR	15	Individual	4
Kim 2010	1.76 (2.55)		36.0 (9.5)	Early	Acute		PMR	15	Individual	4
Kim 2010	2.3 (3.87)		31.8 (8.4)	Early	Acute		TAU2	15		4
Kuipers 1997	12.1 (range 1-26)	Both	38.5 (19-65)			Treatment resistant	CBTp	28	Individual	39
Kuipers 1997	14 (range 1-33)		41.8 (18-63)				TAU1	32		
Kumar 2010	7.63 (7.74)	Inpatient	31.5 (7.98)			Paranoid Schizophrenia	MCT	8	Group	4
Kumar 2010	6.5 (5.21)		34.13 (8.2)				TAU2	8		4
Leclerc 2000	.	Both	40.6 (10.7)				CBT	55	Group	12
Leclerc 2000							TAU2	44		12
Lee 2013	17.75 (4.14)	Inpatient	43.53 (4.87)		Stable		CR	33	Computer	13
Lee 2013	17.53 (3.03)		43.46 (3.53)		Stable		TAU2	33		13
Lewis 2002	Unclear, but early (1st or 2nd episode)	Both	Median 29.1	Early			CBTp	101	Individual	6
Lewis 2002			Median 27.2	Early			SC	106	Individual	6
Lewis 2002			Median 27.2	Early			TAU2	102		6
Li 2015	7.6 (6.49)	Both	29.27 (8.36)				CBT	96	Individual	24
Li 2015	8.82 (8.07)		33.44 (9.51)				SC	96	Individual	24
Liberman 2009	.	Outpatient	37.6 (10.8)				FPE	45	Group	13
Liberman 2009			39.1 (12.3)				TAU2	47		13
Lincoln 2012	11.1 (10)	Outpatient	33.2 (10.4)				CBTp	40	Individual	38
Lincoln 2012	9.7 (6.8)		33.1 (10.9)				TAU1	40		38
Lindenmayer 2013	Not specified, but <5 years	Both	42.48 (9.09)	Early	Stable		CR	27	Computer	12
Lindenmayer 2013			43.95 (11.12)	Early	Stable		CRSS	32	Computer	12
Lopez-Luengo 2016	6.38 (3.42)	Outpatient	29.25 (7.65)		Stable	Auditory hallucinations	CR	20	Computer	13
Lopez-Luengo 2016	11.25 (6.63)		34 (11.64)		Stable		TAU2	20		13
Lukoff 1986		Inpatient	.				SST	14	Group	10
Lukoff 1986							PE	14		10
Moritz 2011		Inpatient	32.63 (12.48)				MCT_CBT	24	Group	4
Moritz 2011			35.46 (9.10)				CR	24	Computer	4

Moritz 2013	.	Both	36.82 (11.12)			Delusions	MCT	76	Group	4
Moritz 2013			32.68 (9.54)				CR	74	Computer	4
Morrison 2014	.	Outpatient	32.95 (13.11)			No medication	CBT	37	Individual	39
Morrison 2014			29.68 (11.95)				TAU2	37		39
Naeem 2015	4.7	Outpatient	31.7 (8.4)	Early			CBTp	59	Individual	17
Naeem 2015	5.8		31.1 (7.4)	Early			TAU1	57		17
Naeem 2016	.	Outpatient	42.0 (11.53)		Stable		CBT	18	Individual	16
Naeem 2016			38.6 (12.03)		Stable		TAU2	15		16
Ng 2006	13.3 (7.6)	Inpatient	37.9 (10.6)				SST	18	Group	8
Ng 2006	14.8 (9.2)		41.3 (11.4)				SC	18	Group	8
Ojeda 2012	10.92 (7.6)	Inpatient	33.81 (9.7)		Stable	Treatment resistant	CR_CRSS	47	Group	13
Ojeda 2012	15.25 (9.4)		37.75 (8.3)		Stable		OT	46		13
Omiya 2016	14.75 (13.53)	Both	43.25 (14.5)				CR	8	Individual	26
Omiya 2016	11.78 (10.62)		39.00 (11.09)				TAU2	9		26
Penn 2009	.	Outpatient	41.7 (11.8)			Auditory hallucinations	CBT	32	Group	12
Penn 2009			39.6 (15.7)				SC	33	Group	12
Penn 2011	.	Outpatient	23.48 (3.89)	Early			PE	23	Individual	36
Penn 2011			20.96 (2.14)	Early			TAU3	23		36
Peters 2010	median 6 years	Outpatient	34 (9.8)		Stable		CBTp	36	Individual	26
Peters 2010	median 7 years		39.6 (10.2)		Stable		TAU1	38		26
Pinto 1999	11.6 (7.9)	Both	33.9 (10.1)			Treatment resistant	CBT_SST	20	Individual	26
Pinto 1999	11.7 (6.6)		35.8 (11.9)				PE	21	Individual	26
Rakitzi 2016	5.4 (1.3)	Outpatient	31.3 (7.2)	Early	Stable		CRSS	24	Group	10
Rakitzi 2016	5.9 (1.1)		33.8 (6.7)	Early	Stable		TAU2	24		10
Rathod 2013	8.56 (8.24)	Both	31.37 (12.43)				CBTp	17	Group	20
Rathod 2013	12.33 (8.88)		35.58 (10.72)				TAU2	17		20
Rector 2003	Years on neuroleptics 13.9 (9.4)	Outpatient	37.5 (8.3)		Stable		CBT	29	Individual	26
Rector 2003	Years on neuroleptics 17.9 (10.0)		41.2 (10.9)		Stable		TAU2	21		26
Roberts 2014	.	Outpatient	40.0 (12.2)				SST	33	Group	26
Roberts 2014	.		39.4 (10.8)				TAU2	33		26
Rus-Calafell 2013	13.15	Outpatient	37.54 (8.05)		Stable		SST	18	Group	8
Rus-Calafell 2013	13.5		42.39 (8.1)		Stable		TAU2	18		8
Sanchez 2014	.	Inpatient	33.6 (9.4)				CR_CRSS	38	Group	13

Sanchez 2014			36.92 (10.5)				BF	54	Group	13
Schaub 2016	3.3 (2.7)	Inpatient	33.3 (10.3)	Early	Post Acute		CPS	100	Group	8
Schaub 2016	3.2 (2.5)		34.0 (12.2)	Early	Post Acute		SC	96	Group	8
Schrank 2016	.	Both	43 (11)				WB	47	Group	11
Schrank 2016	.		42 (11.5)				TAU2	47		11
Sensky 2000	14 (12-17)	Outpatient	39 (35-42)			Treatment resistant	CBT	46	Individual	39
Sensky 2000	15 (11-18)		40 (35-45)				BF	44		39
Shin 2002	.	Outpatient	39.50 (7.85)				PESC	24	Group	10
Shin 2002			34.7 (9.39)				SC	24	Individual	10
Startup 2004	.	Both	30.5 (8.7)				CBTp	47	Individual	52
Startup 2004			31.3 (9.6)				TAU3	43		52
Tan 2016	23.95 (8.18)	Inpatient	46.77 (7.18)		Stable		CR	52	Group	10
Tan 2016	21.51 (6.5)		46.09 (5.52)		Stable		BF	52	Group	10
Tao 2015	.		28.95 (7.38)			FGA only	CR	44		12
Tao 2015	.		29.71 (6.36)				TAU0	42		12
Tarrier 2014	.	Outpatient	34.9 (13.1)			Suicide attempt	CBT	25	Individual	17
Tarrier 2014							TAU2	24		17
Tas 2012	12.63 (9.99)	Outpatient	33.32 (11.57)		Stable		FSIT	22	Group	16
Tas 2012	11.85 (8.73)		34.62 (10.06)		Stable		BF	27	Individual	16
Turkington 2002	.	Outpatient	40.47 (CI 39.78-41.88)		Stable		CBT	257	Individual	20
Turkington 2002					Stable		TAU2	165		20
Valencia 2007	.	Outpatient	29.7 (6.6)		Stable		SST_FPE	49	Group	52
Valencia 2007			30.1 (7.1)		Stable		TAU1	49		52
Valencia 2010	.	Outpatient	29.9 (7.4)		Stable		SST_FPE	54	Group	52
Valencia 2010			29.5 (7.2)		Stable		TAU1	53		52
Valencia 2012	.	Outpatient	24.5 (3.0)	Early	Stable		SST_FPE	44	Group	52
Valencia 2012			24.1 (3.2)	Early	Stable		TAU1	44		52
Valencia 2013	8.2 (5.3)	Outpatient	29.5 (6.8)		Stable		SST	74	Group	26
Valencia 2013	8.3 (6.5)		26.4 (4.0)		Stable		TAU2	74		26
Valmaggia 2005	10.4 (6.6)	Inpatient	35.43 (10.53)			Treatment resistant	CBT	36	Individual	22
Valmaggia 2005	11.1 (8.8)		35.52 (11.42)				SC	26	Individual	22
Velligan 2015	.	Outpatient	43.47 (10.7)				CAT	41	Individual	39
Velligan 2015			39.2 (12.5)				CBT	43	Individual	39
Velligan 2015			39.5 (12.8)				CBT_CAT	40	Individual	39
Velligan 2015			40.3 (11.1)				TAU1	42		39

Veltro 2011	11.91 (7.9)	Outpatient	37.7 (11.16)		SST	12	Group	52
Veltro 2011	14.17 (8.3)		38.8 (6.3)		CRSS	12	Group	52
Vita 2011a	14.94 (9.76)	Outpatient	37.15 (9.1)	Stable	CRSS	26	Group	24
Vita 2011a	17.93 (9.68)		43 (7.76)		BF	28	Group	24
Vita 2011a	14.8 (9.78)		36.87 (11.4)	Stable	CR	30	Group	24
Vita 2011b	12.5 (8.4)	Outpatient	34.6 (7.6)	Stable	CRSS	16	Group	24
Vita 2011b	14.9 (11.5)		39.9 (8.6)	Stable	BF	16	Group	24
Wang 2016	2 (1)	Outpatient	23.8 (6.8)	Early	MPE	46	Group	25
Wang 2016	2.1 (0.9)		24.1 (6.3)	Early	PE	46	Group	25
Wang 2016	2.0 (0.9)		25.0 (7.0)	Early	TAU2	46		25
Wolwer 2011	.	Inpatient	36.7 (13.1)		CRSS	20	Group	6
Wolwer 2011	.				CR	18	Group	6
Wykes 1999	59% >10 years	Outpatient	36.5 (19-55)		CR	17	Individual	13
Wykes 1999	81% >10 years		40.6 (24-64)		OT	16		13
Wykes 2007	.	Outpatient	36		CR	43	Individual	12
Wykes 2007					TAU2	42		12
Mazza 2010*	.	Outpatient	24.37 (2.12)		CRSS	17	Group	12
Mazza 2010*	.		24.71 (2.17)		PST	16		12
Montero 2001*	5.7 (4.5)	Outpatient	27.2 (6.6)		BFT	46	Group	52
Montero 2001*	5.3 (3.6)		26.4 (5.9)		FPE	41	Group	52
Weisman de Mamani 2014*	.	Outpatient	42.73 (14.31)		FT	38	Individual	17
Weisman de Mamani 2014*	.		42.42 (12.7)		FPE	31	Individual	17

*Mazza 2010 was not included due to inconsistency in the model (see Appendix 8 for rationale). Montero 2001 & Weisman de Mamani 2014 were
Intervention Abbreviations: ALL - Protocol with 4 psychotherapies combined; BF – Befriending; CBT -Cognitive behaviour therapy; CR - Cognitiv
cognition; EMDR - Eye movement desensitisation and reprocessing; FT - Family therapy; HIT - Hallucinations focused integrative therapy; MCT -
psychoeducation; OT - Occupational therapy; PE – Psychoeducation; SC - Supportive counselling; SST - Social skills training; TAU - Treatment as
included two therapies) are indicated by Intervention_Intervention.
Outcome measures: BPRS- Brief psychiatric rating scale, CPRS: Comprehensive psychopathological rating scale, FGA: first generation antipsycho
Psychiatric assessment scale, PECC- Psychosis evaluation tool for common use by caregivers (completed by staff in RCTs in this study), RoB; Risk

NMA Appendix 10: Reference list of Included Studies

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Chapter 4

What constitutes sufficient evidence for case-formulation driven CBT for psychosis? Cumulative meta-analysis of the effect on hallucinations and delusions

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Abstract

Objective

Following two decades of research on cognitive behavioural therapy for psychosis (CBTp), it is relevant to consider at which point the evidence base is considered *sufficient*. We completed a cumulative meta-analysis to assess the sufficiency and stability of the evidence base for hallucinations and delusions.

Method

We updated the systematic search from our previous meta-analytic review from August 2013 until December 2019. We identified 20 new RCTs resulting in inclusion of 35 RCTs comparing CBTp with treatment as usual (TAU) or active controls (AC). We analysed data from participants with psychosis ($N = 2407$) over 75 conventional meta-analytic comparisons. We completed cumulative meta-analyses (including fail-safe ratios) for key comparisons. Publication bias, heterogeneity and risk of bias were examined.

Results

Cumulative meta-analyses demonstrated sufficiency and stability of evidence for hallucinations and delusions. The fail-safe ratio demonstrated that the evidence base was sufficient in 2016 for hallucinations and 2015 for delusions. In conventional meta-analyses, CBTp was superior for hallucinations ($g=0.34$, $p<.01$) and delusions ($g=0.37$, $p<.01$) when compared to any control. Compared to TAU, CBTp demonstrated superiority for hallucinations ($g=0.34$, $p<.01$) and delusions ($g=0.37$, $p<.01$). Compared to AC, CBT was superior for hallucinations ($g=0.34$, $p<.01$) but not for delusions although this comparison was underpowered. Sensitivity analyses for case formulation, primary outcome focus and risk of bias demonstrated increases in effect magnitude for hallucinations.

Conclusions

The evidence base for the effect of CBTp on hallucinations and delusions demonstrates sufficiency and stability across comparisons, suggesting limited value of new trials evaluating generic CBTp.

Keywords: *schizophrenia, randomised controlled trials, psychological intervention, positive symptoms, systematic review.*

Introduction

It is now approximately 20 years since the evidence base for Cognitive Behavioural Therapy for psychosis (CBTp) began to accumulate and, as RCTs continue to proliferate, it is relevant to consider at which point the evidence base is considered *sufficient*. Our previous meta-analytic review demonstrated the efficacy of individually-tailored, case-formulation based CBTp in reducing hallucinations (Hedges' g=0.44, p<.005) and delusions (g=0.36, p<.05) when RCTs were focused on specific symptom reduction.[1] These findings were broadly in line with existing meta-analytic results for positive symptoms.[2,3] We concluded that CBTp was an efficacious intervention for hallucinations and delusions, although the lower magnitude of effect for delusions and the absence of a significant effect compared to active treatments led us to conclude that delusions may be less amenable to change via CBTp than hallucinations.

Roughly six years have elapsed since our previous review. During this time a number of new randomised controlled trials (RCTs) have been published in this research field. These include trials employing the typical implementation of individually-case formulated CBTp in Western mental health care systems as were prevalent in the former review alongside a range of trials in new settings and/or employing new styles of intervention; for example culturally-adapted CBTp in Pakistan[4] or virtual-reality based CBTp.[5] There remains well-documented controversy[6] over the effectiveness and implementation of CBTp; both the UK National Institute for Health and Care Excellence[7] and the British Psychological Society *Understanding Psychosis and Schizophrenia* report[8] recommend CBTp while the Cochrane Collaboration maintain that meta-analytic results are neither clear nor robust enough to recommend CBTp

over standard care.[9] Recent literature addressing this controversy argues the importance of attending to methodological issues including blinding, inclusion criteria and pre-specification of methods.[6]

Cumulative meta-analysis is a technique allowing estimation of both the sufficiency and stability of meta-analytic evidence. This technique was first notably applied to treatment trials for myocardial infarction.[10] The method has since been applied as a means of statistically estimating the point at which there is sufficient evidence to conclude that an intervention is efficacious while also estimating the stability of the effect size over time.[11,12] In light of the further accumulation of trials, we concluded that application of cumulative meta-analysis to the CBTp field is warranted.

We firstly aimed to update our 2014 review to assimilate the new body of research and therefore provide an up-to-date estimation of the impact of CBTp upon hallucinations and delusions. We also employed cumulative meta-analysis to comment on the sufficiency of the existing evidence base in demonstrating efficacy and the stability of the evidence over time. A secondary objective was to provide a range of sensitivity analyses to allow more specific estimation of effects under pre-specified conditions such as individually-tailored case-formulation, primary outcome focus, blinded RCTs and RCTs with minimal risk of bias.

Methods

We provide a systematic review including both conventional and cumulative meta-analyses based on PRISMA guidelines.[13] A protocol for this review was registered at the Open Science Framework (https://osf.io/nwxbz/).

Systematic search

Our previous meta-analytic review in this area completed a systematic search on August 3rd, 2013.[1] We repeated the systematic search from this date until 11th December 2019 across the same three databases included in 2013 (PubMed, Embase and PsychInfo). We considered reference lists of published reviews alongside our accumulation of newly published trials via automatic update notifications and expert knowledge via professional networks. We entered a relevant range of text variations of the following key search terms via while utilizing Boolean operators, MeSH terms, exploded terms and limit setting based on specific options within each database; 1) cognitive behavioural therapy 2) auditory hallucinations OR delusions and 3) randomised controlled trials. Exemplary search strings are included in the supplementary materials.

Inclusion/exclusion criteria

We included a) randomised controlled trials comparing b) cognitive behavioural therapy to c) treatment-as-usual (TAU) or an active control condition (e.g. supportive counseling or psycho-education) for d) patients diagnosed with schizophrenia-spectrum disorders which e) assessed hallucinations and/or delusions as post-treatment outcome. Schizophrenia-spectrum disorders included schizophrenia, schizoaffective disorder, delusional disorder, brief psychotic disorder or psychosis not otherwise specified (NOS). We included only studies published in peer-reviewed journals. Conference abstracts were excluded. We also excluded trials which; a) focused on a primary diagnosis of alcohol or substance use dependency; b) included

ultra-high risk patients or focused on prevention of psychosis; c) replaced the core of CBT (i.e. identifying and challenging of maladaptive beliefs) with alternative psychological interventions, e.g. social skills training or mindfulness. We utilised the definition of CBTp applied in our previous meta-analytic research.[1]

Study selection

The PRISMA diagram (Figure 1) depicts the study selection process. Two authors (DT and MvdG) utilised the Rayyan (rayyan.qcri.org) web application to facilitate the study selection process. Abstracts were first screened for duplicates then relevance before a sample of full text PDFs were checked against the inclusion and exclusion criteria. Conflicts in inclusion were resolved via discussion. We attempted to contact the authors of one RCT due to PSYRATS subscales being unavailable in the manuscript but received no response.[14]

Data extraction

Two authors (DT and SB) independently completed the data extraction for new trials included since 2013. The data from trials included in the 2013 review was also checked for consistency by both authors and any inconsistencies were investigated and corrected. Spreadsheets utilised in the previous meta-analyses were adapted and updated for use in the current review. We contacted one author for unavailable data although on closer inspection of the manuscript the intervention in this trial did not meet inclusion criteria. Data was extracted on study characteristics (year of publication, country, sample characteristics, format (individual or group), duration, application of case formulation, primary vs secondary focus and intervention style) and post-treatment outcome data.

Outcome measures

While a considerable proportion of meta-analytic research on cognitive behavioural therapy for psychosis (CBTp) has focused upon its effect in reducing the positive or negative symptoms of psychosis,[2,3,15] there has been less focus upon the more specific, discrete outcomes of hallucinations and delusions. It has been suggested that diagnostically-based tools such as the Positive and Negative Syndromes Scale (PANSS)[16] provide less comprehensive measurement of psychotic symptomatology than symptom-specific outcome measures such as the Psychotic Symptoms Rating Scales (PSYRATS)[17,18] Our primary outcomes were therefore hallucinations and delusions. We extracted all outcome measures which reported hallucinations or delusions as independent scales or subscales. We did not include outcome measures which subsumed items on hallucinations or delusions in broader sub-categories such as positive symptoms (for example the PANSS). In instances that two hallucinations or two delusions scales were reported, data from both were extracted and an average pooled effect size was calculated. All scales included were continuous outcomes.

Risk of bias assessment

To account for risk of bias among the included RCTs, we applied an adapted version of the Cochrane Risk of Bias tool. The final two items of the tool (selective outcome reporting and other sources of bias) were omitted due to limited evidence regarding their impact on validity for meta-analytic comparisons.[19] Utilisation of the four key areas of bias (namely sequence generation, allocation concealment, blinding of

assessors and incomplete outcome data) provided the opportunity for clear sensitivity analyses as applied in previous meta-analytic reviews.[2,20] Risk of bias was assessed independently by two authors (DT and MvdG). Conflicts were resolved via discussion. Risk of bias items were rated *low risk* (0) or *high risk* (1), contributing to a total score of 0-4 for each RCT. Items that were unclear in the published manuscripts were rated conservatively as high risk. Due to an alternative method of risk of bias assessment being employed in the earlier review, risk of bias was assessed over the whole sample of RCTs.

Meta-analyses

Our strategy for analysis was to move gradually from inclusive comparisons to more exclusive sensitivity analyses for a number of criteria based on a) relevant study characteristics and b) risk of bias. These sensitivity analyses were designed to provide information relevant to our aforementioned research objectives; namely our focus on individually-tailored, case formulation-driven CBT with hallucinations and delusions as primary outcome. We therefore first analysed all eligible RCTs each for hallucinations and delusions. We then completed sensitivity analyses examining TAU only, active controls only, case formulation only and primary outcomes only. When study availability allowed sufficient number of RCTs for comparison, we also included smaller categories including group CBT only, secondary outcomes only, self-help CBT only and virtual reality CBT (VR-CBT) only. We note that the minimum number of RCTs required for adequate meta-analytic comparisons is suggested as approximately five.[21] Comparisons we reported in this section which fell below this five RCTs were therefore provided only for indicative information

regarding current best estimates. When possible based on RCT availability, we also performed sensitivity analyses including only RCTs with low risk of bias (one of more item scored on the risk of bias tool) and no known risk of bias (no items scored on the risk of bias tool).

All meta-analytic comparisons were completed using the Comprehensive Meta-analysis (CMA) version 3.3.070 computer software package. CMA provides an aggregated effect size estimating the pooled mean difference between treatment and control groups at post-treatment using Hedges' *g*, which is an estimate of the standardised mean difference between study groups. Hedges' *g* is recognised as providing a more accurate effect estimation in small samples than alternative methods for continuous measures such as Cohen's *d*. We utilised the 0.05 alpha level for all comparisons with 95% confidence intervals provided. We also employed a random effects model in all comparisons due to the expectation of between-study variance.

Cumulative meta-analysis

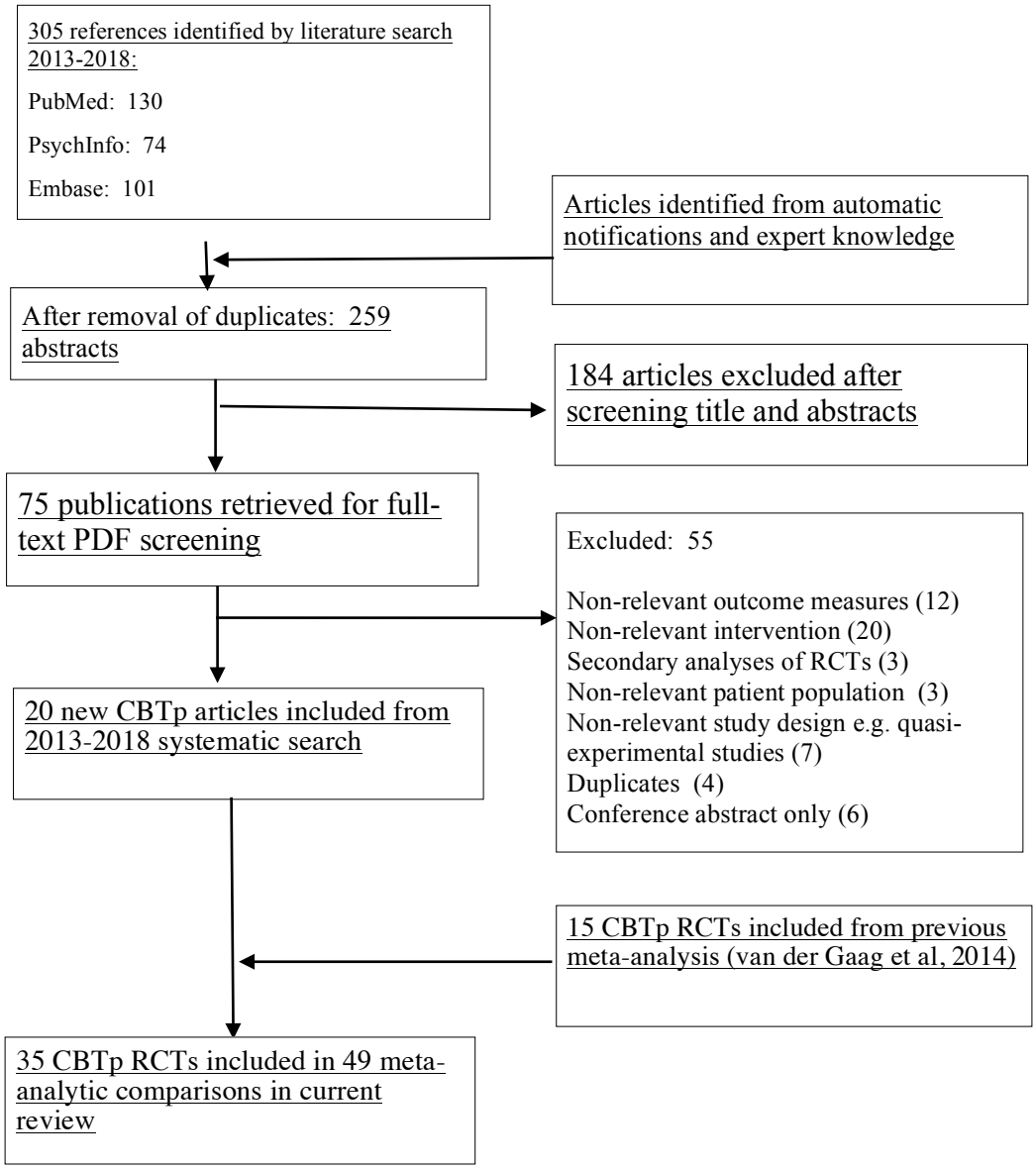
In order to assess the sufficiency and stability of meta-analytic evidence for CBTp for hallucinations and delusions, we completed cumulative meta-analyses for each outcome. The cumulative meta-analysis function in *CMA* was utilised. RCTs were listed by year of publication and a pooled effect size in Hedges' *g* was calculated for the point at which each new study was chronologically added to the evidence base. The cumulative forest plots (Figure 5 & Figures 6-9 in the supplementary materials) provide a visual representation of the stability of evidence as the RCT evidence based has accumulated. We also followed Muellerleile and Mullen's[11] recommendations for

calculating the failsafe ratio from Rosenthal's[22] standard to estimate the sufficiency of the evidence base as each RCT was added. The fail-safe ratio provides an estimate of sufficiency of evidence when the ratio surpasses a value of 1.0.

Publication bias, heterogeneity and power

We utilised the Q statistic and the I^2 statistic to assess heterogeneity. We examined publication bias to estimate the potential impact of unpublished RCTs. We applied power calculations to estimate the number of RCTs required for adequate power in each comparison. Full information for these procedures is provided in the supplementary materials.

Fig. 1. Flowchart of inclusion of studies



Results

Study selection

After the automated removal of duplicates, the updated search resulted in 305 new citations being retrieved for abstract screening, of which 184 were excluded and 75 full text PDFs were retrieved. Following careful matching of exclusion and inclusion criteria, 20 new studies published since the previous meta-analysis were included meaning a total of 35 RCTs were included in this meta-analytic review. The total amount of participants measured at post-treatment was *N*= 2407, which included 1205 patients who received CBT and 1202 patients who received treatment as usual or an active control. We analysed their data over 75 meta-analytic comparisons.
Selected study characteristics are provided in Table 1. 28 RCTs (80%) applied individually-tailored case-formulation while nine studies (26%) did not. 31 RCTs (89%) targeted hallucinations and/or delusions as primary outcome while six (17%) targeted these outcomes as secondary. 29 RCTs utilised TAU as the comparison condition, six RCTs compared CBT with active controls or other psychological interventions while two RCTs included both. Active control treatments included supportive counselling,[26–31] psycho-education,[32] befriending[17] and virtual reality exposure.[33] Only one RCT explicitly excluded participants taking anti-psychotic medication from the CBTp treatment group[34] therefore indicating that CBTp was broadly provided as adjunctive to standard care.

Risk of bias varied among RCTs although the majority (24 RCTs; 67%) achieved the best possible risk of bias score on the adapted Cochrane tool. A further eight RCTs

(23%) scored one risk of bias item while two RCTs (6%) scored two items, two RCTs (6%) scored three items and one RCT (3%) scored four items indicating the highest possible score on the tool. Risk of bias assessment scores are provided in tabular form in the supplementary materials.

Table 1: Selected study characteristics of CBTp RCTs for hallucinations and delusions

Author	Year	Format	Duration inter-vention	Experimental Condition CBT format	CBTp *N*	Age Mean (SD)	Male Sex %	Control Condition Control format	Control *N*	Age Mean (SD)	Male Sex %	Country	CF	Bias risk 0-4	Selected Outcome measure
Lewis et al [31]	2002	Indiv	15-20 hrs in 5 week	CBT	101	29.1	71%	[1] SC [2] TAU	[1] 106 [2] 102	[1] 27.2 [2] 27.0	[1] 71% [2] 68%	UK	Y	0	PSYRATS
Durham et al[26]	2003	Indiv	9 months	CBT	22	36.0 (10.0)	68%	[1] SC [2] TAU	[1] 23 [2] 21	[1] 37.0 (11.2) [2] 36.0 (10.2)	[1] 65% [2] 71%	UK	Y	1	PSYRATS
Trower et al[45]	2004	Indiv	6 months	CT CH	18	36.6 (10.3)	56%	TAU	20	35.1 (10.4)	70%	UK	Y	1	PSYRATS
Cather et al[32]	2005	Indiv	16 weekly sessions	fCBT	15	40.4 (12.0)	57%	PE	13	40.4 (12.0)	57%	USA	Y	1	PSYRATS
Wykes et al[46]	2005	Group	10 weeks	CBT	45	39.7 (10.8)	53%	TAU	40	39.7 (10.1)	65%	UK	N		PSYRATS
Valmaggia et al[27]	2005	Indiv	6 months	CBT	35	35.5 (10.8)	77%	SC	23	35.5 (11.4)	61%	NL	Y	0	PSYRATS
McLeod et al[47]	2007	Group	8 weekly sessions	CBT	10	n.a.	n.a.	TAU	10	n.a.	n.a.	UK	N	3	PSYRATS
O'Connor et al[28]	2007	Indiv	24 weekly sessions	CBT	12	40 (9.4)	45%	SC	12	36.8 (13.5)	67%	CAN	Y	3	MADS
Garety et al[48]	2008	Indiv	20 in 9 months	CBT	60 H 85 D	39.1 (10.3)	71%	TAU	60 H 85 D	37.1 (10.9)	72%	UK	Y	0	PSYRATS
Penn et al[29]	2009	Group	12 weeks	CBT	32	41.7 (11.8)	53%	SC	33	39.6 (15.7)	49%	USA	N	0	PSYRATS
Haddock et al[17]	2009	Indiv	17 sessions	CBT	38	35.7 (12.5)	86%	SC	39	33.9 (9.7)	86%	UK	Y	0	PSYRATS
Peters et al[49]	2010	Indiv	6 months	CBT	36	34.0 (9.8)	72%	TAU	38	39.6 (10.2)	53%	UK	Y	2	BAVQ-R
Foster et al[50]	2010	Indiv	4 weeks	CBT	9	40.0 (10.0)	58%	TAU	11	39.1 (9.2)	58%	UK	N	2	PSYRATS
Lincoln et al[51]	2012	Indiv	29 sessions	CBT	40	33.2 (10.4)	55%	TAU	40	33.1 (10.9)	58%	GER	Y	0	PDI
Krakvik et al[52]	2013	Indiv	6 months 20 sessions	CBT	23	35.3 (8.9)	65%	TAU	22	37.5 (11.2)	64%	NOR	Y	1	PSYRATS
Rathod et al[53]	2013	Indiv	16 weekly sessions	CA-CBT	17	31.4 (12.4)	63%	TAU	18	35.6 (10.7)	59%	UK	Y	0	CPRS DHS
Leff et al[54]	2013	Indiv	6 weekly sessions	Avatar CT	14	n.a.	n.a	TAU	12	n.a.	n.a	UK	Y	1	PSYRATS
Morrison et al[34]	2014	Indiv	9 months	CBT	37	33.0 (13.1)	46%	TAU	37	29.7 (12.0)	59%	UK	Y	0	PSYRATS
Birchwood et al[55]	2014	Indiv	9 months	CT CH	98	38.8(12.2)	62%	TAU	99	35.9(11.9)	53%	UK	Y	0	PSYRATS
Freeman et [56]	2014	Indiv	6 sessions	CBT confidence	15	41.9 (11.5)	73%	TAU	15	41.5 (13.1)	60%	UK	Y	0	PSYRATS
Tarrier et al[57]	2014	Indiv	24 sessions	CBT suicide	25	32.6 (11.7)	n.a.	TAU	24	37.3 (14.2)	n.a.	UK	Y	0	PSYRATS
Freeman et al[58]	2015a	Indiv	8 sessions	CBT sleep	24	39·6 (11.6)	67%	TAU	26	42·2 (13.5)	69%)	UK	N	0	PSYRATS
Naeem et al[37]	2015	Indiv	16 weekly sessions	CBT	53	42.0(11.6)	17%	TAU	49	38.6 (12.0)	13%	CAN	Y	0	PSYRATS
Habib et al[35]	2015	Indiv	10-16 sessions	CBT	21	33.5(10.5)	44%	TAU	21	30.2(6.7)	56%	PAK	Y	0	PSYRATS

Table 1: continued

Author	Year	Format	Duration intervention	Experimental Condition				Control Condition				Country	CF		Selected Outcome measure
				CBT format	CBTp *N*	Age Mean (SD)	Male Sex %	Control format	Control *N*	Age Mean (SD)	Male Sex %			Bias risk 0-4	
Freeman et al[59]	2015b	Indiv	8 weekly sessions	CBT-W	73	40.9(10.5)	58%	TAU	77	42.1(12.2)	57%	UK	Y	0	GPTS & PSYRATS
Waller et al[60]	2015	Indiv	6 weeks	CBT-TW	20	39.1(10.5)	75%	TAU	11	43.0(10.7)	64%	UK	Y	0	DC, DD & DP
Naeem et al[36]	2016	Indiv	12-16 sessions	CBT-GSH	18	42.0(11.5)	44%	TAU	15	38.6(12.0)	60%	CAN	Y	0	PSYRATS
Freeman et al[33]	2016	Indiv	1 session	VR-CBT	15	42.1(13.4)	67%	Exposure	15	40.6(14.4)	67%	UK	Y	0	PSYRATS
Hayward et al[61]	2017	Indiv	16 weekly sessions	Relating therapy	14	41 (n.p)	43%	TAU	15	43 (n.p.)	67%	UK	Y	0	PSYRATS
Hazell et al[62]	2017	Indiv	8 sessions	CBT-GSH	14	39.1(10.2)	29%	WL	14	45.9(13.5)	50%	UK	N	0	HPSVQ
Gottlieb et al [63]	2017	Indiv	10 skills modules	eCBT	19	43.8(13.2)	47%	TAU	18	40.3(11.7)	78%	USA	N	1	PSYRATS
Pot-Kolder et al[5]	2018	Indiv	16 sessions	VR-CBT	58	36.5(10)	69%	TAU	58	39.5(10)	72%	NL	Y	0	ESM
Morrison et al[38]	2018	Indiv	9 months	CBT	242	42.2(10.7)	73%	TAU	245	42.8(10.4)	71%	UK	Y	0	PSYRATS
Husain et al[4]	2017	Indiv	12 weekly sessions	CBT	18	34.1 (9.55)	78%	TAU	18	30.5 (8.15)	55.6%	PAK	Y	0	PSYRATS
Craig et al[30]	2018	Indiv	12 weekly sessions	Avatar CT	75	42.5(10.7)	76%	SC	75	42.9(11.2)	60%	UK	Y	0	PSYRATS
Wong et al[64]	2019	Group	7 weekly session + booster	CBT	25	30.6(10.6)	24%	PE	23	35.1(12.9)	48%	HK	N	1	PSYRATS, BAVQ

Note. CBT, cognitive behavioural therapy. SC, supportive counselling. TAU, treatment as usual. UK, United Kingdom. PSYRATS, psychotic symptoms rating scales. CH, command hallucinations. fCBT, functional cognitive behavioural therapy. PE, psychoeducation. USA, United States of America. NL, Netherlands. CT, cognitive therapy. CAN, Canada. GER, Germany. PAK, Pakistan. HK, Hong Kong. KOR, SK, South Korea. CBT-W, cognitive-behavioural therapy for worry. GPTS, Green et al Paranoid Thoughts Scale. DC, delusional conviction. DD, delusional distress. DP, delusional preoccupation. PDI, Peters et al Delusion Inventory. CBT-TW, "Thinking Well" cognitive-behavioural therapy CBT-GSH, cognitive-behavioural guided self-help. VR-CBT, virtual reality-based cognitive behavioural therapy. WL, waiting list. eCBT, online cognitive-behavioural therapy. CBT-I, cognitive behavioural therapy for insomnia. HPSVQ, Hamilton Program for Schizophrenia Voices Questionnaire. CPRS, Comprehensive Psychopathological Rating Scale. DHS, delusions and hallucinations scale. MADS, Maudsley Assessment of Delusions Scale. BAVQ-R, Beliefs About Voices Questionnaire-Revised. NOR, Norway. ESM, experience sampling method CA-CBT- culturally adapted CBT. H, Hallucinations. D, delusions. n.p., not provided. n.a., not applicable. BAVQ comparisons included only resistance, omnipotence and malevolence subscales.

Effect of CBT on hallucinations

Table 2 provides an overview of all meta-analytic results of the effect of CBTp on hallucinations. Figures 3 and 4 (supplementary materials) provides a forest plot with all eligible RCTs included. When analysing this broad sample of all 28 eligible RCTs for hallucinations, results demonstrated superiority of CBT over controls (g=0.34, p<.01). When including only RCTs with the lowest possible risk of bias scores (n=19), we observed a marginal but statistically non-significant increase in the magnitude of effect (g=0.40, p<.01). Similarly, when including all RCTs comparing CBT against TAU there was a significant effect favouring CBT (g=0.35, p<.01) which had a marginal, non-significant increase when including only those RCTs with the lowest assessed risk (n=14; g=0.41, p<.01). The same pattern was observed when comparing CBT to active controls; CBT demonstrated superiority when all eligible RCTs were included (g=0.34, p<.01), while including only the lowest risk RCTs resulted in a small and statistically non-significant increase in effect magnitude (n=5; g=0.42, p<.01).

We observed the same pattern when including only RCTs with hallucinations as the primary outcome target. When including all such RCTs, CBT demonstrated superiority over control (g=0.40, p<.02), and increased when including only the lowest risk RCTs (n=14; g=0.51, p<.02). Similarly, when analysing the impact of CBT with individually-tailored case formulation versus controls we observed a significant effect when all eligible RCTs were included (g=0.41, p<.01), and when including only the lowest risk RCTs (n=15; g=0.45, p<.01).

When including only blinded RCTs, CBT was superior to any control (g=0.36, p<.01), when including only blinded case formulation RCTs (n=19; g=0.43, p<.01) and when

limiting to RCTs which applied blinded case formulation and hallucinations as primary outcome (n=14; g=0.55, p<.01).

When performing the most stringent comparison- namely including only RCTs which utilised case formulation alongside targeting hallucinations as the primary outcome- we again observed the same pattern of increasing magnitude with bias reduction. The effect sizes demonstrated superiority for CBT when including all eligible RCTs (g=0.51, p<.01), and the lowest bias risk RCTs (n=11; g=0.59, p<.05. See Figure 5, supplementary materials).

Table 2. *Effect sizes of CBTp for auditory hallucinations*

	N	*g*	95% CI	*Z*	Q-value	I^2 (%)
Main comparison with all eligible RCTs						
Any risk of bias score included	28	0.34**	0.20, 0.49	4.63	52.83**	49
High risk of bias (>1)[3]	26	0.34**	0.19, 0.49	4.43	51.12**	51
Lowest risk of bias (0)[4]	19	0.40**	0.22, 0.58	4.40	41.49**	59
CBTp versus TAU						
Any risk of bias score included	22	0.35**	0.18, 0.52	4.00	45.94**	54
High risk of bias (>1)[3]	20	0.34**	0.17, 0.52	3.77	44.24**	58
Lowest risk of bias (0)[4]	14	0.41**	0.19, 0.63	3.65	36.90**	65
CBTp vs active intervention						
Any risk of bias score included	8	0.34**	0.15, 0.53	3.58	7.03	0
High risk of bias (>1)[3]	8	0.34**	0.15, 0.53	3.58	7.03	0
Lowest risk of bias (0)[4]	5	0.42**	0.20, 0.64	3.70	4.15	4
CBTp with hallucinations as primary outcome[1]						
Any risk of bias score included	23	0.40**	0.24, 0.56	4.90	40.42*	46
High risk of bias (>1)[3]	21	0.40**	0.23, 0.57	4.66	38.84**	49
Lowest risk of bias (0)[4]	14	0.51**	0.32, 0.70	5.22	25.67*	49
CBTp with individualised case formulation[2]						
Any risk of bias score included	21	0.41**	0.25, 0.57	5.03	39.86*	50
High risk of bias (>1)[3]	20	0.42**	0.26, 0.59	5.02	39.44*	52
Lowest risk of bias (0)[4]	15	0.45**	0.25, 0.65	4.47	39.98**	62
CBTp with individualised CF + primary outcome[1,2]						
Any risk of bias score included	16	0.51**	0.34, 0.68	5.99	23.15*	35
High risk of bias (>1)[3]	15	0.53**	0.36, 0.70	6.01	22.24	37
Lowest risk of bias (0)[4]	11	0.59**	0.39, 0.80	5.73	18.64*	46
Blinded RCTs only[5]						
All eligible CBTp RCTs	24	0.36**	0.20, 0.51	4.48	49.10**	53
Case formulation only	19	0.43**	0.26, 0.61	4.95	39.17**	54
Case formulation + primary outcome[1,2]	14	0.55**	0.37, 0.73	5.99	21.36	39
Additional analyses						
Group CBTp	4	0.11	-0.18, 0.41	0.76	3.15	5
Hallucinations as secondary outcome	5	0.05	-0.15, 0.24	0.46	3.87	0
Virtual-reality CBTp	2	0.56**	0.22, 0.89	3.27	0.75	0
Self-help CBTp	3	0.47	-0.42, 1.37	1.03	9.26**	78
After removal of 2 outliers						
Any risk of bias score included	26	0.27**	0.15, 0.40	4.37	34.35	27
High risk of bias (>1)[3]	24	0.27**	0.14, 0.39	4.16	32.52	29
Lowest risk of bias (0)[4]	16	0.31**	0.16, 0.46	4.05	24.21	39
Case formulation only	19	0.32**	0.19, 0.45	4.91	23.01	22
Case formulation + primary outcome[1,2]	14	0.41**	0.29, 0.54	6.56	9.64	0
Case formulation, primary outcome + RoB[1,2,3]	9	0.44**	0.31, 0.58	6.46	6.11	0
Excluding RCTs with high ratio non-schiz. spectrum						
Any risk of bias score included	26	0.32**	0.17, 0.47	4.23	49.46**	50
Lowest risk of bias (0)[4]	16	0.38**	0.19, 0.57	3.92	38.78**	61
Case formulation + primary outcome[1,2]	16	0.47**	0.30, 0.64	5.28	24.99	40
Case formulation, primary outcome + RoB[1,2,3]	10	0.58**	0.37, 0.79	5.35	17.58*	49

Note. All comparisons were using random model. Risk of bias scores refer to assessment using adapted version of the Cochrane Risk of Bias tool (0-4). *p<0.05. ** p<0.01. CI, Confidence Interval. *g*, Hedges's g. TAU, Treatment-as-usual. CBTp, Cognitive behavioural therapy for psychosis. CF, case formulation. RCT, randomised controlled trial. RoB. Risk of bias. n/a, not applicable. Sensitivity analysis exclusions were as follows: [1]Hallucinations as primary outcome only: Birchwood et al, 2014. Garety et al, 2008. Haddock et al, 2009. Tarrier et al, 2014. Trouwer et al, 2004.

[2]Case formulation only: Freeman et al, 2015. Gottlieb et al, 2017. Hazell et al, 2017. McLeod et al, 2007. Penn et al, 2009. Wykes et al, 2005. [3]Risk of bias score greater than 1 excluded: McLeod et al, 2007. Peters et al, 2010. [4]Risk of bias score greater than 0 excluded: Cather et al, 2005. Durham et al, 2003. Gottlieb et al, 2017. Krakvik et al, 2013. Leff et al, 2013. McLeod et al, 2007. Peters et al, 2010. Trouwer et al, 2004. Wykes et al, 2005. [5]Non-blinded RCTs excluded: Krakvik et al, 2013. McLeod et al, 2007. Peters et al, 2010.

Effect of CBT on delusions

Table 3 provides the results from all meta-analytic comparisons of CBT for delusions while Figure 4 (supplementary materials) provides a forest plot for all eligible RCTs. When including all eligible RCTs, CBT demonstrated superiority over controls (g=0.37, p<.01). There was a marginal, non-significant reduction in the magnitude of this effect when including only the lowest risk RCTs (g=0.34, p<.01). When including only comparisons against TAU, CBT demonstrated superiority against TAU when including all eligible RCTs (g=0.36, p<.01) while a similar pattern of a small reduction of magnitude was present with the least risky RCTs (g=0.32, p<.01). When comparing CBT to active controls, CBT did not demonstrate significant superiority when including all eligible RCTs (g=0.23, p=.16), and when including only the lowest risk RCTs (g=0.30, p=.28).

A similar pattern was present when including only RCTs with delusions as the primary outcome target; the magnitude of the significant effect in favour of CBT was highest when all eligible RCTs were included (g=0.38, p<.01) and when including only the lowest risk RCTs (g=0.34, p<.01). When including only RCTs with individually-tailored case formulation the effect size was consistent for the all eligible RCTs comparison (g=0.37, p<.01), and when including only the lowest risk RCTs (g=0.37, p<.01).

When only blinded trials were included, CBT was superior to any control (g=0.31, p<.01), which was consistent when limiting to case formulation RCTs (g=0.35, p<.01) and RCTs with case formulation and delusions as primary outcome (g=0.34, p<.01). A similar pattern was observed in the most stringent comparison which included only RCTs applying individualised case-formulation with delusions as the primary outcome target. The effect favouring CBT was of highest magnitude when all eligible RCTs were included (g=0.38, p<.01) while the effect was marginally lower when excluding RCTs with a high risk of bias (g=0.37, p<.01) and RCTs with the lowest risk of bias (g=0.37, p<.01).

Table 3. *Effect sizes of CBTp for delusions*

	N	*g*	95% CI	*Z*	Q-value	I^2 (%)
Main comparison with all eligible RCTs						
Any risk of bias score included	27	0.37**	0.23, 0.52	4.95	54.54**	53
High risk of bias (>1) [3]	25	0.36**	0.20, 0.10	4.64	53.34**	55
Lowest risk of bias (0) [4]	18	0.34**	0.17, 0.50	4.02	39.33**	57
CBTp versus TAU						
Any risk of bias score included	22	0.36**	0.20, 0.52	4.34	48.96**	57
High risk of bias (>1) [3]	21	0.35**	0.18, 0.51	4.15	46.85**	57
Lowest risk of bias (0) [4]	16	0.32**	0.15, 0.49	3.64	34.42**	56
CBTp vs active intervention						
Any risk of bias score included	7	0.23	-0.19, 0.55	1.41	12.51	52
High risk of bias (>1) [3]	6	0.20	-0.45, 0.55	1.14	11.76	57
Lowest risk of bias (0) [4]	3	0.30	-0.25, 0.85	1.07	7.85*	75
CBTp with delusions as primary outcome[1]						
Any risk of bias score included	23	0.38**	0.22, 0.54	4.56	47.94**	54
High risk of bias (>1) [3]	21	0.36**	0.19, 0.53	4.21	45.83**	56
Lowest risk of bias (0) [4]	14	0.34**	0.15, 0.52	3.51	32.01**	59
CBTp with individualised case formulation[2]						
Any risk of bias score included	21	0.37**	0.20, 0.54	4.33	49.43**	60
High risk of bias (>1) [3]	20	0.37**	0.20, 0.54	4.19	49.10**	61
Lowest risk of bias (0) [4]	16	0.37**	0.19, 0.55	4.00	38.09**	61
CBTp with individualised CF + primary outcome[1,2]						
Any risk of bias score included	17	0.38**	0.19, 0.57	3.86	41.93**	62
High risk of bias (>1) [3]	16	0.37**	0.18, 0.57	3.70	41.60**	64
Lowest risk of bias (0) [4]	12	0.37**	0.67, 0.58	3.48	30.68**	64
Blinded RCTs only[5]						
All eligible CBTp RCTs	22	0.31**	0.16, 0.47	3.96	46.77**	55
Case formulation only	19	0.35**	0.17, 0.52	3.90	45.44**	60
Case formulation + primary outcome[1,2]	15	0.34**	0.14, 0.54	3.37	38.11**	63
Additional analyses						
Group CBTp	2	0.35	-0.02, 0.72	1.84	0.74	0
Delusions as secondary outcome	4	0.36	-0.06, 0.78	1.69	7,15	58
Virtual-reality CBTp	2	0.56**	0.24, 0.89	3.36	0.86	0
After removal of 1 outlier						
Any risk of bias score included	26	0.32**	0.19, 0.46	4.71	41.30*	39
High risk of bias (>1) [3]	24	0.31**	0.17, 0.44	4.41	38.72*	41
Lowest risk of bias (0) [4]	17	0.26**	0.13, 0.40	3.81	23.96	33
Case formulation only	20	0.31**	0.16, 0.47	4.07	34.90*	46
Case formulation + primary outcome[1,2]	16	0.31**	0.14, 0.498	3.59	27.72*	46
Case formulation, primary outcome + RoB[1,2,3]	11	0.28**	0.11, 0.45	3.26	15.99	37

Note. All comparisons were using random model. Risk of bias scores refer to assessment using adapted version of the Cochrane Risk of Bias tool (0-4). *p<0.05. ** p<0.01. CI, Confidence Interval. *g*, Hedges's g. TAU, Treatment-as-usual. CBTp, Cognitive behavioural therapy for psychosis. CF, case formulation. RCT, randomised controlled trial. n/a, not applicable. Sensitivity analysis exclusions were as follows: [1]Hallucinations as primary outcome only: Freeman et al, 2014. Garety et al, 2008. Haddock et al, 2009. Tarrier et al, 2014. [2]Case formulation only: Foster et al, 2010. Freeman et al, 2015. Gottlieb et al, 2017. Penn et al, 2009. Waller et al, 2015. [3]Risk of bias score greater than 1 excluded: Foster et al, 2010. O'Connor et al, 2007. [4]Risk of bias score greater than 0 excluded: Cather et al, 2005. Durham et al, 2003. Freeman et al, 2016. Gottlieb et al, 2017. Krakvik et al, 2013. Foster et al, 2010. O'Connor et al, 2017. Waller et al, 2015. [5]Non-blinded RCTs excluded: Foster et al, 2010. Freeman et al, 2016. Krakvik et al, 2013. O'Connor et al, 2007. Waller et al, 2015.

Heterogeneity

There was a significant degree of heterogeneity present in the majority of comparisons. For hallucinations, the degree of significant heterogeneity ranged from 37% to 65% indicating the existence of heterogeneity primarily within the moderate range across comparisons. Heterogeneity was lower in comparisons including RCTs which utilised individualised case-formulation and also targeted hallucinations as primary outcome focus. Heterogeneity in the delusions comparisons was overall higher, ranging from 39% to 75% and therefore indicating moderate to high heterogeneity. The sensitivity analyses for case formulation and primary outcome in the delusions category did not display a pattern of lower heterogeneity.

Publication bias

The examination of funnel plots identified the possibility of unpublished negative studies across both symptom domains. For hallucinations, when all eligible RCTs were included there was an estimation that four unpublished negative trials may exist. Duval and Tweedie's[23] trim and fill procedure provided an adjusted effect size by removing five RCTs. This procedure reduced the magnitude of the effect favouring CBT but the effect remained significant (g=0.24, 95% CI: 0.15-0.33). Egger's[24] test of the intercept was not significant while the classic fail-safe N estimate that 291 unpublished studies would have to exist to bring the p-value above the alpha level of 0.05. For delusions, the funnel plot estimated the existence of eight unpublished trials. The trim and fill procedure provided

an adjusted effect removing seven RCTs which again remained significant although had reduced magnitude (*g*=0.18, 95% CI: 0.09-0.26). Egger's test of the intercept was significant on this comparison while the classic fail-safe N suggested it would require 335 missing studies to bring the p-value to above the 0.05 alpha level.

Post-hoc investigation of outliers

We identified significant heterogeneity across a high proportion of comparisons for auditory hallucinations that was not observed in the previous review. We therefore examined forest plots to identify primary studies as potential outliers contributing to high heterogeneity. Examination of Figure 3 (supplementary materials) suggested that the trial by Habib et al[35] was a significant outlier since its 95% confidence interval did not overlap with that of the pooled effect size. The effect from one RCT by Naeem et al[36] was also identified as a potential outlier. We therefore assessed heterogeneity when excluding both outliers in an exploratory sensitivity analysis. Excluding both RCTs reduced the heterogeneity in the comparison including all eligible RCTs below the alpha 0.05 level to *I*=27% (*Q* =33.35, *p*=.10). Heterogeneity was gradually reduced in subsequent sensitivity analyses and was observed as 0% in the most stringent and homogenous group of RCTs (case formulation, hallucinations as primary outcome and minimal bias risk). We also investigated the possible impact of the outliers on the magnitude of effects. We observed non-significant reduction in the effect magnitude across categories although the pattern of marginally increasing magnitude following stricter sensitivity analyses was maintained. Results from outlier exclusion for hallucinations are reported in Table 2.

Similar examination of confidence intervals in Figure 4 (supplementary materials) identified the effect size from the Naeem et al[37] trial in delusions as an outlier. We

therefore completed the same set of sensitivity analyses when excluding this RCT. Results demonstrated that heterogeneity was broadly reduced; in some comparisons to the extent that heterogeneity was no longer significant. There were also marginal and statistically insignificant reductions in the effect size. Results from outlier exclusion for delusions are reported in Table 3.

Post-hoc sensitivity analyses

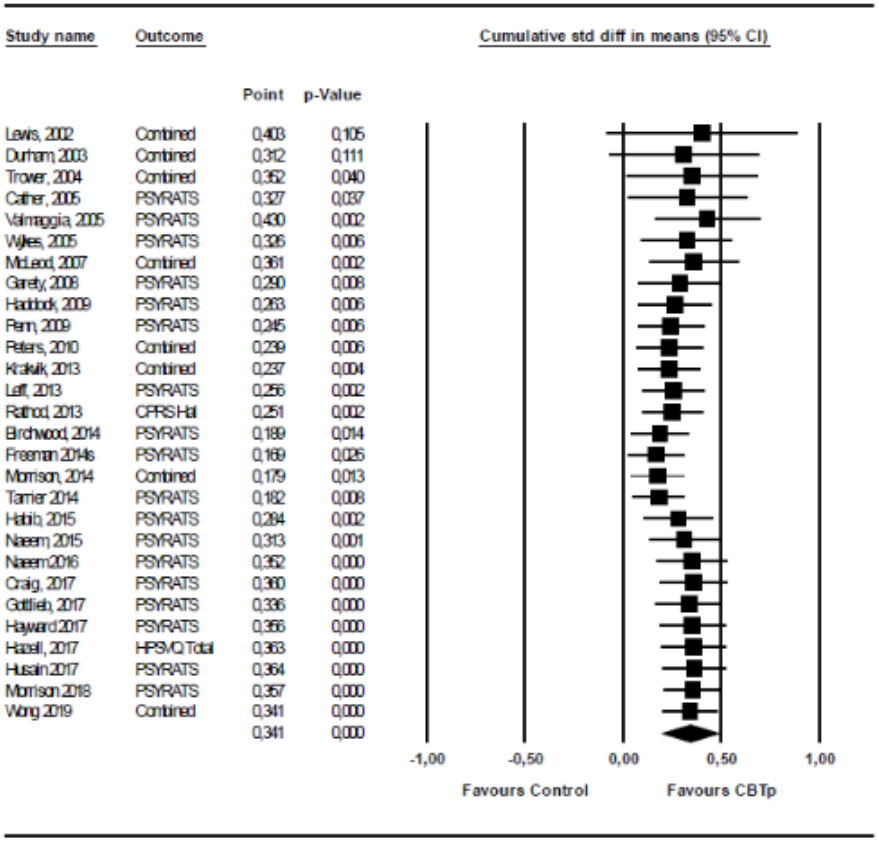
The length of treatment varied considerably between RCTs; the shortest treatment was a single session of VR-CBTp (Freeman et al, 2016) while the longest CBTp treatments lasted nine months. To investigate the impact of this variation we completed two further post hoc analyses; firstly a sensitivity analysis excluding the shortest treatment in the delusions comparison and secondly a meta-regression investigating the impact of treatment length on effects for both hallucinations and delusions. The results of the sensitivity analyses are reported in tables 2 & 3. Removal of the shortest RCT resulted in only marginal changes to effect sizes. The meta- analysis showed that the number of CBTp sessions participants received did not have a significant impact on the effect for hallucinations (p=0.88) or delusions (p=0.63). These findings were consistent when controlling for risk of bias.

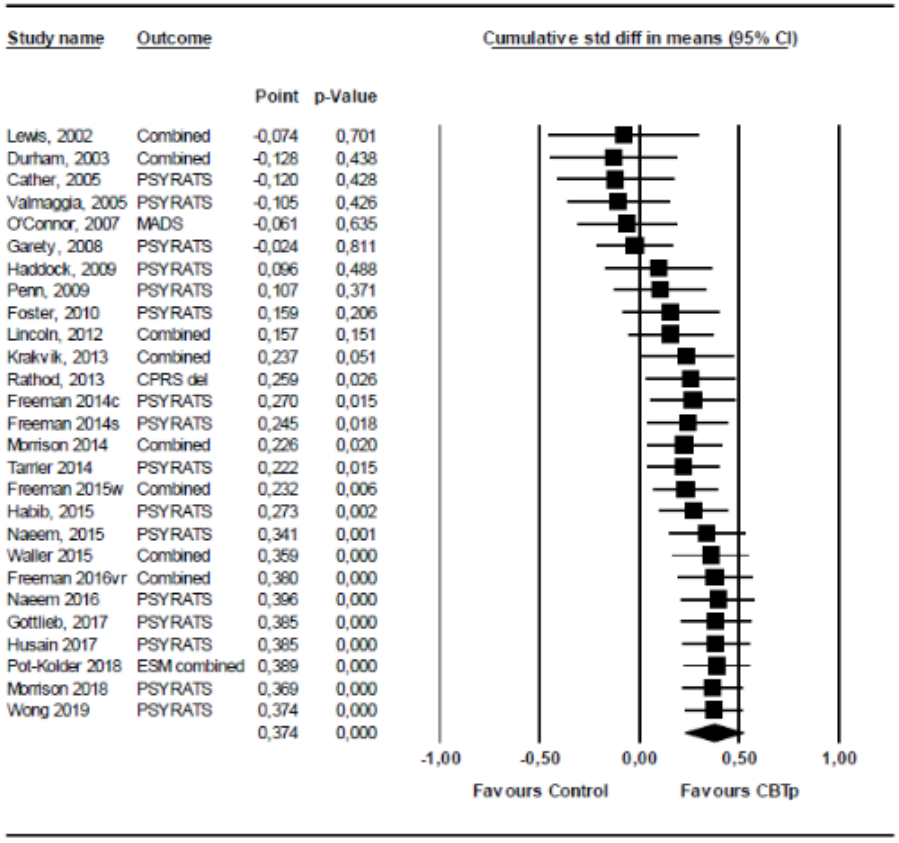
We also conducted a sensitivity analyses when removing two RCTs with a higher proportion of participants with psychosis diagnosed with non-schizophrenia-spectrum disorders.[51,52] Results of these sensitivity analyses are presented in Table 2 and show only marginal changes to effect sizes.

Post-hoc case formulation head-to-head comparison

We completed a direct comparison of the RCTs including CBTp case formulation versus those without. In the delusions analysis, CBTp demonstrated significant effects of similar magnitude for case formulation trials ($g=0.38$, $p<.01$) and non-case formulation trials ($g=0.35$, $p<.05$). In the hallucinations analysis, CBTp demonstrated a significant effect for case formulation trials ($g=0.40$, $p<0.5$) but not for non-case formulation trials ($g=0.10$, $p=0.51$).

Figure 2: *Cumulative meta-analysis forest plots for CBTp for a) hallucinations and b) delusions, all eligible RCTs*





Cumulative meta-analysis

Figure 2 depicts the cumulative forest plots for both the CBTp for hallucinations and delusions comparisons when including all eligible RCTs. This figure demonstrates the stability of the effect size over time. Table 4 provides fail safe ratio calculations for all four cumulative meta-analyses; namely the main analysis comparisons for both hallucinations and delusions when including all eligible RCTs alongside the most stringent sensitivity analysis when including only RCTs that scored zero on the risk of bias assessment, utilised individualised case-formulation and had primary outcome focus. More extensive figures for all cumulative meta-analyses including all relevant data are available in the supplementary materials (Figures 6-9).

For hallucinations, the 1.0 level of the fail-safe ratio demonstrating sufficiency was surpassed in 2016, which was consistent in the sensitivity analysis. For delusions, the 1.0 level was surpassed in 2015 for the main analysis and in 2017 for the sensitivity analysis. Cumulative forest plots for each of the remaining three comparisons are included in the supplementary materials and demonstrate stability of the effect size.

Discussion

Cumulative meta-analysis: *sufficient and stable*

This cumulative meta-analysis allowed us to demonstrate that the existing evidence base for the effect of CBTp on hallucinations and delusions is both statistically stable and sufficient according to Muellerleile and Mullen's[11] guidelines. A notable demonstration of the stability

of the evidence base is that the addition of a large trial with a null finding[38] had only a marginal impact on the effect size (g=0.358 to g=0.351 for hallucinations and g=0.383 to g=0.363 for delusions). The evidence base for hallucinations has been sufficient since 2016, after which another six RCTs were added. Similarly, our review suggests sufficiency of evidence for delusions from 2015 after which point six RCTs have also contributed data. Our findings suggest that further RCTs repeatedly testing CBTp are unlikely to have a significant impact on the magnitude or significance of treatment effects or to alter our conclusions in any substantive way, although we note that in conventional meta-analysis CBTp did not demonstrate superiority for delusions compared to active controls in the context of low power.

Conventional meta-analysis

The conventional meta-analytic comparisons in this review provided broadly similar results to our earlier review[1] despite adding 19 RCTs published during the six years elapsed since the previous systematic search. There were however notable differences in some comparisons. For hallucinations, when including only RCTs utilising both case formulation and primary outcome focus, the effect size increased to g=0.6 when controlling for risk of bias. However, after removing two outliers, this effect shrank to g= 0.44 which is consistent with our 2014 review. We observed a broadly consistent pattern across comparisons for hallucinations; when risk of bias was minimised and when including only case formulation and primary outcome focus, the magnitude of effects increased marginally but not significantly. Effects remained in the range of g=0.3 to g=0.6. The facility to examine risk of bias in this specific form of sensitivity analysis was not included in the previous review, therefore this finding, alongside the broad consistency of results in the hallucinations domain,

further suggests robust evidence of the impact of targeted, formulation-driven CBTp for hallucinations.

The effects of CBTp on delusions were of similar magnitude to those for auditory hallucinations when including all eligible trials, although did not display the pattern of marginally increasing magnitude when excluding RCTs with a higher risk of bias. Effect sizes in delusions comparisons remained in the region of g=0.32-0.38 for all main comparisons with the exception of the non-significant comparisons against active treatments. It should be noted that this category was comparatively underpowered and that the sensitivity analysis which included only RCTs with the lowest bias risk provided a significant effect of a similar magnitude (g=0.3, $p<.05$). Despite the finding that CBTp was not superior to active control treatments for delusions, since CBTp for delusions was demonstrated as meta-analytically effective overall while the active control conditions have no meta-analytical evidence, we suggest that CBTp for delusions continues to be recommended until evidence for other treatments emerges.

Our head-to-head comparison of case-formulation driven CBTp compared to that without also suggests that case-formulation driven CBTp is more effective in reducing hallucinations, while no difference was evident in the effects for delusions. We note that there were significantly more RCTs in the case formulation arm and therefore lower power in the non-case formulation arm, although the lower effect magnitude for non-formulation based CBTp for hallucinations is still indicative of potential inferiority. We note a recent secondary analysis[39] of one RCT included in our review[34] which failed to find a significant effect of case-formulation on outcome. This study also reported a non-significant trend of poorer treatment outcome for case formulation participants. Our findings are on a meta-analytic

level indicative that case-formulation is more beneficial for hallucinations, although definitive comment awaits more RCTs becoming available in the non-case formulation arm. Since many novel CBTp applications adhere less to the traditional formulation-based treatment approach, further pooling and comparison of this developing dichotomy is warranted.

Limitations

A notable limitation in this meta-analytic review was significant heterogeneity across a high proportion of the comparisons. Significant heterogeneity was present only in comparisons for delusions in the previous 2014 review; no hallucinations comparison in the original review demonstrated significant heterogeneity. Post hoc investigation established that heterogeneity introduced to the hallucinations comparisons was largely attributable to two outliers, one of which adapted CBTp for application in other cultural settings [35] while the other applied group-based self-help CBTp [36]. Similarly, another RCT of culturally adapted CBTp contributed to heterogeneity in the delusions comparisons.[42] Our earlier review conceptualised case-formulation driven CBTp RCTs as "apples" in comparison to "oranges;" a broader and more inclusive sample of RCTs applying CBTp principles in alternative style. We may therefore consider the newer, less homogenous CBTp trials and interventions again as such "oranges." The development of such novel approaches and application across wider settings is of importance in the CBTp field therefore we expect further such heterogeneity in future reviews. We also acknowledge that a number of comparisons in our review- namely those examining novel interventions and those comparing CBTp to active interventions- were underpowered. Low power therefore means there exists potential for Type 2 error in missing effects that do exist. We also acknowledge the limitation of our narrow focus relying only on

pre-post change, meaning that we cannot report on enduring effects at longer-term follow-up. Our focus on the specific hallucination and delusion outcomes also meant that other important outcomes such as relapse, functioning or level of distress were not considered, while focusing on schizophrenia-spectrum diagnoses also excludes many experiencing psychosis as a symptom of other diagnoses such as bipolar disorder and substance use disorders.[40,41]

Future research

Our cumulative meta-analysis suggests there is little value in researchers repeatedly testing conventional, formulation-driven CBTp in further RCTs; since the evidence base has demonstrated sufficiency, resources may better be directed toward novel approaches. The question of whether CBTp "works" is no longer central while previous disputes appear to have been settled.[6] Further development of RCTs examining novel approaches such as culturally-adapted CBTp and VR-CBTp will allow clearer conclusion on their efficacy via increased power in meta-analysis including only these interventions. We also note that RCTs examining novel approaches typically provide briefer interventions, although our post-hoc analysis did not suggest a significant impact of treatment duration on outcome. Our results also suggest there may be limited value in "collecting" further conventional meta-analyses which Murray[42] notably compared to the hobbyist pursuit of postage stamps. There is however the possibility that individual-participant data (IPD) meta-analysis techniques may be applied by combining the original databases of CBTp RCTs to provide more precise estimation of effects and the examination of moderating variables (e.g. demographic or clinical characteristics) on specific hallucination and delusions outcomes. Due to the identification of potential publication bias, we also encourage any researchers contributing to

the "file drawer problem" to publish any relevant trials which are not yet available in the public sphere for meta-analytic comparison. Future research may also focus further on the intricacies of the relationship between CBTp and anti-psychotics; despite the demonstrated sufficiency of evidence for CBTp, it remains to date investigated primarily as an adjunctive treatment.[43] Finally, although interesting findings such as the pattern of increasing effect magnitude when primary outcome focus or case formulation are applied, definitive comment on the effectiveness of specific CBTp components awaits detailed dismantling studies. There may therefore be opportunity to apply the developing factorial design principles of intervention optimisation research to the psychosis field.[44]

Conclusions

This meta-analytic review further demonstrates the efficacy of CBTp for auditory hallucinations and delusions and suggests that the evidence base is now both sufficient and stable. The robust performance of the effect on hallucinations in sensitivity analyses supports the notion that CBTp is particularly effective in this domain while heterogeneity and potential publication bias are issues which should be carefully examined in future reviews as further research becomes available for inclusion.

Acknowledgements

We acknowledge Professor Pim Cuijpers for support with this project.

Supplementary Material

Table 4 (Supplementary): *Cumulative meta-analysis sufficiency estimates for hallucinations and delusions*

	Publication year	*N* of accumulated RCTs	Fail-safe N	Fail Safe Ratio
Hallucinations: all eligible RCTs included	2004	3	1	0.04
	2005	6	7	0.18
	2007	7	13	0.29
	2008	8	13	0.26
	2009	10	15	0.25
	2010	11	16	0.25
	2013	14	32	0.4
	2014	18	35	0.35
	2015	20	104	0.95
	2016	21	142	1.24*
	2017	26	241	1.72
	2018	27	296	2.04
Hallucinations sensitivity analysis	2013	3	3	0.12
Lowest RoB, CF and primary outcome	2014	5	4	0.11
	2015	7	38	0.84
	2016	8	61	1.22*
	2017	11	124	1.91
	2018	12	163	2.33
Delusions: all eligible RCTs included	2005	4	0	0
	2007	5	0	0
	2008	6	0	0
	2009	8	0	0
	2010	9	0	0
	2012	10	1	0.02
	2013	12	20	0.29
	2014	16	29	0.32
	2015	20	146	1.33*
	2016	22	209	1.74
	2017	25	275	2.04
	2018	26	301	2.15
Delusions sensitivity analysis				
Lowest RoB, CF and primary outcome	2012	3	0	0
	2013	4	0	0
	2014	5	0	0
	2015	8	31	0.62
	2016	9	45	0.82
	2017	11	75	1.15*
	2018	12	89	1.27

Note. A minimum of three RCTs are required to calculate the Fail-safe N and Fail-safe Ratio. CF, case formulation. RoB, risk of bias. *, denotes point at which sufficiency of evidence was demonstrated by fail-safe ratio.

Table 5 (Supplementary): Adapted Cochrane Risk of Bias Tool

Study	Item 1	Item 2	Item 3	Item 4	Total risk
Lewis *et al*, 2002	+	+	+	+	0
Durham *et al*, 2003	+	+	+	-	1
Valmaggia *et al*, 2005	+	+	+	+	0
Cather *et al*, 2005	+	+	+	-	1
O'Connor *et al*, 2007	-	+	-	-	3
Garety *et al*, 2008	+	+	+	+	0
Penn *et al*, 2009	+	+	+	+	0
Haddock *et al*, 2009	+	+	+	+	0
Foster *et al*, 2010	+	+	-	-	2
Lincoln *et al*, 2012	+	+	+	+	0
Krakvik *et al*, 2013	+	+	-	+	1
Rathod *et al*, 2013	+	+	+	+	0
Morrison *et al,* 2014	+	+	+	+	0
Naeem *et al*, 2015	+	+	+	+	0
Habib *et al*, 2015	+	+	+	+	0
Freeman *et al,* 2015a	+	+	+	+	0
Waller *et al,* 2015	+	+	-	+	1
Naeem *et al,* 2016	+	+	+	+	0
Freeman *et al,* 2016	+	+	+	+	1
Pot-Kolder *et al,* 2018	+	+	+	+	0
Morrison *et al,* 2018	+	+	+	+	0
Trower *et al*, 2004	+	+	+	-	1
McLeod *et al*, 2007	-	-	+	-	3
Peters *et al*, 2010	+	-	-	+	2
Leff *et al*, 2013	+	+	+	-	1
Birchwood, 2014	+	+	+	+	0
Craig *et al*, 2017	+	+	+	+	0
Hazell *et al*, 2017	+	+	+	+	0
Gottlieb *et al*, 2017	+	+	+	-	1
Hayward *et al,* 2017	+	+	+	+	0
Husain *et al,* 2017	+	+	+	+	0
Freeman *et al,* 2014	+	+	+	+	0
Freeman *et al,* 2015b	+	+	+	+	0
Tarrier *et al* 2014	+	+	+	+	0

Note. +, criteria satisfied indicating low risk of bias. -, criteria not satisfied indicating risk of bias. Item 1, random sequence generation. Item 2, allocation concealment. Item 3, blinding of assessors. Item 4, incomplete outcome data. Total risk of bias was calculated as the sum of high risk items to provide an overall risk score. Unclear risk of bias category was disregarded therefore when no information on an item was included in report, high risk of bias was assumed. All items were independently rated by two authors with conflicts resolved via discussion.

Search strings: updated systematic search from 3rd August 2013 until 22nd October 2018

PubMed

((“CBT” OR “cognitive therapy” OR “cognitive behavioural therapy" or "cognitive behaviour therapy" OR "Cognitive behavior therapy" OR "cognitive behavioral therapy")) AND (“auditory hallucinations” OR “auditory verbal hallucinations” OR “AVH” OR "psychosis" OR "psychotic symptoms" OR "delusions" OR "paranoia" OR "paranoid")

-Limited to randomised controlled trials

Result: 119 citations

Embase

('cbt':ab,ti OR 'cognitive therapy':ab,ti OR 'cognitive behavioural therapy':ab,ti OR 'cognitive behaviour therapy':ab,ti OR 'cognitive behavior therapy':ab,ti OR 'cognitive behavioral therapy':ab,ti) AND ('auditory hallucinations':ab,ti OR 'auditory verbal hallucinations':ab,ti OR 'avh':ab,ti OR 'psychosis':ab,ti OR 'psychotic symptoms':ab,ti OR 'delusions':ab,ti OR 'paranoia':ab,ti OR 'paranoid psychosis':ab,ti)

-Limited to R randomised controlled trials, Embase only (ecluded Medline)

Result: 73 citations

PsychInfo

"CBT” OR “cognitive therapy” OR “cognitive behavioural therapy" or "cognitive behaviour therapy" OR "Cognitive behavior therapy" OR "cognitive behavioral therapy" AND “auditory hallucinations” OR “auditory verbal hallucinations” OR “AVH” OR "psychosis" OR "psychotic symptoms" OR "delusions" OR "paranoia" OR "paranoid"

-Limited to clinical trials (2013-2018)

Result: 57 citations

Total: 249 citations

After removal of duplicates by Mendeley: 219 citations for screening

Figure 3: CBTp for hallucinations, all eligible RCTs

Study name	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	
Lewis, 2002	0,398	0,245	0,060	-0,083	0,879	1,623	0,105	Combined
Durham, 2003	0,159	0,311	0,097	-0,450	0,768	0,512	0,609	Combined
Trower, 2004	0,479	0,352	0,124	-0,210	1,168	1,363	0,173	Combined
Cather, 2005	0,196	0,369	0,136	-0,527	0,919	0,532	0,595	PSYRATS
Valmaggia, 2005	0,788	0,291	0,085	0,217	1,359	2,704	0,007	PSYRATS
Wykes, 2005	0,028	0,232	0,054	-0,426	0,482	0,122	0,903	PSYRATS
McLeod, 2007	0,845	0,455	0,207	-0,047	1,738	1,856	0,063	Combined
Garety, 2008	0,046	0,189	0,036	-0,325	0,418	0,244	0,807	PSYRATS
Haddock, 2009	0,111	0,287	0,082	-0,452	0,674	0,387	0,699	PSYRATS
Penn, 2009	0,124	0,277	0,076	-0,418	0,666	0,450	0,653	PSYRATS
Peters, 2010	0,116	0,375	0,140	-0,619	0,850	0,309	0,758	Combined
Krakvik, 2013	0,207	0,294	0,087	-0,369	0,784	0,704	0,481	Combined
Leff, 2013	0,967	0,503	0,253	-0,018	1,952	1,924	0,054	PSYRATS
Rathod, 2013	0,152	0,357	0,127	-0,547	0,851	0,427	0,669	CPRS Hal
Birchwood, 2014	-0,129	0,155	0,024	-0,433	0,174	-0,836	0,403	PSYRATS
Freeman 2014s	-0,182	0,288	0,083	-0,747	0,382	-0,633	0,527	PSYRATS
Morrison, 2014	0,373	0,273	0,075	-0,163	0,908	1,364	0,173	Combined
Tarrier 2014	0,383	0,335	0,112	-0,273	1,039	1,143	0,253	PSYRATS
Habib, 2015	1,498	0,344	0,118	0,824	2,172	4,353	0,000	PSYRATS
Naeem, 2015	0,653	0,202	0,041	0,257	1,049	3,233	0,001	PSYRATS
Naeem 2016	1,188	0,371	0,138	0,460	1,915	3,200	0,001	PSYRATS
Craig, 2017	0,505	0,181	0,033	0,149	0,860	2,782	0,005	PSYRATS
Gottlieb, 2017	-0,341	0,348	0,121	-1,023	0,341	-0,981	0,326	PSYRATS
Hayward 2017	0,944	0,395	0,156	0,170	1,718	2,390	0,017	PSYRATS
Hazell, 2017	0,592	0,382	0,146	-0,157	1,341	1,549	0,121	HPSVQ Total
Husain 2017	0,437	0,344	0,118	-0,237	1,111	1,270	0,204	PSYRATS
Morrison 2018	0,333	0,104	0,011	0,130	0,536	3,214	0,001	PSYRATS
	0,351	0,074	0,005	0,207	0,495	4,764	0,000	

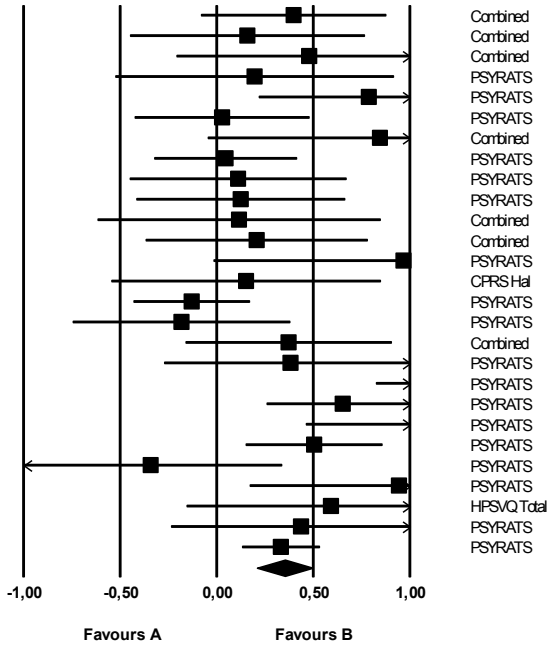


Figure 4: CBTp for delusions, all eligible RCTs

Study name	Outcome	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Lewis, 2002	Combined	-0,074	0,192	0,037	-0,451	0,303	-0,384	0,701
Durham, 2003	Combined	-0,266	0,310	0,096	-0,874	0,342	-0,858	0,391
Cather, 2005	PSYRATS	-0,075	0,368	0,135	-0,797	0,646	-0,205	0,838
Valmeggia, 2005	PSYRATS	-0,057	0,265	0,070	-0,576	0,462	-0,216	0,829
O'Connor, 2007	MADS	0,594	0,492	0,242	-0,371	1,559	1,206	0,228
Garety, 2008	PSYRATS	0,030	0,153	0,023	-0,270	0,329	0,195	0,845
Haddock, 2009	PSYRATS	0,911	0,305	0,093	0,313	1,509	2,986	0,003
Penn, 2009	PSYRATS	0,208	0,246	0,060	-0,274	0,690	0,846	0,398
Foster, 2010	PSYRATS	0,900	0,453	0,206	0,011	1,789	1,985	0,047
Lincoln, 2012	Combined	0,200	0,222	0,049	-0,236	0,635	0,899	0,369
Krakvik, 2013	Combined	0,939	0,311	0,097	0,330	1,549	3,020	0,003
Rathod, 2013	CPRS del	0,584	0,364	0,132	-0,130	1,297	1,603	0,109
Freeman 2014c	PSYRATS	0,477	0,367	0,134	-0,241	1,196	1,301	0,193
Freeman 2014s	PSYRATS	-0,022	0,287	0,083	-0,586	0,541	-0,077	0,939
Morrison 2014	Combined	0,015	0,281	0,079	-0,536	0,567	0,055	0,956
Tarrier 2014	PSYRATS	0,219	0,333	0,111	-0,433	0,871	0,658	0,510
Freeman 2015w	Combined	0,352	0,168	0,028	0,023	0,681	2,099	0,036
Habib, 2015	PSYRATS	0,941	0,320	0,102	0,315	1,568	2,944	0,003
Naeem, 2015	PSYRATS	1,081	0,211	0,044	0,668	1,494	5,130	0,000
Waller 2015	Combined	0,885	0,443	0,196	0,017	1,753	1,998	0,046
Freeman 2016vr	Combined	0,872	0,373	0,139	0,141	1,603	2,339	0,019
Naeem 2016	PSYRATS	0,789	0,355	0,126	0,094	1,484	2,226	0,026
Gottlieb, 2017	PSYRATS	0,126	0,346	0,119	-0,552	0,803	0,364	0,716
Husain 2017	PSYRATS	0,416	0,344	0,118	-0,257	1,090	1,211	0,226
Pot-Kolder 2018	ESM combined	0,485	0,187	0,035	0,118	0,852	2,590	0,010
Morrison 2018	PSYRATS	0,148	0,098	0,010	-0,044	0,340	1,508	0,132
		0,363	0,076	0,006	0,213	0,513	4,752	0,000

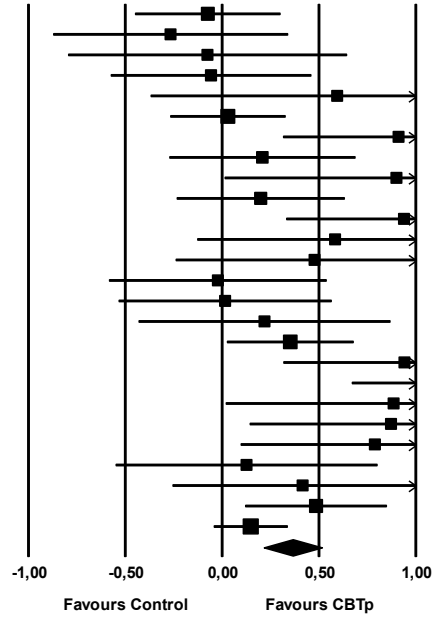
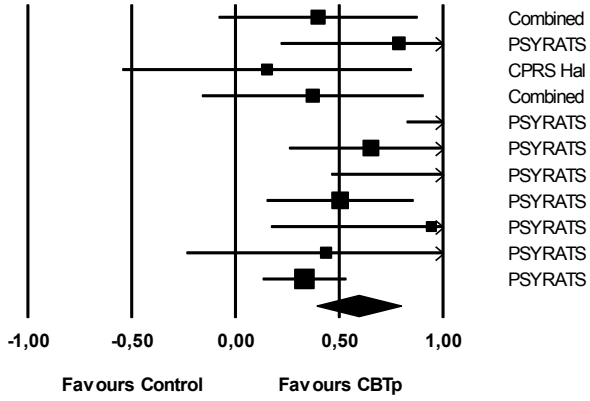


Figure 5: CBTp hallucinations sensitivity analysis RoB, formulation-driven, primary outcome

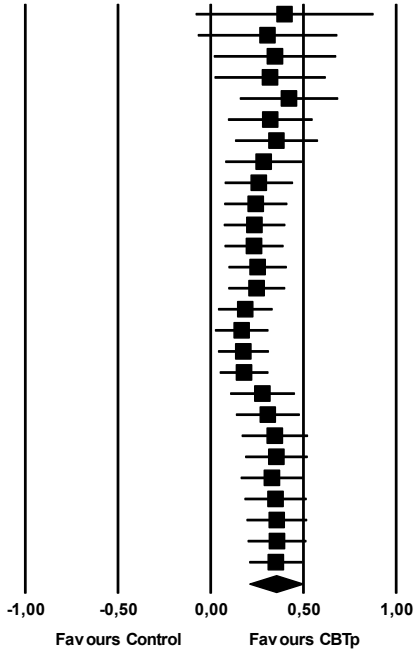
Study name	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	
Lewis, 2002	0,398	0,245	0,060	-0,083	0,879	1,623	0,105	Combined
Valmaggia, 2005	0,788	0,291	0,085	0,217	1,359	2,704	0,007	PSYRATS
Rathod, 2013	0,152	0,357	0,127	-0,547	0,851	0,427	0,669	CPRS Hal
Morrison, 2014	0,373	0,273	0,075	-0,163	0,908	1,364	0,173	Combined
Habib, 2015	1,498	0,344	0,118	0,824	2,172	4,353	0,000	PSYRATS
Naeem, 2015	0,653	0,202	0,041	0,257	1,049	3,233	0,001	PSYRATS
Naeem 2016	1,188	0,371	0,138	0,460	1,915	3,200	0,001	PSYRATS
Craig, 2017	0,505	0,181	0,033	0,149	0,860	2,782	0,005	PSYRATS
Hayward 2017	0,944	0,395	0,156	0,170	1,718	2,390	0,017	PSYRATS
Husain 2017	0,437	0,344	0,118	-0,237	1,111	1,270	0,204	PSYRATS
Morrison 2018	0,333	0,104	0,011	0,130	0,536	3,214	0,001	PSYRATS
	0,592	0,103	0,011	0,390	0,795	5,728	0,000	



Figures 6-9: Cumulative meta-analysis forest plots

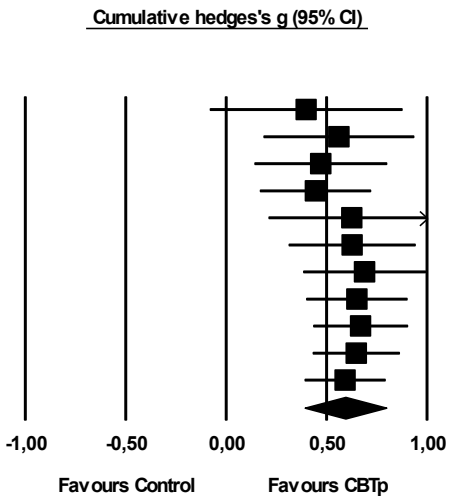
Cumulative meta analysis: CBTp for hallucinations, all eligible RCTs

Study name	Outcome	Cumulative statistics						
		Point	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Lewis, 2002	Combined	0,398	0,245	0,060	-0,083	0,879	1,623	0,105
Durham, 2003	Combined	0,306	0,193	0,037	-0,071	0,684	1,591	0,112
Trower, 2004	Combined	0,346	0,169	0,029	0,015	0,678	2,050	0,040
Cather, 2005	PSYRATS	0,320	0,154	0,024	0,019	0,621	2,085	0,037
Valmaggia, 2005	PSYRATS	0,422	0,136	0,018	0,156	0,688	3,106	0,002
Wykes, 2005	PSYRATS	0,321	0,117	0,014	0,092	0,551	2,741	0,006
McLeod, 2007	Combined	0,355	0,115	0,013	0,130	0,579	3,096	0,002
Garety, 2008	PSYRATS	0,286	0,106	0,011	0,077	0,494	2,689	0,007
Haddock, 2009	PSYRATS	0,259	0,095	0,009	0,074	0,445	2,743	0,006
Penn, 2009	PSYRATS	0,243	0,087	0,008	0,071	0,414	2,775	0,006
Peters, 2010	Combined	0,236	0,085	0,007	0,069	0,403	2,773	0,006
Krakvik, 2013	Combined	0,234	0,082	0,007	0,074	0,394	2,859	0,004
Leff, 2013	PSYRATS	0,253	0,081	0,007	0,095	0,411	3,131	0,002
Rathod, 2013	CPRS Hal	0,248	0,079	0,006	0,094	0,402	3,148	0,002
Birchwood, 2014	PSYRATS	0,187	0,076	0,006	0,038	0,335	2,469	0,014
Freeman 2014s	PSYRATS	0,167	0,074	0,006	0,022	0,312	2,251	0,024
Morrison, 2014	Combined	0,176	0,071	0,005	0,038	0,315	2,498	0,012
Tarrier 2014	PSYRATS	0,180	0,067	0,005	0,048	0,312	2,665	0,008
Habib, 2015	PSYRATS	0,279	0,089	0,008	0,104	0,454	3,118	0,002
Naeem, 2015	PSYRATS	0,308	0,088	0,008	0,135	0,481	3,486	0,000
Naeem 2016	PSYRATS	0,346	0,092	0,008	0,166	0,526	3,764	0,000
Craig, 2017	PSYRATS	0,354	0,087	0,008	0,184	0,524	4,086	0,000
Gottlieb, 2017	PSYRATS	0,330	0,087	0,008	0,161	0,500	3,814	0,000
Hayward 2017	PSYRATS	0,350	0,086	0,007	0,181	0,519	4,053	0,000
Hazell, 2017	HPSVQ Total	0,356	0,084	0,007	0,191	0,521	4,237	0,000
Husain 2017	PSYRATS	0,358	0,081	0,007	0,198	0,517	4,395	0,000
Morrison 2018	PSYRATS	0,351	0,074	0,005	0,207	0,495	4,764	0,000
		0,351	0,074	0,005	0,207	0,495	4,764	0,000



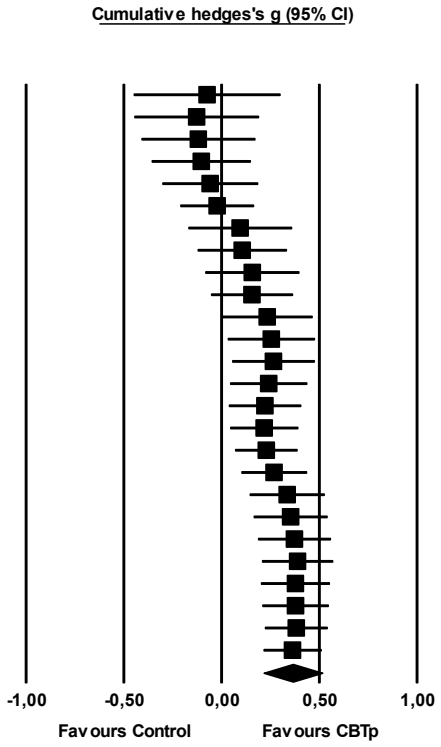
Cumulative meta analysis hallucinations: sensitivity analysis RoB, formulation-based, primary outcome-focused CBTp

Study name		Cumulative statistics						
		Point	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Lewis, 2002	Combined	0,398	0,245	0,060	-0,083	0,879	1,623	0,105
Valmaggia, 2005	PSYRATS	0,561	0,192	0,037	0,185	0,938	2,922	0,003
Rathod, 2013	CPRS Hal	0,471	0,169	0,029	0,139	0,803	2,783	0,005
Morrison, 2014	Combined	0,445	0,142	0,020	0,167	0,723	3,134	0,002
Habib, 2015	PSYRATS	0,626	0,212	0,045	0,209	1,042	2,946	0,003
Naeem, 2015	PSYRATS	0,627	0,162	0,026	0,310	0,944	3,876	0,000
Naeem 2016	PSYRATS	0,689	0,157	0,024	0,382	0,996	4,403	0,000
Craig, 2017	PSYRATS	0,651	0,129	0,017	0,397	0,904	5,034	0,000
Hayward 2017	PSYRATS	0,670	0,121	0,015	0,432	0,907	5,534	0,000
Husain 2017	PSYRATS	0,648	0,111	0,012	0,430	0,866	5,819	0,000
Morrison 2018	PSYRATS	0,592	0,103	0,011	0,390	0,795	5,728	0,000
		0,592	0,103	0,011	0,390	0,795	5,728	0,000



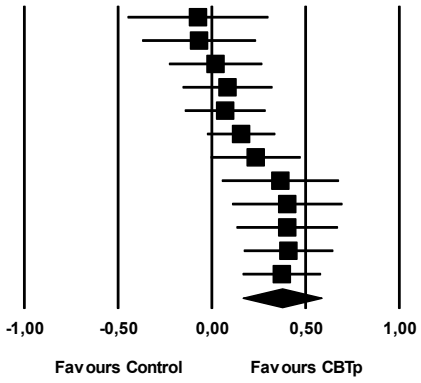
Cumulative meta analysis: CBTp for delusions, all eligible RCTs

Study name	Outcome	Cumulative statistics						
		Point	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Lewis, 2002	Combined	-0,074	0,192	0,037	-0,451	0,303	-0,384	0,701
Durham, 2003	Combined	-0,127	0,163	0,027	-0,448	0,193	-0,779	0,436
Cather, 2005	PSYRATS	-0,119	0,149	0,022	-0,412	0,174	-0,795	0,427
Valmaggia, 2005	PSYRATS	-0,104	0,130	0,017	-0,359	0,151	-0,798	0,425
O'Connor, 2007	MADS	-0,058	0,126	0,016	-0,305	0,188	-0,463	0,643
Garety, 2008	PSYRATS	-0,023	0,097	0,009	-0,213	0,168	-0,234	0,815
Haddock, 2009	PSYRATS	0,095	0,136	0,019	-0,172	0,362	0,699	0,484
Penn, 2009	PSYRATS	0,106	0,117	0,014	-0,124	0,336	0,901	0,367
Foster, 2010	PSYRATS	0,157	0,123	0,015	-0,085	0,399	1,274	0,203
Lincoln, 2012	Combined	0,156	0,108	0,012	-0,055	0,367	1,447	0,148
Krakvik, 2013	Combined	0,233	0,119	0,014	-0,000	0,467	1,957	0,050
Rathod, 2013	CPRS del	0,255	0,114	0,013	0,031	0,479	2,228	0,026
Freeman 2014c	PSYRATS	0,265	0,109	0,012	0,053	0,478	2,445	0,014
Freeman 2014s	PSYRATS	0,241	0,102	0,010	0,042	0,440	2,372	0,018
Morrison 2014	Combined	0,222	0,095	0,009	0,036	0,409	2,334	0,020
Tarrier 2014	PSYRATS	0,218	0,090	0,008	0,043	0,394	2,434	0,015
Freeman 2015w	Combined	0,229	0,082	0,007	0,067	0,390	2,779	0,005
Habib, 2015	PSYRATS	0,269	0,086	0,007	0,100	0,438	3,114	0,002
Naeem, 2015	PSYRATS	0,336	0,099	0,010	0,143	0,529	3,410	0,001
Waller 2015	Combined	0,353	0,097	0,009	0,163	0,544	3,638	0,000
Freeman 2016vr	Combined	0,373	0,096	0,009	0,186	0,561	3,898	0,000
Naeem 2016	PSYRATS	0,389	0,094	0,009	0,205	0,573	4,150	0,000
Gottlieb, 2017	PSYRATS	0,378	0,091	0,008	0,200	0,556	4,173	0,000
Husain 2017	PSYRATS	0,378	0,087	0,008	0,207	0,550	4,327	0,000
Pot-Kolder 2018	ESM combined	0,383	0,083	0,007	0,221	0,544	4,631	0,000
Morrison 2018	PSYRATS	0,363	0,076	0,006	0,213	0,513	4,752	0,000
		0,363	0,076	0,006	0,213	0,513	4,752	0,000



Cumulative meta-analysis delusions; sensitivity analysis RoB, formulation-based, primary outcome focused CBTp

Study name	Outcome	Cumulative statistics						
		Point	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Lewis, 2002	Combined	-0,074	0,192	0,037	-0,451	0,303	-0,384	0,701
Valmaggia, 2005	PSYRATS	-0,068	0,156	0,024	-0,373	0,237	-0,437	0,662
Lincoln, 2012	Combined	0,020	0,127	0,016	-0,230	0,270	0,158	0,875
Rathod, 2013	CPRS del	0,084	0,123	0,015	-0,157	0,325	0,680	0,496
Morrison 2014	Combined	0,071	0,111	0,012	-0,145	0,288	0,646	0,519
Freeman 2015w	Combined	0,156	0,094	0,009	-0,028	0,339	1,666	0,096
Habib, 2015	PSYRATS	0,234	0,123	0,015	-0,008	0,475	1,894	0,058
Naeem, 2015	PSYRATS	0,366	0,160	0,026	0,052	0,679	2,287	0,022
Naeem 2016	PSYRATS	0,402	0,151	0,023	0,107	0,698	2,669	0,008
Husain 2017	PSYRATS	0,402	0,139	0,019	0,130	0,674	2,896	0,004
Pot-Kolder 2018	ESM combined	0,409	0,122	0,015	0,169	0,648	3,345	0,001
Morrison 2018	PSYRATS	0,373	0,107	0,012	0,163	0,584	3,478	0,001
		0,373	0,107	0,012	0,163	0,584	3,478	0,001



Chapter 5

Efficacy and moderators of cognitive behavioural therapy for psychosis versus other psychological interventions: An individual-participant-data meta-analysis

David Turner, Mirjam Reijnders, Mark van der Gaag, Eirini Karyotaki, Lucia Valmaggia, Steffen Moritz, Tania Lecomte, Douglas Turkington, Rafael Penadés, Helio Elkis, Corinne Cather, Frances Shawyer, Kieron O'Connor, Zhan-Jiang Li, Eliza Martha de Paiva Barretto & Pim Cuijpers

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Abstract

Background: Study-level meta-analyses have demonstrated the efficacy of cognitive-behavioural therapy for psychosis (CBTp). Limitations of conventional meta-analysis may be addressed using individual-participant-data (IPD). We aimed to determine a) whether results from IPD were consistent with study-level meta-analyses and b) whether demographic and clinical characteristics moderate treatment outcome.

Methods: We systematically searched PubMed, Embase, PsychInfo and CENTRAL. Authors of RCTs comparing CBTp with other psychological interventions were contacted to obtain original databases. Hierarchical mixed effects models were used to examine efficacy for psychotic symptoms. Patient characteristics were investigated as moderators of symptoms at post-treatment. Sensitivity analyses were conducted for risk of bias, treatment format and study characteristics.

Results: We included 14 of 23 eligible RCTs in IPD meta-analyses including 898 patients. 10 RCTs minimised risk of bias. There was no significant difference in efficacy between RCTs providing IPD and those not (p>0.05). CBTp was superior vs. other interventions for total psychotic symptoms and PANSS general symptoms. No demographic or clinical characteristics were robustly demonstrated as moderators of positive, negative, general or total psychotic symptoms at post-treatment. Sensitivity analyses demonstrated that number of sessions moderated the impact of treatment assignment (CBTp or other therapies) on total psychotic symptoms (p=0.02).

Conclusions: IPD suggest that patient characteristics, including severity of psychotic symptoms, do not significantly influence treatment outcome in psychological interventions for psychosis while investing in sufficient dosage of CBTp is important. IPD provide roughly equivalent efficacy estimates to study-level data although significant benefit was not replicated for positive symptoms. We encourage authors to ensure IPD is accessible for future research.

Keywords: psychosis, cognitive-behavioural therapy, individual-participant data, meta-analysis, psychological intervention

Introduction

The efficacy of psychological interventions for psychosis have been established[1–5] while counter-argument questioning *effectiveness* exists.[6,7] Meta-analytic studies represent the pinnacle of evidence-based psychological intervention in psychosis. Using traditional "two-step" study-level meta-analytic methods in pooling effect sizes from published articles, we have demonstrated that cognitive-behavioural therapy for psychosis (CBTp) represents the most efficacious psychological intervention for positive symptoms in psychosis,[8] while social skills training is most efficacious in the treatment of negative and general symptoms.[9]

There are however inherent limitations of the conventional "two-step" approach. Comparisons often lack adequate power to detect effects hence risk Type II errors, while precision of effect size estimates may be improved. Lack of power and poor availability of relevant variables at the study-level also preclude identification of moderators of treatment outcome.[10] Individual-participant data (IPD) meta-analyses address these issues by utilising original databases from RCTs rather than relying on data from published trials. This approach maximises power to detect effects and allows the examination of moderators via participant characteristics that vary at the IPD level.[11]

IPD methodology has been applied to psychosis research, including investigation of non-response rates to antipsychotic medication.[12] We note that IPD meta-analysis is distinct to network meta-analysis and cumulative meta-analysis, two other novel meta-analytic methods that have recently been applied in psychosis-related research.[13-15] The present meta-analysis is, to

our knowledge, the first attempt to apply IPD methodology to psychological interventions in psychosis. We report the results of an IPD meta-analysis comparing CBTp to other psychological interventions alongside an exploratory moderator analysis investigating the impact of demographic and clinical characteristics on treatment outcome. We had two research objectives; 1) to determine whether evidence for the efficacy of CBTp from IPD is consistent with previous meta-analytic evidence and 2) to determine whether demographic and clinical characteristics of psychosis patients moderate the outcome of psychological therapies. We hypothesised that IPD would provide broadly equivalent efficacy outcomes to previous research while our moderator analysis was conducted in an exploratory manner based upon available IPD without pre-specified hypotheses.

Methods

Identification and inclusion of studies

A systematic literature search was completed on 25th September 2017. The search strategy has been described elsewhere[8] and is included in the supplementary materials. We examined 7037 abstracts from four databases; Pubmed (2011), PsycInfo (2457), Embase (1071) and the Cochrane Central Register of Controlled Trials (1498). Abstracts were identified by combining terms indicative of psychological interventions for psychosis and relevant psychotic disorders (MeSH terms and text words). We checked reference lists from earlier meta-analyses to ensure that no published studies were missed. From 7037 abstracts (5881 after the removal of duplicates), we retrieved 621 full-text papers for consideration.

We included (a) RCTs in which (b) CBTp (c) was compared with another psychological intervention (d) for patients with a psychotic disorder, (e) based on an established standardised diagnostic interview, (f) in which the aim was to reduce psychotic or psychiatric symptoms.

The psychological interventions that were included as comparison conditions are operationally defined elsewhere.[8] Studies targeting patients with comorbid general medical disorders or prodromal psychosis were excluded. Trials were excluded if the comparison condition was not an active psychological intervention (e.g. treatment as usual, waiting list). Medication adherence or compliance RCTs were excluded. Language restrictions were set to English and German.

After identifying potential RCTs for inclusion, the corresponding authors of each were contacted by email and invited to participate by providing the sociodemographic and clinical characteristics alongside the outcome data from their trials. If authors did not respond within two weeks a reminder was sent. If no answer was received, we considered the trial unavailable. In instances in which authors responded but were unsure whether data could be provided, contact was maintained until it was clear that data was unobtainable.

Risk of bias assessment

The risk of bias of the included RCTs was assessed using four criteria of the Cochrane Collaboration risk of bias tool;[16] sequence generation, allocation concealment, blinding of outcome assessors and incomplete outcome data. Only the data reported in the published papers

was used as this was considered to be the most conservative estimate. Two independent researchers (DT and EK) carried out the risk of bias assessment. Disagreements were resolved through discussion.

Assessment of psychotic symptoms

Psychotic symptoms were measured using three commonly used scales measuring positive, negative and general symptoms of psychosis; the Positive and Negative Syndrome Scale (PANSS),[14] the Brief Psychiatric Rating Scale (BPRS)[15,16] and the Scale for the Assessment of Negative Symptoms (SANS).[17] Further information on these scales is provided in the supplementary materials. In instances of multi-scale use, we selected the main outcome using the following rank order: (1) PANSS; (2) BPRS; (3) SANS. To facilitate comparison across RCTs and outcome measures, a standardised variable was created each for the combined positive, negative and total subscales using z-scores. Total and subscale scores per participant were utilised rather than item-level data therefore we relied on scoring algorithms applied in the original RCTs. Higher scores indicated greater severity in all scales.

Differences between included and non-included RCTs

To examine whether RCTs included in the IPD meta-analysis differed in post-treatment outcome from RCTs for which we were unable to obtain databases, we completed conventional "two step" meta-analyses. We obtained comparative effect sizes using Comprehensive Meta-Analysis

software (CMA; version 2.2.057). We corrected for small samples based on the procedures suggested by Hedges and Olkin[21] therefore provided effect sizes in Hedges' *g*.

Publication bias

Publication bias was tested in all RCTs meeting inclusion criteria and in the subset included in IPD meta-analyses. We inspected funnel plots and applied Duval and Tweedie's trim and fill procedure.[22] We also conducted Egger's test of the intercept to quantify bias captured by the funnel plot and test for significance.

Missing data

Participants with missing baseline data were deleted from the IPD dataset (*n*=12). The proportion of missing post-treatment outcome data was 9% (*n* = 80) for the PANSS and 3% (*n* = 26) for the other psychotic symptom scales. Missing outcome data at post-treatment was not imputed. It has been repeatedly demonstrated in IPD meta-analyses that imputed analyses do not significantly differ from completer analyses[10,23,24] while mixed models already make optimal use of available data.

IPD meta-analyses

All analyses were conducted using the 'xtmixed' command in Stata/SE software (version 14.2). Firstly, we applied a mixed effects model to examine the efficacy of CBTp vs. other

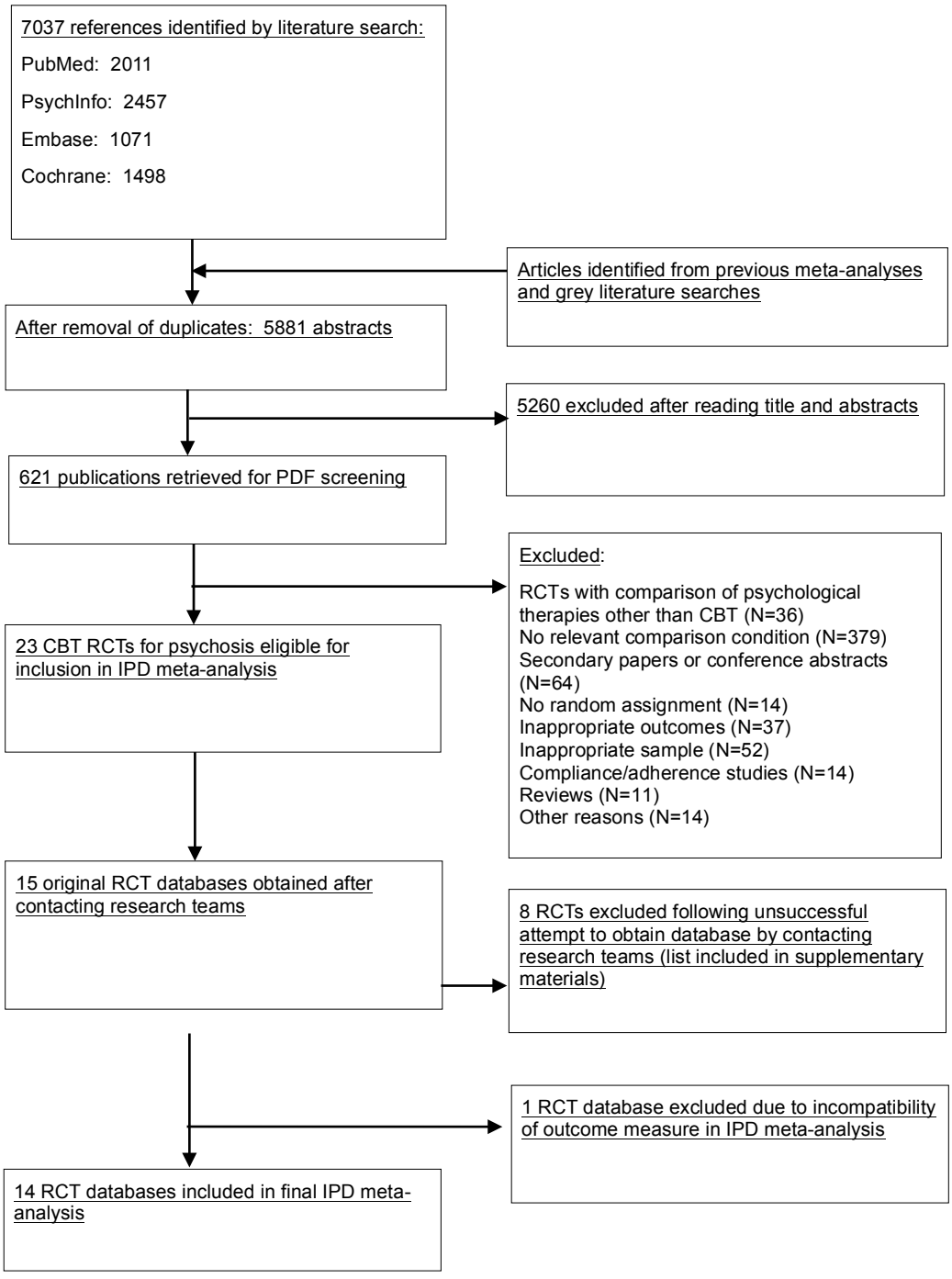
psychological interventions in reducing positive, negative, general, and total psychotic while controlling for baseline psychotic symptom severity and accounting for clustering of patients within studies. These analyses were conducted using all the separate standardised subscales of the PANSS (positive, negative, general, and total), the BPRS (positive, negative, and total), and the SANS (total) as dependent variables. The analyses were repeated using all standardised positive subscales combined, all standardised negative subscales, and all standardised total subscales as dependent variables. Both the treatment dummy (CBTp=1 and other therapeutic interventions=0), and psychotic symptom severity at baseline were used as predictors in the models.

We again used a mixed effects model to examine whether sociodemographic and clinical variables moderate the efficacy of CBTp vs. other psychological interventions in reducing positive, negative and total psychotic symptoms while controlling for baseline psychotic symptom severity and accounting for clustering of patients within studies. Sociodemographic moderator variables included age, gender, marital status (married; not married), education level (secondary/lesser; tertiary/further), ethnicity (Caucasian; ethnic minority), occupation (employed; unemployed; student), type of diagnosis (schizophrenia; schizo-affective disorder; other), and illness duration in years. Clinical moderator variables included the PANSS negative and general psychotic symptoms at baseline and number of treatment sessions. The treatment dummy, psychotic symptom severity at baseline and the interaction between the treatment dummy and the moderators were used as predictors. All analyses were carried out per moderator, using the combined standardised positive, negative and total subscales as dependent variables.

All continuous moderator variables were centred on the study level, to ensure that the interaction term explains only patient level variation in treatment response instead of study level variation.

Finally, sensitivity analyses were conducted in which all of the previously described analyses were redone using only studies that were assessed as having minimal risk of bias. We also conducted post-hoc sensitivity analyses in instances where there were conceptual differences between included studies in interventions, outcomes and treatment format (group vs individual).

Figure 1. Flowchart of inclusion of studies



Results

Selection of studies

Figure 1 provides a flowchart describing the inclusion process. Of 621 full-text papers retrieved, 598 were excluded while 23 RCTs met our inclusion criteria. Of these 23 studies, 15 provided patient-level data (65%). Eight studies for which authors were contacted did not contribute data and were therefore excluded from the IPD meta-analysis (please see the supplementary materials for a list of these RCTs). One study did contribute [25] data but utilised an outcome measure which was not comparable to other RCTs and was therefore excluded. This resulted in 14 trials being included in the IPD meta-analysis.

Characteristics of included studies and patients

Study characteristics are summarised in Table 1. The 14 RCTs included a total of 898 patients. 460 received CBTp and 438 received other psychological interventions. Comparison interventions were befriending (5 RCTs), supportive counselling (4), cognitive remediation (2), socials skills training (1), psychoeducation (1) and family intervention (1). Four studies were conducted in the UK, two in the US, two in Canada, two in Australia, and one in China, Brazil, Germany, Spain and the Netherlands. Eleven utilised individual treatment format, two used group format and one implemented both. Treatment duration ranged from four to 52 weeks. A summary of patient characteristics is provided in the supplementary materials alongside a histogram summarising the distribution of PANSS total severity at baseline. The mean PANSS total score at baseline

was 71, which falls within the *moderately ill* range[26] and is comparable to previous meta-analyses.[27]

Table 1. *Selected characteristics of randomised controlled trials of CBTp versus other psychological interventions for psychosis*

Study & publications	Country	Sample characteristics	Relevant comparisons & *n*	Symptom outcome measures	Format	Bias Risk (0-4)	Duration (weeks to PT)	Follow-up
Barretto *et al* [36]	Brazil	DSM-IV Schizophrenia, 6 months clozapine treatment-resistant. Outpatients.	CBT (12) vs. BF (10)	BPRS, PANSS	Individual	2	21	6 months
Cather *et al* [37]	USA	Schizophrenia or schizoaffective disorder. Outpatients	CBT (15) vs. PE (13)	PANSS, PSYRATS	Individual	1	16	N/A
Durham *et al* [38]	UK	Schizophrenia, Schizoaffective disorder or delusional disorder suffering positive symptoms. Outpatient & inpatient.	CBT (22) vs. SC (23)	PANSS, PSYRATS	Individual	0	39	3 months
Garety *et al* [31]	UK	Recently relapsed non-affective psychosis (ICD 10 F2 & DSM-IV), with carers. Positive symptoms.	CBT (27) vs. FI (28)	PANSS, PSYRATS,	Individual	0	52	24 months
Haddock *et al* [32]	UK	DSM-IV schizophrenia or schizoaffective disorder. History of violence. Current anti-psychotic medication & positive symptoms.	CBT (38) vs. BF (39)	PANSS, PSYRATS	Individual	0	26	12 months
Jackson *et al* [39]	Australia	First episode psychosis including schizophrenia, schizophreniform, schizoaffective, bipolar, delusional disorder & psychosis NOS. Inpatient & outpatient.	CBT (31) vs. BF (31)	BPRS, SANS	Individual	2	12	12 months
Lecomte *et al* [33]	Canada	Early psychosis (< 2 years). Current psychotic symptoms. Stabilized outpatients.	CBT (48) vs. SST (54)	BPRS	Group	2	13	6 months, 12 months
Li *et al* [40]	China	DSM-IV schizophrenia. Adequate antipsychotic dose. Inpatients & outpatients.	CBT (96) vs. SC (96)	PANSS	Individual	0	24	12, 36 & 60 weeks
Moritz *et al* [29]	Germany	Broad psychotic inpatients meeting criteria for schizophrenifom disorder.	CBT (24) vs. CR (24)	PANSS, PSYRATS	Both	0	4	N/A
Penades *et al* [41]	Spain	DSM-IV schizophrenia. Chronic. Prevalence of negative symptoms & cognitive impairment.	CBT (20) vs. CR (20)	PANSS	Individual	0	17	6 months
Penn *et al* [34]	USA	Schizophrenia or schizoaffective disorder & current auditory hallucinations. Outpatients.	CBT (32) vs. SC (33)	PANNS, PSYRATS	Group	0	12	3 months, 12 months
Sensky *et al* [42] & Turkington *et al* [43]	UK	DSM-IV & ICD-10 schizophrenia. Treatment resistant. Outpatients.	CBT (46) vs. BF (44)	CPRS, SANS,	Individual	0	39	9 months, 5 years
Shawyer *et al* [30]	Australia	DSM-IV schizophrenia or related condition including command hallucinations in previous 6 months. Outpatients.	CBT (21) vs. BF (22)	PANSS, PSYRATS, CH	Individual	0	15	6 months
Valmaggia *et al* [44]	Netherlands	DSM-IV schizophrenia including residual delusions or auditory hallucinations. Medication resistant.	CBT (36) vs. SC (26)	PANSS, PSYRATS	Individual	0	22	6 months

Table 1: BF, Befriending; BPRS, Brief Psychiatric Rating Scale; CBT, Cognitive-Behavioural Therapy; CH, Command Hallucinations; CPRS, Comprehensive Psychopathological Rating Scale; CR, Cognitive Remediation; FI, Family Intervention; *n,* Number of participants in each treatment group; PANSS, Positive and Negative Symptoms Scale; PE, Psycho-education; PSYRATS, Psychotic Symptom Rating Scale; PT, Post-treatment SANS, Scale for Assessment of Negative Symptoms; SC, Supportive Counselling; SST, Social Skills Training

Risk of bias

Risk of bias varied between RCTs (Table 1 & supplementary materials). Of the 14 studies, 10 reported adequate sequence generation and nine reported satisfactory allocation concealment. All studies reported blinding of outcome assessors. All studies utilised intention-to-treat analyses to address missing outcome data. 10 studies were assessed as successfully minimising all four risk of bias criteria, while four successfully met two or three criteria. No studies were assessed as having the highest possible risk of bias score.

Available and unavailable data: conventional meta-analysis

To test for differences between available and unavailable data, we ran a conventional meta-analysis comparing the 14 studies included in the IPD meta-analysis with the 9 trials which met our inclusion criteria but did not contribute primary data. For total symptoms with all 23 studies included, results showed a small significant effect in favour of CBTp (g=0.16, p=0.01). Analysing only the 14 studies included in the IPD meta-analysis resulted in a small significant effect in favour of CBTp (g=0.17, p=0.01). There was no significant effect when analysing the 9 remaining non-included studies although the magnitude of effect size was similar (g=0.14, p=0.28). The difference between the IPD studies and those not-included was not significant (p=0.80).

For positive symptoms it was possible to include 16 studies in the overall comparison; results demonstrated a small significant effect in favour of CBTp (g=0.15, p=0.03). Including only the 11 IPD studies resulted in a small non-significant effect in favour of CBTp (g=0.13, p=0.09). The effect was also non-significant when analysing the remaining

5 non-included studies (g=0.19, p=0.12). The difference between the IPD and non-IPD studies was not significant (p=0.65). For negative symptoms, CBTp did not demonstrate significant superiority when all 10 available studies were included (g=0.05, p=0.52), nor when analysing only the 6 IPD studies (g=0.06, p=0.60) or the 4 remaining non-IPD studies (g 0.04, p=0.71). The difference between the IPD and non-IPD studies was not significant (p=0.92).

Publication bias

The funnel plots assessing publication bias for the total symptoms and positive symptoms analyses on the overall 23 studies suggested the existence of one unpublished negative trial in each. Egger's[28] test did not suggest that the extent of publication bias was significant for the total (p=0.13) or positive (p=0.10) symptoms comparisons. The classic fail-safe N estimated that it would require 32 and 15 missing trials respectively to cause loss of effect significance. Duval and Tweedie's[22] trim and fill procedure trimmed one study in each comparison, resulting in a marginal reduction in the magnitude of effect in both total symptoms (g=0.14, 95% CI: 0.03~0.23) and positive symptoms (g=0.13, 95% CI: -0.00~0.24). This resulted in the positive symptoms comparison losing significance. There was no evidence of publication bias in the negative symptoms comparison.

Table 2. *Individual participant data main effects of CBTp versus other interventions pooled*

Variable	Full sample of RCTs			RCTs assessed as low risk of bias		
	No of observations (no. of studies)	Mean (SE) β_b	2-tailed *p* Value	No of observations (no. of studies)	Mean (SE) β_b	2-tailed *p* Value
PANSS Positive symptoms	584 (11)	-0.10 (0.06)	.101	503 (8)	-0.13 (0.07)	.068
PANSS Negative symptoms	538 (10)	-0.69 (0.07)	.295	457 (7)	-0.05 (0.07)	.469
PANSS General symptoms	536 (10)	-0.17* (0.07)	.019	454 (7)	-0.08 (0.08)	.304
PANSS Total	538 (10)	-0.15* (0.07)	.027	456 (7)	-0.10 (0.08)	.168
BPRS Positive	119 (2)	-0.04 (0.16)	.823			
BPRS Negative	66 (1)	-0.02 (0.21)	.934			
BPRS Total	119 (2)	-0.16 (0.17)	.362			
SANS Total	143 (2)	-0.21 (0.14)	.135	90 (1)	-0.15 (0.17)	.380
Positive scales combined	703 (13)	-0.10 (0.06)	.114	503 (8)	-0.13 (0.07)	.068
Negative scales combined	747 (13)	-0.09 (0.06)	.110	547 (8)	-0.07 (0.70)	.297
Total scores combined	657 (12)	-0.16* (0.07)	.016	456 (7)	-0.10 (0.80)	.168

Table 2. PANSS, Positive and Negative Syndrome Scale. BPRS, Brief Psychiatric Rating Scale. SANS, Scale for the Assessment of Negative Symptoms. RCT, Randomised Controlled Trial. SE, standard error.

IPD meta-analyses

Baseline differences

We tested for differences between patients who received CBTp vs. other interventions at baseline. One-way ANOVA's demonstrated that patients who received CBTp did not have significantly higher positive, negative, general or total psychotic symptoms at baseline than those who received other psychological interventions. Regression analyses showed no significant relationship between age, number of sessions, illness duration or any psychotic symptom measures. Crosstabs showed that gender, type of diagnosis, education level, occupation, and ethnicity were equally distributed between the intervention groups.

Patients who received CBTp were significantly less often married (*11%*) and more often not married (*69%*) than patients who received other interventions (*16%* and 65% respectively, χ^2=5.01, *p* =0.03). The average number of sessions received significantly differed between patients who received CBTp (*M* =14.75, *SD*=5.78) and other interventions (*M* = 12.83, *SD*=7.24, *F*(1)=6.97, *p*=0.01).

Efficacy of CBTp vs. other psychological interventions

All results from the IPD meta-analyses examining the efficacy of CBTp vs. other psychological interventions are presented in Table 2. CBTp demonstrated superiority over other psychological interventions pooled at post-treatment for PANSS general symptoms (*b*=-0.17, *p*=0.02), PANSS total symptoms (*b*=-0.15, *p*=0.03) and when combining the total scores for the PANSS and BPRS across available RCTs (*b*=-0.16, *p*=0.02). No significant difference was demonstrated for positive or negative symptoms.

Moderators of psychotic symptom reduction in CBTp vs. other therapeutic interventions

All IPD meta-analysis outcomes for sociodemographic and clinical variables as potential moderators of efficacy are presented in Table 3. Employment status significantly moderated the relationship between therapy type and combined negative psychotic symptoms at post-treatment when controlling for baseline negative psychotic symptoms. More specifically, patients who were students and received CBTp reported significantly lower negative psychotic symptoms at post-treatment than patients who were students and received other therapeutic interventions (*b*=-0.68, *p*=0.04). To check whether this moderation could be explained by the age difference between the occupational groups, age

was added as a covariate. The effect remained significant (*b*=-0.69, *p*=0.04). On post- hoc examination of the effect, we determined a high likelihood of a chance finding due to very small numbers of students in the CBTp (*n*=19) and 'other psychological therapies' group (*n*=19) when compared to non-students (*n*=253 in each the CBTp and other therapies groups) including instances of extreme outliers. We therefore excluded this comparison from further reporting in sensitivity analyses. No other significant moderators were found.

Risk of bias sensitivity analyses

Sensitivity analyses for risk of bias in the efficacy comparisons are presented in Table 2. Risk of bias sensitivity analyses on moderators are presented in Table 3. In the efficacy sensitivity analyses, the effects demonstrated previously were no longer significant for the PANSS general subscale (*b*=-0.08, *p*=0.30), PANSS total symptoms (*b*=-0.10, *p*=0.16) or the combined total scores of the PANSS and BPRS (*b*=-0.10, *p*=0.17). Age was a significant moderator for combined positive symptoms; older patients who received CBTp reported significantly lower positive psychotic symptoms at post-treatment than younger patients who received other psychological interventions (*b*=-0.01, *p*=0.04). Number of sessions was also found to be a significant moderator for total psychotic symptoms; patients who received CBTp and who received more sessions reported significantly lower total psychotic symptoms at post-treatment than patients who received less sessions and other psychological interventions (*b* =-0.14, *p*=0.02). No other significant moderators were found.

Sensitivity analyses on conceptual differences

Four studies included in the IPD used conceptually different aims and interventions than the remainder. Two used CBTp variants that were conceptually distinct; the first utilised individualised metacognitive training (MCT+. 24) a variant of CBTp targeting cognitive biases. Another utilised a cognitive-behavioural acceptance-based approach.[30] Two studies were not primarily aimed at reducing psychotic symptoms therefore reported these as secondary outcomes.[31,32] We conducted additional sensitivity analyses in which all analyses were redone without these studies (Table 4 & 5, supplementary materials). In the efficacy comparisons, CBTp demonstrated superiority over other psychological interventions at post-treatment for PANSS general symptoms (*b*=-0.19, *p*=0.03) and for total psychotic symptoms as measured by the combined total scores of the PANSS and BPRS (*b*=-0.16, *p*=0.04). No significant moderators were found.

Sensitivity analyses on treatment format

Two RCTs utilised group rather than individual or mixed format.[28,29] Sensitivity analyses excluding these studies are presented in Table 4 and Table 5 (supplementary materials). CBTp demonstrated superiority over other psychological interventions for PANSS general symptoms (*b*=-0.18, *p*=0.02), PANSS total symptoms (*b*=-0.17, *p*=0.02) and when combining PANSS and BPRS total scores across RCTs (*b*=-0.16, *p*=0.02). There were no significant moderators of treatment outcome.

Table 3. *Results of moderator analysis*

	Full sample of RCTs			RCTs assessed as low risk of bias		
	N obs. (*N* stud.)	β_b (*SE*)	*p*	*N* obs. (*N* stud.)	β_b (*SE*)	*p*
Moderator & psychotic symptoms outcome measure (z scores)						
Age						
Positive scales combined						
Treatment grp	699 (13)	0.04 (0.04)	.295	501 (8)	0.06 (0.05)	.265
Age x treatment grp		-0.01 (0.01)	.066		-0.01* (0.01)	.043
Negative scales combined						
Treatment grp	671 (13)	0.04 (0.04)	.310	473 (8)	0.03 (0.05)	.527
Age x treatment grp		-0.00 (0.01)	.789		0.00 (0.01)	.755
Total scores combined						
Treatment grp	653 (12)	0.07 (0.05)	.131	454 (7)	0.04 (0.05)	.480
Age x treatment grp		-0.01 (0.01)	.313		-0.00 (0.01)	.643
Gender						
Positive scales combined						
Treatment grp	703 (13)	0.07 (0.06)	.232	503 (8)	0.11 (0.07)	.104
Gender x treatment grp		0.06 (0.12)	.620		0.19 (0.14)	.187
Negative scales combined						
Treatment grp	747 (13)	0.12* (0.05)	.023	547 (8)	0.15* (0.07)	.020
Gender x treatment grp		0.06 (0.12)	.585		0.15 (0.13)	.275
Total scores combined						
Treatment grp	657 (12)	0.11 (0.06)	.085	456 (7)	0.10 (0.07)	.152
Gender x treatment grp		0.06 (0.13)	.624		0.19 (0.15)	.210
Education						
Positive scales combined						
Treatment grp	491 (9)	0.08 (0.07)	.208	293 (4)	0.17 (0.09)	.051
Tertiary vs secondary		-0.02 (0.15)	.876		0.30 (0.19)	.113
Negative scales combined						
Treatment grp	510 (10)	0.05 (0.06)	.447	312 (5)	0.05 (0.08)	.508
Tertiary vs secondary		-0.08 (0.14)	.565		-0.03 (0.17)	.879
Total scores combined						
Treatment grp	492 (9)	0.12 (0.07)	.084	293 (4)	0.13 (0.09)	.143
Tertiary vs secondary		-0.10 (0.15)	.522		0.18 (0.19)	.342
Marital status						
Positive scales combined						
Treatment grp	620 (11)	-0.04 (0.10)	.658	456 (7)	-0.03 (0.10)	.742
Not married vs married		-0.04 (0.17)	.830		-0.03 (0.18)	.863
Negative scales combined						
Treatment grp	621 (11)	-0.03 (0.10)	.734	457 (7)	-0.02 (0.10)	.857
Not married vs married		0.05 (0.17)	.742		0.13 (0.18)	.468
Total scores combined						
Treatment grp	621 (11)	-0.02 (0.10)	.843	456 (7)	-0.01 (0.10)	.920
Not married vs married		-0.05 (0.18)	.758		0.03 (0.18)	.857
Diagnosis						
Positive scales combined						
Treatment grp	636 (12)	0.06 (0.05)	.198	502 (8)	0.07 (05)	.167
Schizo-affective vs schizophrenia		-0.02 (0.21)	.918		0.11 (0.25)	.650
Other diagnosis vs schizophrenia		0.39 (0.25)	.115		0.04 (0.79)	.959
Negative scales combined						
Treatment grp	680 (12)	0.05 (0.05)	.256	546 (8)	0.04 (0.05)	.451
Schizo-affective vs schizophrenia		-0.08 (0.21)	.715		-0.19 (0.25)	.448
Other diagnosis vs schizophrenia		-0.19 (0.24)	.430		-0.13 (0.79)	.872
Total scores combined						
Treatment grp	590 (11)	0.08 (0.05)	.125	455 (7)	0.05 (0.06)	.358
Schizo-affective vs schizophrenia		0.19 (0.22)	.391		0.25 (0.25)	.332
Other diagnosis vs schizophrenia		0.13 (0.26)	.604		-0.71 (0.81)	.378
No. of sessions						
Positive scales combined						
Treatment grp	221 (6)	0.08 (0.08)	.345	141 (4)	0.16 (0.10)	.114
No. of sessions vs treatment grp		-0.01 (0.03)	.728		-0.03 (0.04)	.440
Negative scales combined						
Treatment grp	251 (6)	0.04 (0.08)	.634	171 (4)	-0.01 (0.09)	.886
No. of sessions vs treatment grp		-0.02 (0.02)	.438		-0.03 (0.02)	.213
Total scores combined						
Treatment grp	175 (5)	0.07 (0.10)	.465	94 (3)	0.08 (0.12)	.491

No. of sessions vs treatment grp		0.03 (0.04)	.421		-0.14* (0.06)	.024
Employment status						
Positive scales combined						
Treatment grp	509 (9)	0.07 (0.10)	.516	410 (6)	0.05 (0.11)	.639
Unemployed vs employed		0.04 (0.17)	.791		0.09 (0.18)	.636
Student vs employed		0.28 (0.34)	.416		0.17 (0.38)	.645
Negative scales combined						
Treatment grp	536 (10)	0.03 (0.10)	.772	437 (7)	0.07 (0.11)	.495
Unemployed vs employed		-0.06 (0.16)	.718		-0.06 (0.17)	.742
Student vs employed		-0.68* (0.33)	.039		-0.55 (0.37)	.135
Negative scales, controlling for age						
Treatment grp	526 (10)	-0.00 (0.10)	.992			
Unemployed vs employed		-0.07 (0.16)	.661			
Student vs employed		-0.69* (0.33)	.037			
Total scores combined						
Treatment grp	510 (9)	0.07 (0.11)	.539	410 (6)	0.08 (0.11)	.450
Unemployed vs employed		-0.01 (0.17)	.973		0.10 (0.18)	.573
Student vs employed		-0.35 (0.35)	.319		-0.17 (0.38)	.660
Ethnicity						
Positive scales combined						
Treatment grp	489 (8)	0.01 (0.80)	.949	328 (4)	0.14 (0.11)	.228
Other vs. Caucasian		-0.05 (0.15)	.721		0.11 (0.19)	.554
Negative scales combined						
Treatment grp	490 (8)	0.03 (0.08)	.678	329 (4)	0.10 (0.11)	.396
Other vs. Caucasian		-0.10 (0.15)	.489		0.07 (0.19)	.731
Total scores combined						
Treatment grp	490 (8)	-0.01 (0.09)	..946	328 (4)	0.13 (0.12)	.277
Other vs. Caucasian		-0.20 (0.16)	.206		0.01 (0.20)	.943
Illness duration						
Positive scales combined						
Treatment grp	383 (7)	0.03 (0.06)	.573	253 (3)	0.04 (0.07)	.627
Illness duration vs treatment grp		-0.01 (0.01)	.398		-0.01 (0.01)	.505
Negative scales combined						
Treatment grp	471 (8)	0.05 (0.05)	.282	341 (4)	0.04 (0.06)	.523
Illness duration vs treatment grp		-0.00 (0.01)	.663		-0.00 (0.01)	.960
Total scores combined						
Treatment grp	384 (7)	0.08 (0.06)	.207	253 (3)	0.03 (0.07)	.703
Illness duration vs treatment grp		-0.01 (0.01)	.395		0.00 (0.01)	.994
Baseline PANNS Severity						
PANSS Positive						
Treatment grp	537 (10)	0.04 (0.05)	.396	456 (7)	0.05 (0.05)	.353
PANNS Negative baseline severity vs treatment grp		0.01 (0.01)	.384		0.02 (0.01)	.178
PANSS Positive						
Treatment grp	537 (10)	0.04 (0.05)	.392	456 (7)	0.05 (0.05)	.347
PANNS General baseline severity vs treatment grp		0.01 (0.01)	.225		0.02 (0.01)	.098
PANSS Negative						
Treatment grp	538 (10)	0.04 (0.05)	.364	457 (7)	0.03 (0.05)	.522
PANNS General baseline severity vs treatment grp		-0.00 (0.01)	.832		0.01 (0.01)	.412

Table 3: PANSS; Positive and Negative Syndromes Scale. RCTs; randomised controlled trials; SE; standard error

Discussion

To our knowledge, this is the first IPD meta-analysis examining the efficacy and moderators of psychological interventions for psychosis. Results were broadly consistent with conventional study-level meta-analyses research in demonstrating some superiority of CBTp over other psychological interventions although there was a slightly different pattern of results; CBTp was superior when combining any "total symptom" scores, on the PANSS total and on PANSS general symptoms. The previously observed effect on positive symptoms[3,8] was not replicated using IPD. We note that including a smaller sample of RCTs due to failure to obtain databases for the whole eligible sample may have had impact; as a relative efficacy meta-analysis comparing bona fide interventions, power remained relatively low to detect small effects and prevent type 2 errors. The absence of superiority of CBTp for negative symptoms is consistent with our previous research.[8,9]

Our moderator analysis was exploratory based upon demographic and clinical variables available in the obtained databases. We found little evidence that any of these variables- age, gender, education level, marital status, diagnosis, employment status, ethnicity, illness duration or importantly baseline psychotic symptom severity- had significant impact upon treatment outcome. Sensitivity analyses and post-hoc examination demonstrated that the few significant moderating effects observed were not robust. This finding has clinical implications regarding assumptions about who may or may not benefit from psychological intervention; using demographic and clinical variables (e.g. severity of psychotic symptoms) in deciding whether or not a patient is allocated to psychological interventions may be unhelpful. This suggests that a broad range of patients with different backgrounds, circumstances, clinical presentations, symptom severity and clinical profiles may be equally able to benefit from psychological intervention. Our ability to reliably support this

stance would be stronger with further development of our IPD database to include RCTs we were unable to obtain. This remains an important area of future research while adding absolute efficacy trials (versus treatment as usual) would also allow further insight.

Also of note was that patients who received a higher number of CBTp sessions had lower total psychotic symptoms at post-treatment than those who received less sessions and other therapies. This effect arrived via the sensitivity analysis minimising risk of bias which increases its validity. It is clinically acknowledged that severe mental health populations including psychosis patients are more likely to benefit from longer, more comprehensive interventions. However, this finding contrasts the beneficial effects reported in a meta-analysis of brief CBTp interventions, which also concluded that "dose" of sessions or contact time did not moderate treatment outcome.[33] We note that conventional meta-analysis does not contain the facility to examine moderating effects at the individual participant level and therefore must rely on the less specific study-level data, such as mean number of sessions completed across participants. This therefore may provide less precise estimates. Our finding has implications for clinicians and service providers in suggesting that when investing in CBTp as opposed to minimal or supportive interventions, it is important that when feasible, a sufficient dose is provided rather than brief CBTp. Confirmation of this finding awaits future RCTs comparing conceptually-equivalent CBTp of varying length (e.g. 10 vs 20 sessions). We do not therefore intend this finding to act as justification to limit brief intervention in instances in which brief CBTp is the only viable option for specific services, risking further limitation in vital access to intervention.

We acknowledge various limitations. An inherent problem in IPD meta-analyses is availability bias due to difficulty obtaining RCT databases. We obtained 60% of eligible

databases meaning that our IPD analyses did not include data from 40% of possible RCTs. Our conventional two-step meta-analysis did not suggest there were significant differences between included and non-included RCTs, although we are conscious of the possible impact that failure to obtain proportionately more eligible RCTs may have upon the power to detect effects despite improved precision using IPD. We encourage researchers to store data in a manner conducive to future collaboration and be open to database sharing since IPD may provide clearer insight for clinical decision-making than is possible with single RCTs or conventional meta-analysis.

A further limitation was the process subsuming variables into categories allowing meaningful inclusion in moderator analyses. Demographic and clinical variable availability, categorisation and reporting style varied across RCTs meaning we had the challenge of combining diverse information into broader categories. For example, marital status became "married" or "not married" since variation between databases meant it was not possible to reliably aggregate more nuanced data. This approach risks reductionism and limits the examination of differences between subgroups. We also note the inclusion of two RCTs of group-based CBTp[28,29] and one RCT that combined group and individual approaches.[24] While the inclusion of participant data from these RCTs was also at the individual level, the effects of group interventions may differ from those of individualised, case-formulation driven approaches. Our sensitivity analysis including only individual format RCTs (supplementary materials) demonstrated the same pattern of efficacy results as the main analysis. One strength is that all included RCTs utilised both blinding and intention-to-treat analyses, which improves the reliability of the results. Most RCTs also demonstrated minimal risk of bias.

This IPD meta-analysis suggested that CBTp is efficacious in reducing total and general symptoms of psychosis compared to other interventions. Results also suggested that patient characteristics, including psychotic symptom severity, do not significantly influence who benefits from these interventions. This finding has important implications for clinical policy and specifically for clinicians when deciding whether to refer or engage patients in therapy. Results also suggest that when investing in CBTp, the provision of a sufficient dose is important for treatment outcome. We note the exploratory nature of the findings from our moderator analysis.

Acknowledgements

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Supplementary materials

Table 4 (Supplementary). *Individual participant data main effects sensitivity analyses*

Variable	Homogenous RCTs			Individual format		
	No of observations (no. of studies)	Mean (SE) βb	2-tailed *p* Value	No of observations (no. of studies)	Mean (SE) βb	2-tailed *p* Value
PANSS Positive symptoms	397 (7)	-0.06 (0.08)	.439	522 (10)	-0.11 (0.07)	.104
PANSS Negative symptoms	397 (7)	-0.04 (0.07)	.569	476 (9)	-0.08 (0.07)	.221
PANSS General symptoms	395 (7)	-0.19* (0.09)	.028	474 (9)	-0.18* (0.08)	.022
PANSS Total	398 (7)	-0.15 (0.08)	.065	476 (9)	-0.17* (0.07)	.021
BPRS Positive	119 (2)	-0.04 (0.16)	.823	53 (1)	0.05 (0.25)	.837
BPRS Negative	66 (1)	-0.02 (0.21)	.934			
BPRS Total	119 (2)	-0.16 (0.17)	.362	53 (1)	-0.10 (0.25)	.688
SANS Total	143 (2)	-0.21 (0.14)	.135	143 (2)	-0.21 (0.14)	.135
Positive scales combined	516 (9)	-0.06 (0.07)	.427	575 (11)	-0.10 (0.07)	.142
Negative scales combined	606 (10)	-0.08 (0.06)	.204	619 (11)	-0.11 (0.06)	.065
Total scores combined	517 (9)	-0.16* (0.07)	.037	529 (10)	-0.16* (0.07)	.023

Table 4. PANSS, Positive and Negative Syndromes Scale. BPRS, Brief Psychiatric Rating Scale. SANS, Scale for the Assessment of Negative Symptoms. SE, standard error. RCTs, randomised controlled trials.

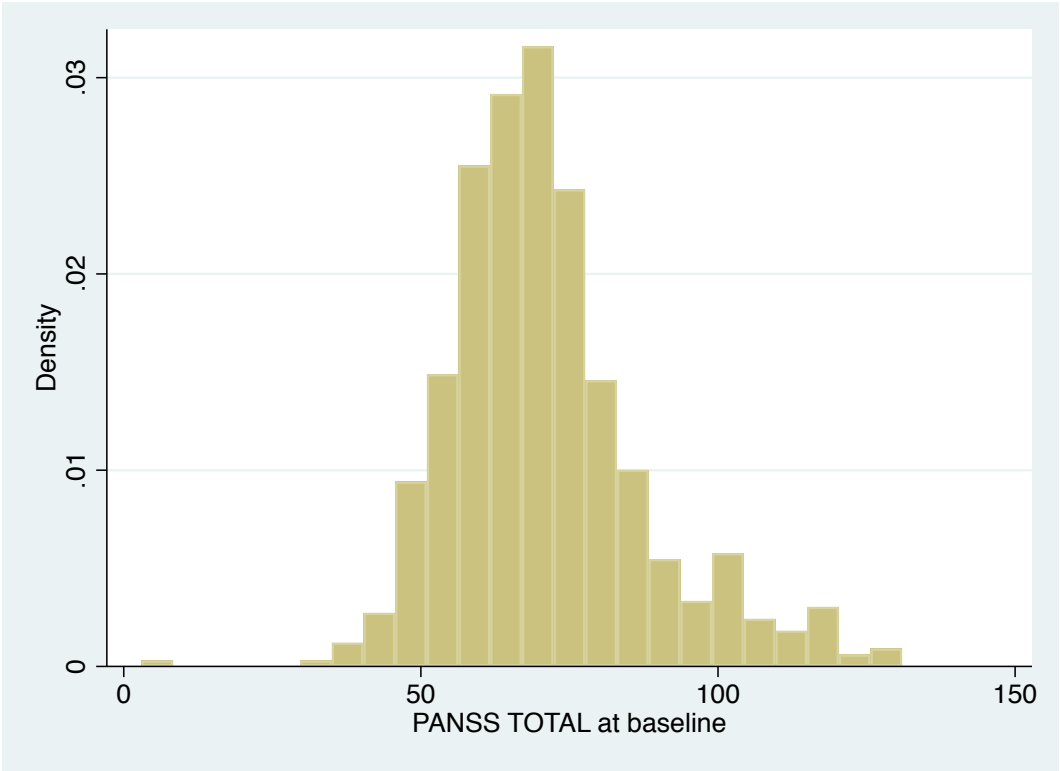


Table 5 (Supplementary). *Results sensitivity analyses for moderator analysis*

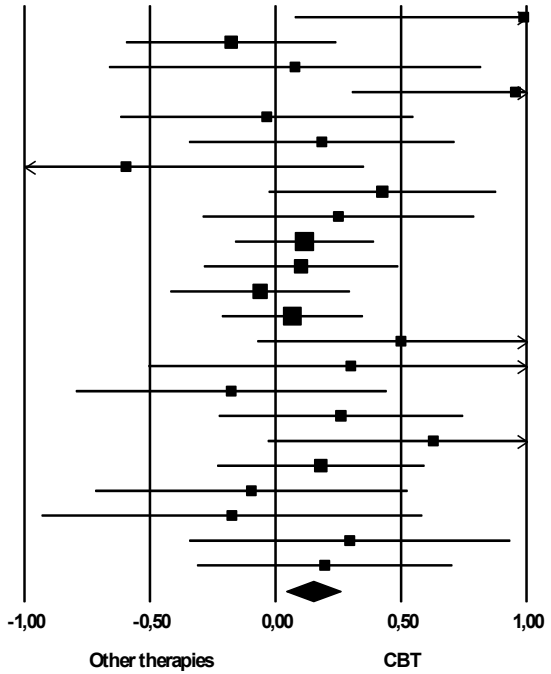
	Homogenous RCTs			Individual format only		
	N observations (*N* studies)	Mean (SE) βb	2-tailed *p* Value	*N* observations (*N* studies)	Mean (SE) βb	2-tailed *p* Value
Moderator & psychotic symptoms outcome measure (z scores)						
Age						
Positive scales combined						
Treatment group	512 (9)	0.03(0.05)	.554	575 (11)	0.04 (0.05)	.355
Age x treatment group		-0.01 (0.01)	.181		-0.01 (0.01)	.055
Negative scales combined						
Treatment group	530 (10)	0.04 (0.05)	.465	547 (11)	0.07 (0.05)	.158
Age x treatment group		-0.00 (0.01)	.753		-0.00 (0.01)	.952
Total scores combined						
Treatment group	513(9)	0.07 (0.05)	.179	529 (10)	0.07 (0.05)	.146
Age x treatment group		-0.01 (0.01)	.431		-0.01 (0.01)	.472
Gender						
Positive scales combined						
Treatment group	516 (9)	0.04 (0.07)	.563	575 (11)	0.07 (0.06)	.267
Gender x treatment group		-0.01 (0.14)	.923		0.05 (0.13)	.734
Negative scales combined						
Treatment group	606 (10)	0.14* (0.06)	.026	619 (11)	0.13* (0.06)	.033
Gender x treatment group		0.06 (0.13)	.625		0.09 (0.13)	.477
Total scores combined						
Treatment group	517 (9)	0.11 (0.07)	.124	529 (10)	0.10 (0.07)	.157
Gender x treatment group		0.02 (0.15)	.902		0.05 (0.14)	.715
Education						
Positive scales combined						
Treatment group	451 (8)	0.08 (0.07)	.233	427 (8)	0.13 (0.07)	.082
Tertiary vs secondary		-0.05 (0.15)	.747		0.11 (0.16)	.479
Negative scales combined						
Treatment group	470 (9)	0.03 (0.07)	.654	446 (9)	0.08 (0.07)	.237
Tertiary vs secondary		-0.12 (0.14)	.387		-0.05 (0.15)	.724
Total scores combined						
Treatment group	452 (8)	0.11 (0.07)	.141	428 (8)	0.16* (0.07)	.031
Tertiary vs secondary		-0.15 (0.16)	.362		0.05 (0.16)	.763
Marital status						
Positive scales combined						
Treatment group	480 (8)	-0.03 (0.10)	.742	495 (9)	-0.09 (0.12)	.455
Not married vs married		-0.06 (0.19)	.741		-0.15 (0.21)	.485
Negative scales combined						
Treatment group	480 (8)	-0.06 (0.10)	.556	496 (9)	-0.03 (0.11)	.799
Not married vs married		-0.04 (0.18)	.833		-0.06 (0.20)	.749
Total scores combined						
Treatment group	481 (8)	-0.05 (0.11)	.621	496 (9)	-0.10 (0.12)	.440
Not married vs married		-0.17 (0.19)	.389		-0.21 (0.21)	.323
Diagnosis						
Positive scales combined						
Treatment group	449 (8)	0.04 (0.06)	.468	575 (11)	0.06 (0.05)	.220
Schizo-affective vs schizophrenia		-0.13 (0.25)	.602		-0.11 (0.29)	.696
Other diagnosis vs schizophrenia		-0.38 (0.27)	.157		0.39 (0.25)	.118
Negative scales combined						
Treatment group	539 (9)	0.07 (0.05)	.188	619 (11)	0.05 (0.05)	.328
Schizo-affective vs schizophrenia		0.06 (0.24)	.789		-0.12 (0.28)	.653
Other diagnosis vs schizophrenia		-0.20 (0.25)	.438		-0.18 (0.24)	.460
Total scores combined						
Treatment group	450 (8)	0.09 (0.06)	.155	529 (10)	0.08 (0.06)	.151
Schizo-affective vs schizophrenia		0.12 (0.26)	.632		0.14 (0.30)	.639
Other diagnosis vs schizophrenia		0.21 (0.27)	.437		0.14 (0.26)	.593
No. of sessions						
Positive scales combined						
Treatment group	134 (4)	0.08 (0.12)	.467	221 (6)	0.08 (0.08)	.345
No. sessions vs treatment group		-0.00 (0.04)	.989		-0.01 (0.03)	.728
Negative scales combined						
Treatment group	211 (5)	0.03 (0.09)	.689	251 (6)	0.04 (0.08)	.634
No. sessions vs treatment group		-0.01 (0.02)	.536		-0.02 (0.02)	.438
Total scores combined						
Treatment group	135 (4)	0.04 (0.11)	.757	175 (5)	0.07 (0.10)	.465

No. sessions vs treatment group		0.04 (0.04)	.292		0.03 (0.04)	.421
Employment status						
Positive scales combined						
Treatment group	414 (7)	0.06 (0.11)	.596	447 (8)	0.04 (0.12)	.739
Unemployed vs employed		0.04 (0.18)	.828		-0.01 (0.19)	.962
Student vs employed		0.29 (0.36)	.429		0.24 (0.35)	.488
Negative scales combined						
Treatment group	440 (8)	0.04 (0.10)	.706	474 (9)	-0.02 (0.11)	.849
Unemployed vs employed		-0.03 (0.16)	.879		-0.12 (0.17)	.485
Student vs employed		-0.75* (0.35)	.030		-0.71* (0.33)	.033
When controlling for age						
Treatment group	430 (8)	-0.08 (0.16)	.614	466 (9)	-0.21 (0.17)	.212
Unemployed vs employed		-0.03 (0.17)	.854		-0.11 (0.17)	.540
Student vs employed		-0.75* (0.35)	.030		-0.68* (0.33)	.042
Total scores combined						
Treatment group	415 (7)	0.06 (0.11)	.557	448 (8)	0.04 (0.12)	.716
Unemployed vs employed		-0.03 (0.18)	.874		-0.07 (0.19)	.706
Student vs employed		-0.43 (0.37)	.241		-0.38 (0.36)	.281
Ethnicity						
Positive scales combined						
Treatment group	393 (6)	-0.08 (0.10)-	.405	364 (6)	0.03 (0.10)	.751
Other vs. Caucasian		0.15 (0.17)	.432		0.07 (0.18)	.709
Negative scales combined						
Treatment group	393 (6)	-0.01 (0.10)	.936	365 (6)	0.08 (0.10)	.432
Other vs. Caucasian		-0.14 (0.17)	.421		-0.11 (0.17)	.519
Total scores combined						
Treatment group	394 (6)	-0.08 (0.10)	.422	365 (6)	0.05 (0.11)	.642
Other vs. Caucasian		-0.27 (0.18)	.146		-0.10 (0.19)	.593
Illness duration						
Positive scales combined						
Treatment group	383 (7)	0.03 (0.06)	.573	383 (7)	0.03 (0.06)	.573
Duration vs treatment group		-0.01 (0.01)	.398		-0.01 (0.01)	.398
Negative scales combined						
Treatment group	471 (8)	0.05 (0.05)	.282	471 (8)	0.05 (0.05)	.282
Duration vs treatment group		-0.00 (0.01)	.663		-0.00 (0.01)	.663
Total scores combined						
Treatment group	384 (7)	0.08 (0.06)	.207	384 (7)	0.08 (0.06)	.207
Duration vs treatment group		-0.01 (0.01)	.395		-0.01 (0.01)	.395
Baseline PANNS Severity						
Positive scales combined						
Treatment group	397 (7)	0.04 (0.06)	.495	475 (9)	0.04 (0.05)	.413
PANNS Negative baseline severity vs treatment group		0.00 (0.01)	.861		0.01 (0.01)	.575
Positive scales combined						
Treatment group	397 (7)	-0.04 (0.06)	.502	475 (9)	0.04 (0.05)	.416
PANNS General baseline severity vs treatment group		0.01 (0.01)	.507		0.01 (0.01)	.165
Negative scales combined						
Treatment group	397 (7)	-0.03 (0.05)	.567	476 (9)	0.05 (0.05)	.277
PANNS General baseline severity vs treatment group		-0.01 (0.01)	.355		-0.00 (0.01)	.974

Table 5: PANSS, Positive and Negative Syndromes Scale. RCTs, randomised controlled trials; SE, standard error.

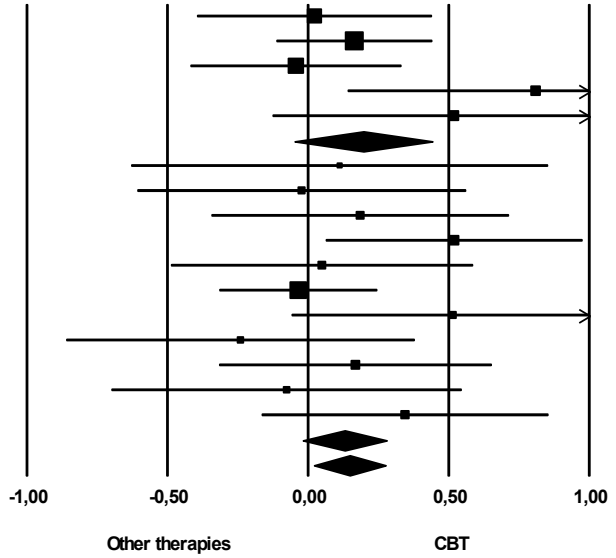
Supplementary Figure 1: Traditional 2-step meta-analysis; CBT vs other therapies for all psychotic symptoms

Study name	Outcome	Std diff in means	Lower limit	Upper limit	p-Value
Barretto 2009	Combined	0,989	0,075	1,904	0,034
Bechdolf 2004	Combined	-0,177	-0,598	0,245	0,411
Cather 2005	Combined	0,078	-0,665	0,821	0,837
Drury 1996	PAS Observer ratings	0,956	0,302	1,610	0,004
Durham 2003	Combined	-0,035	-0,621	0,551	0,908
Garety 2008	Combined	0,185	-0,346	0,715	0,495
Haddock 1999	BPRS-total	-0,595	-1,545	0,354	0,219
Haddock 2009	Combined	0,426	-0,029	0,881	0,067
Jackson 2007	Combined	0,251	-0,292	0,793	0,365
Klingberg 2011	Combined	0,115	-0,163	0,394	0,417
Lecomte 2008	BPRS-total	0,102	-0,287	0,491	0,608
Lewis 2002	Combined	-0,061	-0,421	0,298	0,738
Li 2014	Combined	0,067	-0,216	0,350	0,641
Moritz 2011	Combined	0,500	-0,075	1,075	0,088
O'Connor 2007	Combined	0,300	-0,509	1,109	0,467
Penades 2006	Combined	-0,176	-0,797	0,445	0,578
Penn 2009	Combined	0,261	-0,228	0,750	0,296
Pinto 1999	Combined	0,629	-0,033	1,291	0,063
Sensky 2000	Combined	0,180	-0,235	0,595	0,394
Shawyer 2012	Combined	-0,096	-0,720	0,528	0,763
Tarrier 1993	Combined	-0,173	-0,934	0,587	0,655
Tarrier 1998	Combined	0,296	-0,346	0,937	0,366
Valmaggia 2005	Combined	0,196	-0,315	0,707	0,452
		0,149	0,040	0,257	0,007



Supplementary Figure 2: Traditional 2-step meta-analysis; CBT vs other therapies for positive symptoms

Group by IPD	Study name	Outcome	Statistics for each study: Std diff in means	Lower limit	Upper limit	p-Value
N	Bechdolf 2004	PANSS-positive	0,023	-0,397	0,443	0,915
N	Klingberg 2011	PANSS-positive	0,164	-0,115	0,443	0,248
N	Lewis 2002	Combined	-0,043	-0,421	0,334	0,822
N	Pinto 1999	SAPS	0,810	0,139	1,480	0,018
N	Tarrier 1998	BPRS-positive	0,518	-0,128	1,165	0,116
N			0,194	-0,051	0,439	0,120
Y	Cather 2005	Combined	0,112	-0,631	0,856	0,767
Y	Durham 2003	Combined	-0,023	-0,609	0,564	0,939
Y	Garety 2008	Combined	0,186	-0,346	0,717	0,494
Y	Haddock 2009	Combined	0,520	0,061	0,978	0,026
Y	Jackson 2007	BPRS-positive	0,049	-0,490	0,589	0,857
Y	Li 2014	PANSS positive	-0,035	-0,318	0,248	0,809
Y	Moritz 2011	Combined	0,515	-0,061	1,090	0,080
Y	Penades 2006	PANSS-positive	-0,240	-0,862	0,382	0,449
Y	Penn 2009	Combined	0,169	-0,319	0,656	0,498
Y	Shawyer 2012	Combined	-0,076	-0,701	0,548	0,811
Y	Valmaggia 2005	Combined	0,345	-0,167	0,857	0,187
Y			0,128	-0,021	0,277	0,093
Overall			0,146	0,018	0,273	0,025



Supplementary Figure 3: Traditional 2-step meta-analysis; CBT vs other therapies for negative symptoms

Study name	Outcome	Std diff in means	Lower limit	Upper limit	p-Value
Bechdolf 2004	PANSS-negative	-0,163	-0,584	0,257	0,446
Cather 2005	PANSS-negative	0,009	-0,733	0,752	0,980
Jackson 2007	SANS	0,452	-0,094	0,998	0,105
Klingberg 2011	Combined	0,067	-0,212	0,345	0,640
Li 2014	PANSS negative	0,167	-0,117	0,450	0,249
Penades 2006	PANSS-negative	-0,112	-0,732	0,508	0,723
Pinto 1999	SANS	0,343	-0,307	0,992	0,301
Sensky 2000	SANS	0,000	-0,413	0,413	1,000
Tarrier 1998	SANS	0,073	-0,563	0,709	0,821
Valmaggia 2005	PANSS-negative	-0,370	-0,878	0,139	0,154
		0,053	-0,084	0,190	0,451

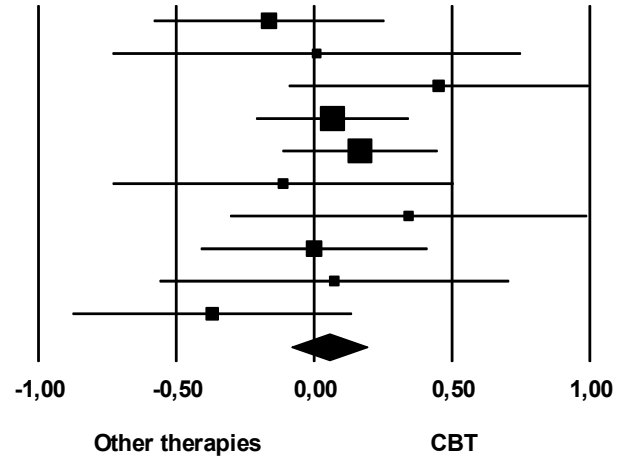


Table 6 (Supplementary): Adapted Cochrane Risk of Bias Tool

Study	Item 1	Item 2	Item 3	Item 4	Total risk
Barretto *et al* 2009	+	+	-	-	2
Cather *et al* 2005	-	+	-	-	1
Durham *et al* 2003	-	-	-	-	0
Garety *et al* 2008	-	-	-	-	0
Haddock *et al* 2009	-	-	-	-	0
Jackson *et al* 2008	+	+	-	-	2
Lecomte *et al* 2008	+	+	-	-	2
Li *et al* 2015	-	-	-	-	0
Moritz *et al* 2011	-	-	-	-	0
Penades *et al* 2006, 2010	-	-	-	-	0
Penn *et al* 2009	-	-	-	-	0
Sensky *et al* 2000, 2008	-	-	-	-	0
Shawyer *et al* 2012	-	-	-	-	0
Valmaggia *et al* 2005	-	-	-	-	0

Table 6. +, high risk of bias. -, low risk of bias. Item 1, random sequence generation. Item 2, allocation concealment. Item 3, blinding of assessors. Item 4, incomplete outcome data. Total risk of bias was calculated as the sum of high risk items to provide an overall risk score. Unclear risk of bias category was disregarded therefore when no information on an item was included in report, high risk of bias was assumed. All items were independently rated by two authors with conflicts resolved via discussion.

Patient characteristics from RCTs included in IPD

The 14 RCTs included a total of 898 patients. 460 received CBTp and 438 received other psychological interventions 539 (60%) were male. Eight of the 14 studies included only inpatients, while two included only outpatients. Four studies included inpatients and outpatients. Age ranged from 15 to 70 (mean 33.85, *SD* = 11.52). 342 patients (38%) completed secondary or lower education while 234 (26%) completed tertiary or higher education. Educational background status was unknown for four patients (0.5%) and not measured or missing for 318 (35.5%). 122 patients (13.6%) were married and 601 (66.9%) were not married. Marital status was unknown for one patient (0.1%) and not measured or missing for 174 (19.4%). 692 patients (77%) were diagnosed with schizophrenia, 72 (8%) with schizo-affective disorder, 51 (5.7%) with another psychotic disorder (schizophreniform disorder; bipolar/depression with psychotic features; delusional disorder; other psychosis or psychosis NOS) while diagnosis was not measured or missing for 83 patients (9.3%). The number of sessions ranged from 0 to 33 (*M* = 13.88, *SD* = 6.54). 152 patients (16.9%) were employed, 432 (48.1%) were not employed, 36 (4%) were students and employment was not measured or missing in 278 patients (31%). 247 patients (27.5%) were Caucasian and 327 (36.4%) identified as an another ethnicity (black/afro-Caribbean; Asian; Hispanic/Latin American; other). Ethnicity was not measured or missing in 324 patients (36.1%). Illness duration varied from 0 to 44 years (*M* = 9.57, *SD* = 8.56).

Outcome measures overview

Positive and Negative Syndrome Scale

The PANSS [13] is a 30-item clinician administered scale which provides a total score alongside subscales for positive, negative and general symptoms.

Brief Psychiatric Rating Scale

The BPRS [14] is a clinician-administered semi-structured scale primarily developed for assessing psychiatric symptoms, including psychotic symptoms. It provides an overall score and sub-categorisation into subscales including positive symptoms, negative symptoms, activation and affect. It exists as an 18-item or 24-item measure. [15]

Scale for the Assessment of Negative Symptoms

The SANS [16] is a scale designed to assess the extent of negative symptomatology in psychosis. The SANS is divided into 5 subscales, namely affective flattening, alogia, avolition-apathy, anhedonia-asociality and attention which are rated 0-5 based on severity to provide a total score. We focused only upon total SANS score therefore did not analyse subscale data.

Search strings: Completed 25th September 2017

Medline/Pubmed

Schizophrenia and Disorders with Psychotic Features AND (psychotherapy OR psychological intervention OR behaviour therapy OR cognitive therapy OR family therapy OR cognitive remediation OR social skills training OR sensory art therapies OR art therapy OR psychoeducation OR psychoanalytic therapy OR counseling OR supportive therapy)

-Limited to randomised controlled trials

Result: 2011 citations

Psychinfo

Schizophrenia OR psychosis AND (psychotherapy OR psychological intervention OR behaviour therapy OR cognitive therapy OR cognitive behaviour therapy OR family therapy OR family intervention OR cognitive remediation OR social skills training OR creative arts therapy OR psychoeducation OR psychodynamic psychotherapy OR counseling OR supportive therapy)

-Limited to clinical trials, Embase only (not Medline)

Result: 2457 citations

Embase

'Schizophrenia and Disorders with Psychotic Features' AND (psychotherapy OR psychological intervention OR behaviour therapy OR cognitive therapy OR family therapy OR cognitive

remediation OR social adaptation OR art therapy OR psychoeducation OR psychoanalysis OR counseling OR supportive therapy)

-Limited to randomised controlled trials

Result: 1071 citations

Cochrane Register

Schizophrenia and Disorders with Psychotic Features AND (psychotherapy OR psychological intervention OR behaviour therapy OR cognitive therapy OR family therapy OR cognitive remediation OR social skills training OR sensory art therapies OR art therapy OR psychoeducation OR psychoanalytic therapy OR counseling OR supportive therapy) AND randomized controlled trial*

Result: 1498 citations

Total from 4 databases: 7037 citations

After removal of duplicates: 5881 citations

List of eligible RCTs excluded due to failure to obtain data (8 RCTs)

1. Bechdolf A, Knost B, Kuntermann C, Schiller S, Klosterkötter J, Hambrecht M, Pukrop R. Erratum: A randomized comparison of group cognitive-behavioural therapy and group psychoeducation in patients with schizophrenia (Acta Psychiatrica Scandinavica (2004) 110 (21-28)). *Acta Psychiatr Scand* (2004) 110:483. doi:10.1111/j.1600-0447.2004.00435.x

2. Drury V, Birchwood M, Cochrane R, MacMillan F. Cognitive therapy and recovery from acute psychosis: A controlled trial. I. Impact on psychotic symptoms. *Br J Psychiatry* (1996) 169:593–601. doi:10.1192/bjp.169.5.593

3. Klingberg S, Wölwer W, Engel C, Wittorf A, Herrlich J, Meisner C, Buchkremer G, Wiedemann G. Negative symptoms of schizophrenia as primary target of cognitive behavioral therapy: Results of the randomized clinical TONES study. *Schizophr Bull* (2011) 37: doi:10.1093/schbul/sbr073

4. Lewis S, Tarrier N, Haddock G, Bentall R, Kinderman P, Kingdon D, Siddle R, Drake R, Everitt J, Leadley K, et al. Randomised controlled trial of cognitive-behavioural therapy in early schizophrenia: Acute-phase outcomes. *Br J Psychiatry* (2002) 181: doi:10.1192/bjp.181.43.s91

5. Pinto A, La Pia S, Mennella R, Giorgio D, Sc D, Desimone L. Cognitive-Behavioral Therapy and Clozapine for Clients With Treatment-Refractory Schizophrenia. *Rehab Rounds.* (1999) 50:901–904.

6. Tarrier N, Barrowclough C, Vaughn C, Bamrah JS, Porceddu K, Watts S, Freeman H. The community management of schizophrenia. A controlled trial of a behavioural intervention

with families to reduce relapse. *Br J Psychiatry* (1988) 153:532–542. doi:10.1192/bjp.153.4.532

7. Tarrier N, Beckett R, Harwood S, Baker A, Yusupoff L, Ugarteburu I. A trial of two cognitive-behavioural methods of treating drug-resistant residual psychotic symptoms in schizophrenic patients: I. Outcome. *Br J Psychiatry* (1993) 162:524–532. doi:10.1192/bjp.162.4.524

8. Tarrier N, Morrison AP, Hopkins R, Drake R, Lewis S, Haddock G. A pilot study evaluating the effectiveness of individual inpatient cognitive-behavioural therapy in early psychosis. *Soc Psychiatry Psychiatr Epidemiol* (1999) 34:254–258.

Chapter 6

Impact of brief metacognitive training targeting the "jumping to conclusions" bias on overconfidence in psychosis: secondary analysis of a randomised controlled trial

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Submitted to *Schizophrenia Research* (2022)

Abstract

Background: Metacognitive training (MCT) is a psychological intervention targeting cognitive biases in psychosis with demonstrated efficacy for positive symptoms, insight and cognitive biases. Less is known regarding the specific effects of individual MCT modules. Such modules have the potential to reduce cognitive biases in clinical settings less conducive to prolonged intervention. This secondary analysis of a randomised controlled trial aimed to investigate the impact of an individual MCT module focused on the "jumping to conclusions" (JTC) bias on over-confident perceptual decision-making.

Method: Thirty-one patients with psychosis aged 19-65 were randomly allocated to receive either a) Brief MCT intervention; or b) An attention control condition. The primary outcomes were overconfidence (Snowy Pictures Task) and JTC reasoning bias (Beads Task).

Results: Participants in the MCT group demonstrated a large significant reduction in overconfidence ($d = 0.97$) in comparison to the control group. There was also a large significant reduction in JTC ($d = 1.16$), although this comparison violated the necessary data assumptions for ANCOVA. However, a non-parametric sensitivity analysis replicated the significant positive effect.

Conclusions: Brief MCT intervention has potential in reducing overconfidence and JTC among psychosis patients. Further research is warranted addressing several important limitations of our trial by including follow-up assessment to determine the durability of effects and blind assessment.

Keywords: meta-cognitive training, MCT, overconfidence, psychosis, cognitive biases

Introduction

Metacognitive training (MCT) is a psychological intervention based on the tenets of cognitive-behavioural principles, with a specific focus on the cognitive biases implicated in positive symptoms of psychosis.[1] The approach has also been applied to a variety of other diagnoses including depression and obsessive-compulsive disorder. Early meta-analytic research on MCT provided ambiguous results.[2–4] while more recent meta-analyses have demonstrated significant effects on psychotic symptoms,[5–7] insight[8] and cognitive biases.[9] However, well-designed RCTs on MCT for psychosis are warranted to improve understanding of the specificity of its effects among psychosis populations, potentially facilitating later application of meta-analytic methods.[10,11]

While the above evidence refers to MCT as a whole treatment package, less research exists on the effects of individual MCT modules targeted at specific biases.[12] Understanding the impact of modules targeting specific cognitive biases may help understand the mechanisms by which MCT exerts it's effects. The application of MCT in a single module may also be attractive in settings in which circumstances such as poor attention span and a short length of stay often hinder more extensive and structured interventions. The broader implementation of short-term interventions may be relevant in light of the many challenges services face due to Covid-19 related efficiency savings.[13] Understanding the impact of shorter versions of MCT in targeting specific biases may therefore allow its application as a brief intervention that may be more cost-efficient, aimed at short-term improvement in decision-making capacity and facilitation of broader patient engagement in psychiatric services. [14–16]

One such relevant target is the "jumping-to-conclusions" (JTC) bias, in which hasty, over-confident decisions are made based on limited evidence. This cognitive bias has been implicated in delusional appraisal and formation,[26] with meta-analytical evidence demonstrating that people with psychosis

are 4-6 times more likely to demonstrate this bias.[17] Evidence suggests that individuals with psychosis display over-confidence in perceptual and judgemental errors and less confidence in correct appraisals.[18] The JTC bias is included as a target of the overall MCT treatment package whilst RCTs investigating the impact of single-session MCT have also been conducted, typically applying variants of the probabilistic reasoning "Beads Task"[19] as the primary outcome. Brief MCT-based interventions addressing the JTC bias and overconfidence have also been successfully applied in non-clinical populations.[20] A recent RCT examining a lengthier, digitally-supported CBTp based intervention targeting reasoning biases did not demonstrate a reliable effect on the JTC bias despite an effect on paranoia.[21]

In this secondary analysis, we aimed to examine the impact of a single-session MCT module addressing the JTC bias on over-confident decision making among psychosis patients. We used an alternative outcome measure specifically tailored to assess over-confidence in perceptual judgements - the Snowy Pictures Task.[22] We hypothesised that participation in MCT would reduce the extent of over-confident decision making at post-treatment compared to an attention-control condition.

Methods

Design

This paper presents the findings from the secondary analysis of data subsumed within a broader randomised controlled trial investigating the impact of a brief MCT intervention targeting the jumping-to-conclusions bias on treatment-decision making capacity in psychosis patients. Prior to the initial randomisation in the broader RCT, discussion between D.T. and S.M. led to the

suggested inclusion of a further measure related to the JTC bias in addition to the existing Beads Task.[19,22] Delay in ethical approval being granted for the inclusion of the additional outcome measure along with time constraints in the broader RCT meant that the additional outcome measure was not administered for the first six RCT patients randomised. Following eventual ethical approval, the additional outcome measure was integrated in the standard procedure for all participants. The current paper therefore reports on a subset of RCT participants (n=31) who engaged in the later included Snowy Pictures Task.[22]

The methods and results of the broader RCT conducted on the entire sample are presented in more extensive detail elsewhere.[14] Below we outline the specific procedure followed for the secondary analysis. The broader RCT protocol was pre-registered on the Open Science Framework before recruitment and randomisation began (https:// osf.io/kunc4/). Ethical approval was granted via the University of Edinburgh Health in Social Science Ethics Committee and South of Scotland Research Ethics Committee (REC no. 15/SS/0162). We note that the pre-registered protocol was not updated to include the Snowy Pictures task when this was added. An ethical amendment was however approved to accommodate the addition. The Snowy Pictures Task[22] was the only outcome measure added to the original protocol not reported in the original trial.

Procedure

Following informed consent, patients with psychosis were firstly assessed at baseline with the full battery of outcome measures over one or two appointments. Following the completion of these measures, a follow up appointment was scheduled within two weeks to complete the intervention or control condition and administer post-treatment outcome measures.

Randomisation was achieved via the Sealed Envelope online randomisation service using a permuted blocks sequence. This online randomisation service provides a remote randomisation process which is concealed from the participant, investigator and clinical staff (sealedenvelope.com). Referring NHS clinical staff and participants and were blind to group allocation, although this was not achieved for the researchers/clinicians administering outcome measure batteries, the intervention and control condition (D.T. and A.L.).

On arrival at the second appointment, patients were randomised (1:1) to receive either a) a brief single-session MCT intervention targeting the JTC bias or b) an attention control condition. Both the intervention and control condition lasted approximately one hour. The post-treatment outcome measures were administered directly after the single intervention session or control session, meaning the possibility of missing data was minimised.

Table 1. Demographic and clinical characteristics

	Overall (*N*=31)	Experimental (*n*= 16)	Control (*n*=15)
Age, mean (SD)	45.35 (13.1)	44.19 (14.0)	46.6 (12.5)
Gender (male:female)	25:06	11:5	14:1
Ethnicity (white:other)	31:0	16:0	15:0
Inpatient:outpatient	8:23	4:12	4:11
Diagnosis			
Schizophrenia, N (%)	22 (71%)	10 (62%)	12 (80%)
Schizoaffective, N (%)	5 (16%)	3 (19%)	2 (13%)
Psychosis NOS, N (%)	4 (13%)	3 (19%)	1 (7%)
Duration			
0-1 years, N (%)	3 (10%)	3 (19%)	0
1-3 years, N (%)	2 (7%)	2 (13%)	0
3-5 years, N (%)	0	0	0
5-10 years, N (%)	1 (3%)	1 (6%)	0
Over 10 years, N (%)	25 (81%)	10 (62%)	15 (100%)
PANSS Positive,	19.29 (7.4)	20.89 (7.6)	17.61 (7.1)
PANSS Negative	15.03 (5.0)	15.00 (4.9)	15.06 (5.2)
PANSS Disorganisation	22.68 (8.0)	22.05 (7.8)	23.33 (8.3)
PANSS Excitement	15.14 (4.5)	15.11 (4.5)	15.17 (4.63)
PANSS Distress	21.70 (5.4)	23.84 (5.5)	19.44 (4.37)
PANSS Total	68.06 (16.1)	67.94 (17.5)	68.20 (15.0)
HADS Total	12.64 (5.8)	13.88 (6.2)	11.33 (5.30)

Note: HADS, Hospital Anxiety and Depression Scale. PANSS, Positive and Negative Syndrome Scale. Psychometric data is reported as mean and standard deviation**.** van der Gaag (2006) algorithm was used for calculation of the PANSS.

Participants

Participants (*N* = 31) were aged 16-65 years old. All participants were English-speaking inpatients or outpatients with a clinical diagnosis of schizophrenia, schizo-affective disorder, delusional disorder, brief psychotic disorder or psychosis not otherwise specified and in contact with National Health Service (NHS) mental health services in Scotland (NHS Lanarkshire or NHS Dumfries & Galloway). Patients were excluded where psychosis was deemed to be the result of a general medical condition or substance use disorder or during recent acute exacerbations of their condition meaning participation could be of detriment. Patients under care of forensic mental health services,

involved in on-going legal proceedings or diagnosed with moderate to severe learning disabilities were also excluded. No restrictions were made in terms of symptom threshold, meaning patients ranging from clinically mild to severe were included.

Recruitment was open from February 2016 until February 2017. Patients were recruited from a number of NHS mental health services including outpatient Community Mental Health Teams (CMHT) and Psychological Therapy Teams (PTTS) alongside acute and rehab inpatient settings.

Intervention

As described elsewhere,[14] a single-session "best of" intervention was compiled consisting of the most effective material from the JTC-focused modules of the MCT intervention package.[23] MCT incorporates elements from cognitive-behavioral and psycho-educational interventions addressing specific cognitive biases in psychosis. The version we administered most closely represents "MCT+" in which the therapist plays a more active role in engaging the patient in personally significant examples and challenging thinking biases, closer to the style of traditional cognitive-behavioral therapy for psychosis than generic MCT. Patients were guided in this manner through a Powerpoint presentation providing various information, examples, reasoning tasks and perceptive exercises aiming to address the JTC bias. Example slides from the presentation are provided in Appendix 1. The intervention was administered by final year NHS Trainee Clinical Psychologists. Participants were encouraged to engage with the therapist during the session regarding their delusional interpretation by discussing and challenging reasoning biases at specific parts of the presentation. A table summarising the key components of the intervention is provided as in Appendix 2.

Attention control condition

The control condition consisted of an hour-long educational Powerpoint talk on the localisation of brain function covering the manner in different brain areas have different functions, unrelated to psychosis or mental health. This was designed to control for therapist time and attention focused on a psychologically-relevant topic, while removing any specific focus on cognitive bias or reduction of psychiatric symptoms. The manner in which the attention control was presented meant participants were masked regarding which was the intervention and control group. Participants were debriefed regarding masking and the general study hypothesis following the post-treatment assessments.

Primary outcome measures

The primary outcomes for this secondary analysis were the Snowy Pictures Task[22] and a variant of the Beads Task,[24] both of which constitute perceptual tasks previously applied to measure cognitive bias in participants with psychosis.[25,26]

Snowy Pictures Task

We administered the Snowy Pictures Task[22] at baseline and post-treatment to assess overconfidence in incorrect perceptual judgements. Participants viewed a Powerpoint presentation of 24 "snowy" or "grainy" static images. Half of these images masked an unclear underlying image, which was difficult to perceive while half had no underling image and therefore simply constituted the grainy particles alone (see Figure 2). Participants were asked judge on a 4-point Likert scale whether an underlying image was present by answering "yes-very sure," "yes, unsure," no-unsure" or "no-very sure." Scores were graded for level of confidence in response for each item. It has been demonstrated that psychosis patients show overconfidence in false perceptual judgements and lower

certainty in correct judgements.[25] A 5 second time limit was set for each image and a pseudorandom order was presented.

The Beads Task

A computerised 60/40 version of the "beads task"[24] was administered at baseline and post-treatment via PowerPoint presentation to assess the JTC bias. This task requires participants to judge which of 2 mixed jars containing different ratios of purple and green beads a sequence of single beads have been taken from. The task therefore assesses how many "draws to decision" (DTD) participants require before making a judgement on which jar the sequences of beads belongs to, therefore assessing tendency to "jump to conclusions" on limited information.

Secondary outcome measures

The MacArthur Competency Assessment Tool for Treatment[27] was administered at baseline and post-treatment for all participants. The MacCAT-T was the primary outcome measure for the broader RCT. Since this outcome has been covered extensively in the broader RCT, we report this outcome measure here primarily to determine the consistency of results in the sub-sample regarding treatment-decision making capacity. The MacCAT-T is a clinician-administered semi-structured interview assessing 4 key domains: a. understanding of treatment-relevant information, b. appreciation of information relevant to intervention or diagnosis, c. reasoning ability when considering options and d. expressing a choice regarding mental healthcare options.

The Hospital Anxiety and Depression Scale[28] was administered at baseline and post-treatment to assess and monitor general psychological distress while the Cognitive Bias Questionnaire for Psychosis[29] was administered at both measurement points as a measure of general cognitive bias

and alternative measure of the JTC bias. The Positive and Negative Syndromes Scale[30] was administered at baseline only to characterise the sample on severity using the van der Gaag[31] algorithm for positive symptoms, negative symptoms, disorganisation, excitements and distress. Researchers received training in all relevant outcome measures. Patients also completed a questionnaire collecting demographic information.

Statistical analyses

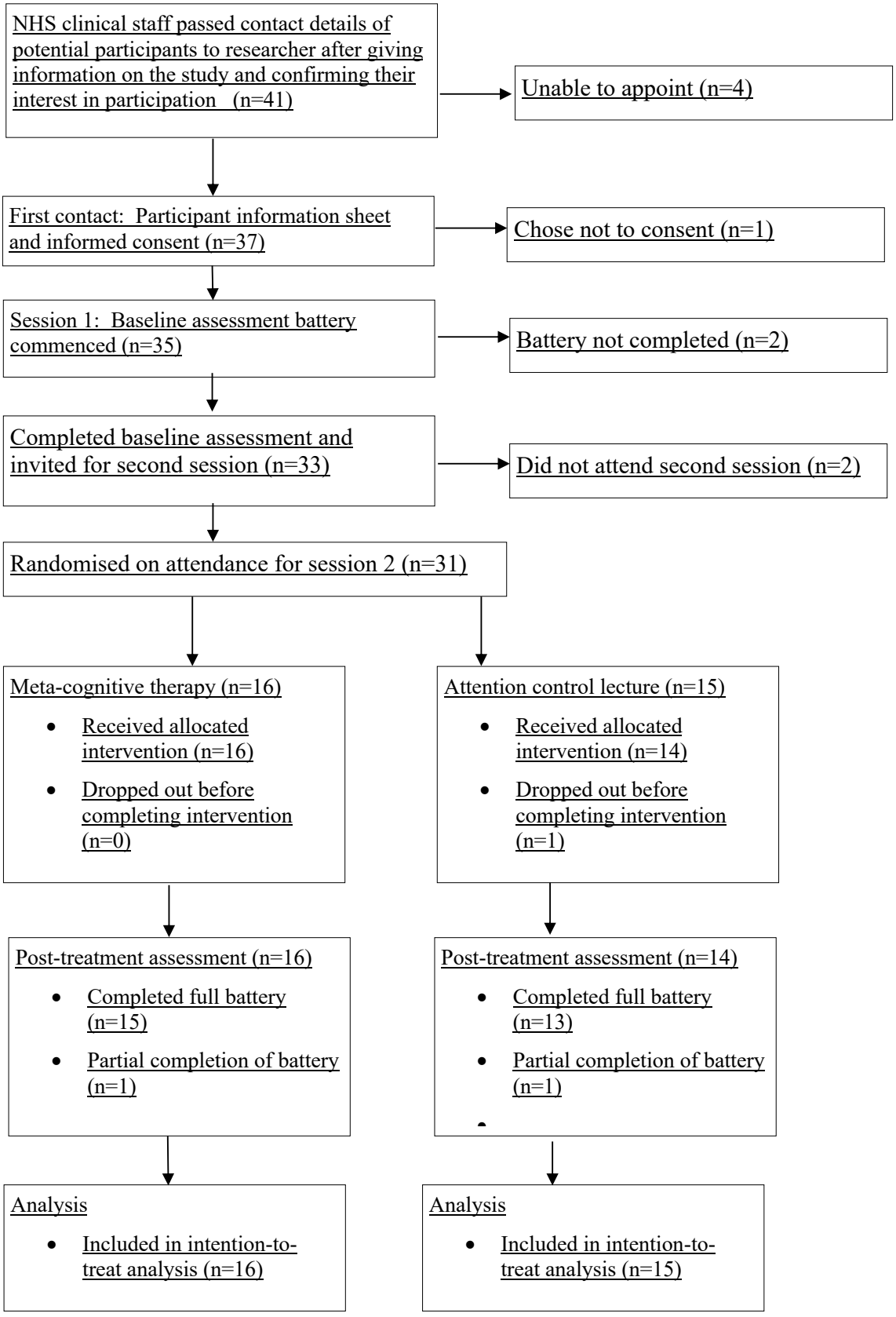
The SPSS statistical package was utilised for all analyses and intention-to-treat principles were comprehensively applied. For missing data at post-treatment, multiple imputation estimated an imputed outcome using baseline PANSS scores and group assignment. We assessed normality via histograms and boxplots and assessed skewedness and kurtosis by statistical significance ($p < .05$). In instances where the necessary assumptions for parametric testing were violated post-hoc non-parametric Kruskal-Wallis H tests were conducted as sensitivity analyses. ANCOVA was applied for the analysis of all primary and secondary outcomes measured at baseline and post-treatment, in which baseline scores were entered as covariates to assist power and precision.[32] We assessed baseline scores for significant differences between groups to ensure that the assumption of independence of covariate and treatment effect was satisfied. Partial eta-squared effect sizes were converted to Cohen's *d* to assist interpretation of the strength of the effects. ANCOVA results were checked for consistency in both Type I and Type III models and lack of model fit assessed.

Results

Participants

The study flow diagram (Figure 1) shows the results of the recruitment, randomisation, treatment and assessment process. 31 participants were randomised for full inclusion resulting in 16 participants in the MCT treatment arm and 15 in the attention control. This reflects a subset of the original RCT sample ($N = 37$) since the first six patients randomised in the RCT were not administered the Snowy Pictures Task.[22] Missing data on the primary outcomes was low (3%). Table 1 provides the demographic and clinical information of the sample. There was a majority of male participants (83%). All patients identified as white ethnicity. 75% of participants were outpatients and 25% inpatients. The majority were diagnosed with schizophrenia (71%), while 16% were diagnosed with schizoaffective disorder and 13% with psychosis NOS. The vast majority (81%) had over 10 years since their first diagnosis rising to 100% in the control group, indicating that the majority of the sample were long-term contacts of NHS mental health services. The HADS indicated a mean of moderate depression and anxiety across the sample and similarly the PANSS indicated moderate severity.[33]

Fig. 1. Study flow diagram for subsample in RCT from addition of confidence task



Primary outcome measures ANCOVAs

Table 3 provides the results on our primary outcome measures. There was a large significant positive effect of the MCT intervention on the Snowy Pictures Task relative to controls ($d = 0.97$, $p = 0.02$). A positive effect was also demonstrated on the ANCOVA for the Beads Task ($d = 1.16$, $p = 0.01$) although the data violated the assumptions of ANCOVA. Sensitivity analysis with the Kruskal-Wallis non-parametric H test demonstrated a significant positive effect consistent with the ANCOVA ($\chi^2 = 5.62$, $p = 0.02$).

Table 2. ANCOVA results for primary and secondary outcome measures (intention-to-treat)

	Baseline		Post-treatment		*F*-Test	Between-group effect size (*d*)
	MCT-JTC	AC	MCT-JTC	AC	Group effect (*F*)	
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)		
Snowy Pictures Task	32.63 (8.09)	38.53 (7.61)	28.38 (6.95)	37.40 (7.46)	6.64* (p=0.02)	0.97
Beads Task	3.75 (3.07)	3.47 (3.38)	6.25 (3.55)	3.40 (3.27)	9.40** (p=0.01) †	1.16 †
MacCAT-T Understanding	3.59 (1.43)	3.09 (1.41)	4.17 (1.54)	3.37 (1.57)	1.09 (p=0.31)	0.40
MacCAT-T Appreciation	3.13 (1.15)	2.87 (1.25)	3.63 (0.62)	2.92 (1.39)	5.33* (p=0.03)	0.87
MacCAT-T Reasoning	6.13 (1.26)	5.27 (1.87)	6.81 (1.28)	5.40 (2.03)	2.98 (p=0.96)	0.65
MacCAT-T Expressing Choice	2.00 (.00)	1.93 (0.26)	1.94 (0.25)	1.93 (0.26)	†	†
MacCAT-T Total	14.77 (3.49)	13.22 (3.99)	16.55 (2.92)	13.63 (4.20)	5.04* (p=0.03)	0.85
HADS Anxiety	8.19 (4.49)	8.13 (3.80)	8.25 (4.00)	7.40 (4.08)	0.65 (p=0.42)	0.31
HADS Depression	5.69 (3.63)	3.20 (2.54)	6.50 (3.06)	3.37 (2.28)	5.51 (p=0.03) †	0.89 †
HADS Total	13.88 (6.16)	11.33 (5.30)	14.50 (5.42)	10.67 (5.11)	2.38 (p=0.13)	0.58
CBQP JTC subscale	10.88 (3.79)	10.20 (1.82)	10.38 (2.55)	10.47 (1.41)	0.77 (p=0.39)	0.33
CBQP Total	47.44 (11.42)	44.67 (8.69)	44.06 (9.13)	43.05 (8.00)	0.526 (p=0.47)	0.27

Note: AC, Attention control; ANCOVA, Analysis of Covariance. CBQP, Cognitive Biases Questionnaire for Psychosis: MacCAT-T, MacArthur Competency Assessment Tool for Treatment; MCT, Meta-cognitive training; HADS, Hospital Anxiety and Depression Scale; JTC, jumping-to-conclusions. *$p<0.05$; **$p<0.1$ †Data in these analyses violated the assumptions of ANCOVA.

Secondary outcome measures ANCOVAs

There were large significant positive effects for both the MacCAT-T total score (d = 0.85, p = 0.03) and the *appreciation* subscale (d = 0.87, p = 0.03). The ANCOVAs for the *understanding* and *reasoning* subscales were non-significant. The analyses for the CBQP and its JTC subscale were also non-significant, as were ANCOVAs for the HADS total score and anxiety subscale. The HADS depression subscale had significant baseline differences (p=0.36) and therefore violated the assumptions of ANCOVA, a finding which was also consistent with the broader RCT.

Discussion

This secondary analysis found that an adapted version of MCT targeting the JTC bias reduced overconfidence in perceptual decision making among psychosis patients. Despite having demonstrated a large positive effect of the intervention on the Snowy Pictures Task[22] when compared to an attention control condition, the important limitations of this study mean that our results should be considered as preliminary evidence that MCT may reduce overconfidence in psychosis. We also found a large positive effect favouring the intervention on another more widely applied test of the JTC bias, the Beads Task, which contradicts a number of earlier trials.[35-40] Our results are supportive of MCT as an interveition aimed at reducing cognitive bias in general,[19,20] but should be interpreted with caution until a more definitive trial is available.

This study has a number of important limitations. Firstly, the immediate measurement of the primary outcome measures following the single-session intervention means it is unclear whether the effects are durable. Nevertheless, there was also a positive impact of this design since it limited missing data to 3% and all but one randomised participant completed the intervention and primary

outcome measures battery. Combined with the implementation of intention-to-treat analysis, this helped limit the likelihood of attrition. A further limitation was that it was beyond the scope of the project to employ blind assessors, meaning that the same researchers administering the intervention and attention control also administered all outcome measures. The structured nature of MCT and the primary outcomes may limit potential bias in this domain although in ideal circumstances a wider team with full blinding would be employed. Furthermore this was a low-powered trial with only16 participants in the intervention arm and 15 in the control with a limited range of focused outcome measures, which limits generalisibility.

We also note that all participants in the control group had >10-year history of psychosis compared to 62% in the MCT group and 81% overall. This may limit the generalisability of our results to first-episode or less chronic psychosis groups. There is also the possibility that the higher number of chronic patients included in the control group influenced the results on the primary outcome measures, although the fact that the pattern of results in this secondary analysis reflected those of the broader RCT despite less polarity in length of illness may indicate this is unlikely. Our results do however suggest that over-confident perceptual judgment in chronic patients is amenable to brief intervention such as the MCT JTC module applied.

It is also of interest that this secondary analysis along with the original trial found large effects of the brief MCT intervention on the Beads Task, while reliable effects were not demonstrated in the larger and more comprehensive SlowMo trial,[21] which also focused on reasoning bias. One hypothetical reason for this difference is that SlowMo focused primarily on "slowing down for a moment to find ways of feeling safer" and therefore assigns less focus toward challenging the JTC bias directly. A number of other trials have however reported negative or inconsistent effects on the Beads Task or similar measures of the JTC bias (for example the Fish Task).[35-40] It is of interest that our randomised trial appears to be an outlier in this respect. One hypothetical influence could be the

timing of post-treatment outcomes, since we administered the Beads Task directly following the intervention in the same sitting. This meant the MCT intervention was very 'fresh' for participants while it is likely that broader post-treatment assessments in trials such as SlowMo and other trials examining full MCT treatment packages required an additional post-treatment battery assessment session at a later date.

Clinical implications

Our results suggest that overconfidence in perceptual judgements and decision-making among psychosis patients is a valid (amenable) target of brief intervention. The option of applying such brief, modular interventions aimed at improving cognitive biases and perceptual decisions making may be attractive in settings in which longer, structural interventions face barriers due to length of stay,[34] patient and staff characteristics or Covid 19-related financial constraints.[13]

Future research

The results of this RCT indicate that a larger, more definitive trial addressing the limitations of this study is warranted. Of primary importance would be the addition of blind assessment and follow-up assessments at later timepoints to determine the extent to which the effect of the brief MCT intervention on overconfidence is enduring; our current methodology only allows to examine immediate effects. Future research applying brief MCT interventions targeting overconfidence and related cognitive biases may also be applied to a wider range of psychosis patients than our primarily chronic sample, including focus on first episode psychosis. Research examining the specific effects of other MCT modules to help determine their relative impact and value to the broader MCT package is also warranted.

Conclusions

This secondary analysis suggested that overconfidence in psychosis patients may be amenable to change via brief MCT-based intervention. Our results await verification in larger RCTs with more comprehensive methodology although support the clinical potential of brief intervention targeting cognitive bias.

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Appendix 1: Examples of MCT "jumping to conclusions" module slides

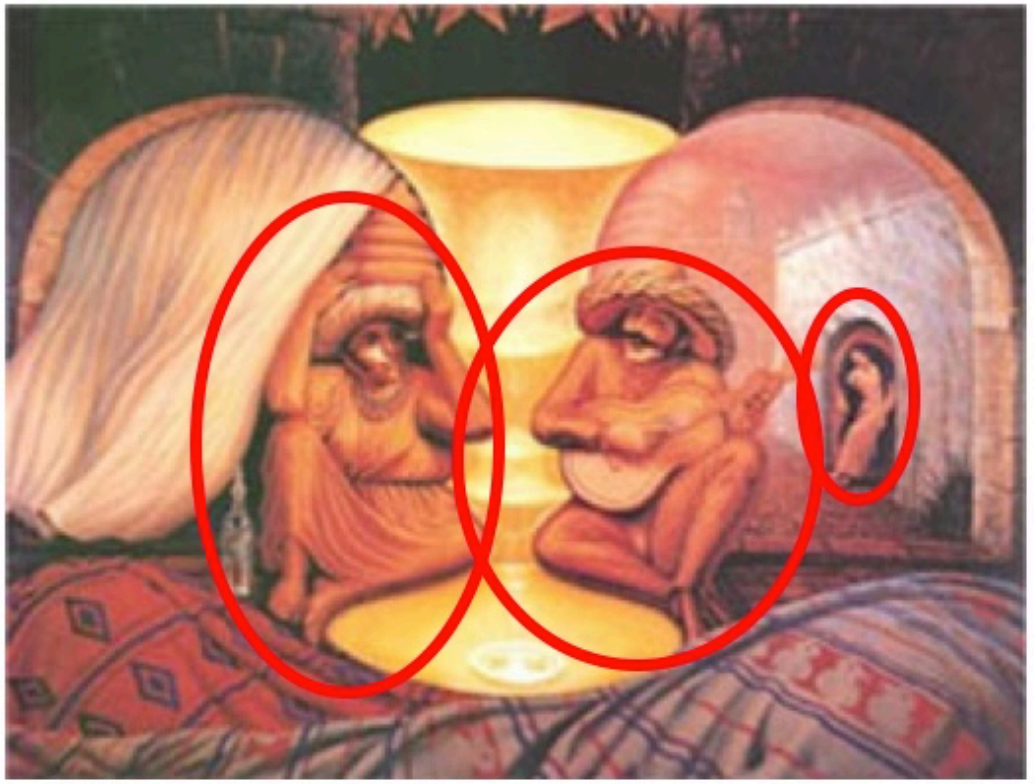
How jumping to conclusion promotes misinterpretations during psychosis - examples

Event	Explanation during psychosis	Other explanations
You hear a crackling noise on the phone line.	The CID are eavesdropping on you.	Wire damage; typical sounds of a distant call; poor reception during mobile phone call.
People on the bus look at you when you walk on	They are monitoring where you are going	They are bored and just looked your way as there was nothing else to see
White dust on the kitchen table, wasn't there before.	An attempt to poison you with anthrax has been made; the police planted drugs to frame you.	Someone has just been baking; no one has dusted for a while.

Can you contribute a short personal experience?

Worksheet 1

What do you see?



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Old woman, young woman, man with moustache?

What does this person feel or do? How confident are you?

Cutout!

1. Boy screaming for help after an earthquake
2. Demonstration (Uganda)
3. Player waves the Israeli flag
4. Singer in a gospel choir

a. Poisoning
b. Why did I marry him? (Murray, ca. 1940)
c. Suicide
d. The desperate mother

Appendix 2. Components of 1-hour MTC-JTC intervention

1. An introduction to the jumping-to-conclusions bias in psychosis
2. Inferences without 100% proof; examples from daily life (2 examples)
3. Jumping-to-conclusions "in action;" examples from politics and medicine of the pitfalls of using jumping-to-conclusions in decision-making (4 examples)
4. How jumping-to-conclusions promotes misinterpretation; discussion and examples including a worksheet for personal experiences and alternative interpretation
5. Jumping-to-conclusion and it's role in conspiracy theories; illustration via the moon landing conspiracy theory
6. Worksheet exercise; providing evidence for and against personal delusional beliefs including conviction rating
7. Picture-identification tasks (3 tasks); participants were required to identify all possible interpretations of images as progressive detail was revealed and state their confidence in their interpretation
8. Face illusion tasks (3 tasks); participants were required to identify all details or alternative interpretations when presented with images, for example the old woman/young woman/old man face illusion
9. Scene identification from cut-out (4 tasks); four tasks in which a cut-out image from a larger scene was provided from which participants were required to infer the correct wider context from four options using evidence in the picture and state confidence
10. Misfits task (5 tasks): presentation of five classic paintings in which participants were required to identify the correct title from four options based upon clues within the painting and state confidence
11. Summary of jumping-to-conclusions session and suggested tactics

Chapter 7

General discussion

Introduction

This thesis attempted to help further develop the knowledge and evidence base for psychological interventions for psychosis. A key objective was the provision of a comprehensive and contemporary overview of the meta-analytic evidence for psychosocial interventions for psychosis, including a deliberate focus on methodological stringency to help estimate the quality of the included outcome research and assist confidence in the validity of findings. Related to this objective was the aim to use these findings to conclude on the current 'state of the evidence' for psychological interventions in light of on-going debate regarding their efficacy.[1] The inclusion of novel methodological techniques and approaches allowed the consideration of important contextual questions. Firstly, the application of cumulative meta-analysis provided the possibility to assess the development of the evidence base from a longitudinal perspective and comment on stability and sufficiency. Secondly, the exploratory application of individual-participant data meta-analysis allowed a preliminary investigation of what factors influence treatment outcome. Similarly, the inclusion of network meta-analysis methodology allowed evidence to be drawn from a broad range of indirect comparisons alongside those direct comparisons examined in conventional meta-analysis. Finally, the application of a brief psychological intervention to improve overconfident perceptual decision-making among psychosis patients allowed investigation of the potential for psychological interventions to improve a common deficit in psychosis patients.

This general discussion section will begin with a brief recap on the key findings of the studies included in the previous chapters before focusing on the broader implications of these findings from both research and clinical perspectives. The strengths and limitations of this thesis will then be considered before outlining relevant potential developments for

future research. Finally, overall conclusions will be drawn by utilising the somewhat unique opportunity provided by this compilation of psychosis intervention outcome research.

Summary of the main findings

CBTp outperforms other psychological intervention for positive symptoms

Chapter 2 reported on a comparative meta-analysis of six psychological interventions for psychosis, namely CBTp, cognitive remediation, psycho-education, supportive counselling and befriending. This review demonstrated that CBTp consistently outperformed other psychological interventions in reducing the positive symptoms of psychosis by a small effect size of $g = 0.16$ when all eligible RCTs were included and $g = 0.14$ when including only RCTs with minimal risk of bias. It should be noted that this effect size denotes *relative efficacy* (i.e. comparison between active intervention conditions) whereas *absolute efficacy* effect sizes compared to treatment-as-usual are typically of higher magnitude. This was demonstrated in **chapter 4** in our meta-analysis investigating the effects of CBTp on the more specific positive symptom outcome measures of hallucinations and delusions. CBTp was consistently beneficial for hallucinations across comparisons against treatment as usual and active interventions. Effect sizes ranged from $g = 0.3$ for broad 'inclusive' comparisons in which all eligible trials were included, to a high of $g = 0.6$ when including only case-formulation based CBTp trials with primary outcome focus assessed as having minimal risk of bias. CBTp was also consistently beneficial versus treatment as usual for delusions and when including any form of control for delusions with effect sizes ranging from $g = 0.3 – 0.4$. These effect sizes were robust when including only trials with minimal bias risk, although

were non-significant in comparisons against active interventions, which suffered from limited power.

SST outperforms other psychological intervention for negative symptoms

The comparative meta-analysis in **chapter 2** also demonstrated consistent superiority of social skills training compared to other psychological interventions for negative symptoms, with effect sizes ranging from $g = 0.3$ when including all eligible trials and $g = 0.6$ when reducing risk of bias.

The evidence is less clear regarding the effects of psychological intervention on 'overall' psychotic symptoms

While the comparative meta-analysis in **chapter 2** demonstrated superiority of CBTp for overall symptoms in the less stringent comparisons, no significant effect was demonstrated when removing trials assessed as having risk of bias. The network meta-analysis in **chapter 3** demonstrated superiority of mindfulness-based psycho-education compared to other interventions for overall symptoms, although all studies in this comparison originated from one country and therefore leads to critical questions regarding cultural generalisability and broader validity.

The evidence base for CBTp for positive symptoms (hallucinations and delusions) is stable and sufficient

The inclusion of cumulative meta-analysis procedures in **chapter 4** as part of the meta-analysis investigating the effects of CBTp in reducing hallucinations and delusions demonstrated that, according to the procedures set out by Muellerleile and Mullen,[2] the evidence base for CBTp in reducing hallucinations has been *sufficient* and *stable* since

2016. This effect was consistent when considering only trials with minimal risk of bias. The evidence base for delusions was shown as sufficient and stable since 2015, although when considering only trials with minimal risk of bias sufficiency and stability was demonstrated in 2017.

Exploratory utilisation of individual-participant data in meta-analysis does not indicate that demographic or clinical characteristics influence treatment outcome

Conventional meta-analysis methodology does not allow the investigation of moderator variables that vary at the participant level on treatment outcome. This therefore means that it is not possible to determine which individual patient profiles most benefit from particular interventions. **Chapter 5** presented the first individual-participant data meta-analysis on psychological interventions for psychosis outcome trials, which provides the best-available statistical power to investigate the impact of demographic and clinical variables on psychosis patient treatment outcome. Results suggested that demographic and clinical variables do not significantly impact treatment outcome although the number of sessions (or "dosage" of CBTp) significantly moderates treatment outcome.

Brief psychological intervention has the potential to improve overconfident perceptual decision-making in psychosis patients

Chapter 6 reported the results of a randomised controlled trial assessing a brief metacognitive training intervention targeting the "jumping-to-conclusions" reasoning bias as a means of improving overconfident perceptual decision-making among psychosis patients. Results demonstrated that the brief intervention was significantly beneficial in reducing overconfidence ($d = 0.97$) alongside the "jumping to conclusions bias" ($d = 1.16$) although the latter comparison violated the necessary data assumptions for

ANCOVA. A non-parametric sensitivity analysis was applied post-hoc and demonstrated consistent results. Limitations in this trial mean results should be interpreted as preliminary.

Discussion

Efficacy of CBTp

When considered broadly, the research included in this thesis provides clear support for the premise that psychological intervention is a valid treatment option for psychosis patients. Discussion of psychological interventions for psychosis in contemporary terms most often refers to CBTp or its variants and derivatives. Despite the widespread implementation of CBTp in European healthcare systems including the UK and the Netherlands, the premise that CBTp for psychosis "works" is not yet taken for granted due to the on-going debate regarding whether CBTp is in fact ineffective and has been "oversold."[1,3]

Importantly, the meta-analytical comparisons in **chapter 4** in which the effect of CBTp on hallucinations and delusions were examined address a key aspect of this debate. While one recent meta-analysis reported that the beneficial effects of CBTp specifically targeted toward positive symptoms were maintained when limiting inclusion to only blinded RCTs,[4] another, notably with broader overall study inclusion criteria, found no effect when including only blinded RCTs.[5] **Chapter 4** however reported that CBTp continued to demonstrate superiority when including only blinded RCTs both when all eligible RCTs were included and when including only RCTs implementing individualised case-

formulation with primary outcome focus. This finding was valid in both the hallucinations and delusions comparisons. These findings therefore add weight to the argument that CBTp is an effective means of reducing hallucinations and delusions and therefore positive symptoms. This premise is strengthened by the finding that the effects of CBTp were robust to various sensitivity analyses for blinding and methodological quality overall.

A potential explanation for diverging findings in comparison to previous negative meta-analytic studies or those which demonstrated a less reliable effect of CBTp[3, 5] may lie in study selection; the categorisation of the therapies delivered in RCTs can often be complex and controversial[1] as can the selection of outcome variables. Notably, the cumulative meta-analysis in **chapter 4** focused intentionally on hallucinations and delusions as outcome measures, alongside RCTs implementing case-formulation driven CBTp with the relevant symptoms as primary outcome. In this sense, the RCTs that were included utilised the form of CBTp designed most specifically to target the core positive symptoms of psychosis while other meta-analyses have included interventions such as cognitive-behavioural social skills training in the positive symptoms category,[5] despite such interventions not specifically targeting positive symptoms. Studies implementing case-formulation and primary outcome focus provided stronger effect sizes in sensitivity analysis in the cumulative meta-analysis. A further possible reason for diverging findings is statistical power, since as more RCTs have become available, the availability of RCTs especially in the more stringent sensitivity bias categories for risk of bias or primary outcome focus has improved. The ability to detect effects in such categories may therefore be improved in the more recent meta-analysis in **chapter 4**. Furthermore, previous negative meta-analyses[5,42] have focused primarily on assessor blinding in risk of

bias sensitivity analyses rather than employing the broader Cochrane risk of bias assessments which are accepted as standard. This may also have impact on results.

Furthermore, the cumulative meta-analysis in **chapter 4** demonstrates that the evidence base for CBTp for psychosis is *sufficient* and *stable* when measuring the effect on hallucinations and delusions. It can be hypothesised that broader measures of positive symptoms may also be approximated by this analysis, although cumulative techniques have not yet been applied to positive symptom outcomes such as the Positive and Negative Syndromes Scale (PANSS).[6] When considered alongside the finding of superiority of CBTp compared to other psychological interventions, this conclusion on the cumulative progression of the evidence base may mitigate reservations regarding the validity of CBTp.

Efficacy of other psychological interventions for psychosis

As a result of it's more widespread implementation in research and practice, the majority of meta-analytical findings in this thesis are in relation to CBTp. **Chapter 2** concluded through comparative meta-analysis that social skills training represents an efficacious means of reducing the negative symptoms of psychosis. Negative symptoms in psychosis are recognised as a key element of the psychopathology,[7] although there are comparatively fewer tailored intervention packages available attempting to reduce them. Negative symptoms have been a primary outcome focus within a small number of CBTp RCTs[8] and quasi-experimental studies.[9] There also exist cognitive-behavioral social skills training (CB-SST) trials integrating the approaches.[10,11] The further development of

interventions focusing on negative symptoms has the potential to influence significant improvement in quality of life of many psychosis patients.

This thesis only provided brief coverage of cognitive remediation, psycho-education and befriending in the comparative meta-analysis in **chapter 2**. Supportive counselling was included in a number of comparisons throughout the included studies although primarily as a comparative control accounting for 'common factors,' with no specific focus on its own merits out with **chapter 2**. This thesis therefore adds little to the understanding of these interventions other than the demonstration of their relative inferiority to CBTp for positive symptoms and SST for negative symptoms, although cognitive remediation did demonstrate a significant effect small effect (g=0.2) versus other interventions pooled. This effect was not robust against sensitivity analyses for risk of bias, but due to the risk of Type 2 error as a consequence of reduced power it is too early to rule out efficacy. Cognitive remediation is however well studied in comparison with the other aforementioned interventions and boasts a considerable meta-analytical evidence base. Cognitive remediation has been demonstrated as an efficacious intervention for negative symptoms; a recent network meta-analysis focusing specifically on this intervention demonstrated a similar pattern to many comparisons in this thesis in that effect sizes increased (g = 0.4) when including only trials with more robust methodology.[12] In combination with the above finding, the results from the network meta-analysis and other reviews[13–15] therefore bolster confidence in this intervention. There is also meta-analytic evidence that social cognition training, commonly a variant of cognitive remediation, may improve social performance although no significant benefit was found for psychotic symptoms.[16]

Also noteworthy is the omission of some well-known forms of psychological intervention for psychosis from this thesis, including family therapy,[17] psychodynamic therapy[18] and art therapy.[19] The reason for omission was our commitment to producing meta-analytical evidence and drawing conclusions in a firmly evidence-based manner, rather than drawing conclusions from a) individual randomised controlled trials, which have more potential to suffer from Type I "false positive" errors, or b) running low powered meta-analysis with an insufficient number of RCTs and therefore providing results of limited validity.[20] The lack of RCTs comparing these forms of intervention against other active treatments therefore resulted in their exclusion from the comparative efficacy meta-analysis in **chapter 2**. The network meta-analysis in **chapter 3** suggested that family therapy was, when including direct and indirect comparisons, one of the least effective interventions for total symptoms psychosis. Family therapy has previously indicated favourable meta-analytic results in reducing relapse when compared to any form of control[21] and continues to be recommended in the UK National Institute for Clinical and Care Excellence (NICE) guidelines[22] while to date no detailed meta-analytical evidence exists for art therapy or psychodynamic therapy.

Related topics

Moderators of outcome in psychological interventions for psychosis

Although the individual-participant data meta-analysis in **chapter 5** concluded that no demographic or clinical variables moderated treatment outcome, it must be recognised that this evidence is at present preliminary. The moderator analysis was conducted from an exploratory angle, which introduces potential bias due to the absence of clearly defined

hypothesis testing. Also of note is that this was a relative efficacy meta-analysis as opposed to an absolute efficacy meta-analysis, therefore examination of moderators against all forms of control conditions (including treatment as usual) has the potential to find different results.

The Dodo verdict

The meta-analytic reviews contained in this thesis most commonly provide support for effects of specific factors as operating in psychological interventions in psychosis, although it is too early to comment conclusively on whether the effects of the interventions assessed are achieved primarily by common or specific factors.[23] **Chapters 2 and 4** demonstrated that when compared to control conditions specifically designed to account for the common factors present in all talking therapies (most commonly supportive counselling without the 'specific' ingredients of any psychological model), CBTp was superior in reducing positive symptoms (g = 0.23 versus supportive counselling) and hallucinations (g = 0.3-0.4 versus active treatments). This effect was not however observed for delusions. It is possible that the absence of an effect for delusions may be attributed to limited power; the comparison in which CBTp was compared to active interventions in trials with minimal bias risk contained only three RCTs. However, one of Wampold's[23] key arguments is that outcome research, via the presence of various research biases, often inflates true effect sizes therefore despite the effects noted above, the evidence provided remains preliminary.

An attempt was made to address these biases within the scope of the included reviews. The effects of publication bias were investigated using the appropriate analyses; minimal

impact on results was noted. **Chapter 2** also included an attempt to assess the impact of *researcher allegiance,* another key consideration noted by Wampold. What is often however problematic with such comparisons is that in meta-analyses which often already suffer from limited RCT availability and hence low power, dichotomising RCTs into those demonstrating researcher allegiance and those not further limits power and risks Type II errors. This is demonstrated in **chapter 1** in the researcher allegiance sensitivity analysis for positive symptoms in which the non-allegiance comparison contained only three RCTs, which falls below the minimum recommended for meaningful meta-analytic comparisons.[20] Due to such on-going issues with power, alongside the absence of complex and costly dismantling studies, definitive comment on whether psychological interventions for psychosis have their key impact via specific effects awaits further clarification.

Overconfidence in perceptual decision-making in psychosis

The preliminary finding in **chapter 6** that a brief adapted metacognitive training intervention addressing the "jumping-to-conclusions" bias improved overconfident decision-making in psychosis patients represents an interesting developmental step in this area. The potential to address cognitive biases and impaired decision making in a brief, modular manner has the potential for implementation in acute settings in which it is challenging to provide lengthier, more comprehensive psychological interventions for psychosis.

Implications for clinical practice

The assessment of the evidence base for CBTp for hallucinations and delusions as *stable* and *sufficient* helps counter the previously noted doubts regarding the value of the widespread implementation in mental health services, for example in the UK National Health Service (NHS). It has been recommended that CBTp is offered as a treatment option for all patients diagnosed with psychosis[26] although in practice access to CBTp for all patients has been reported as lacking.[27–29] The findings add weight to the existing recommendation of CBTp by, among others, NICE (UK), the US National Guidelines Clearing House (NGC)[30] and the Dutch multidisciplinary guidelines for schizophrenia.[31] Findings from cumulative meta-analysis in **chapter 4** counter those utilised by the Cochrane Collaboration by providing robust evidence that CBTp is a worthy intervention for hallucinations and delusions and therefore is suitable for wide clinical implementation.

As previously discussed, **chapter 2** demonstrated that social skills training represents the best available psychological intervention for the negative symptoms of psychosis. There exists little clinical culture of social skills training provision in Europe (for example in the UK or the Netherlands) in comparison to the United States despite CBTp being comparatively widely implemented for positive symptoms. Attempts to further the implementation of social skills training in European clinical settings therefore has potential as a means of improving wider life functioning than a narrower positive symptoms focus. Intervention packages combining cognitive-behavioural and social skills methods already exist although primarily apply group[10] rather than individual[32] format. Adaptation of such programmes for a European context may be of benefit. The results from the cumulative meta-analysis suggest greater strength of individualised, case-formulation driven interventions when targeting positive symptoms although this may be

less valid for social skills training due to the potential impact of group sessions when targeting social skills and negative symptoms.

On a broader note, the various findings reported in this thesis firmly support the clinical application of psychological interventions for patients with psychosis. Most of the evidence presented is from RCTs in which psychological therapies have been provided primarily as adjunctive to anti-psychotic treatment, although there is initial evidence that CBTp is also efficacious in patients not taking medication.[33] These findings may help overcome some remaining scepticism in clinical psychiatry regarding psychological interventions.

Strengths

The research collated in this thesis has a number of collective strengths. A key strength shared by all the included studies is a commitment to utilising the best available methods to facilitate the contribution of reliable data to supplement the evidence base. This includes the utilisation of meta-analytic methods that capitalise on high-quality existing data from published randomised controlled trials in four of the studies alongside the implementation of a randomised controlled trial in the final study. Although alternatives to the standard randomised controlled trial have been developed including factorial approaches,[34] such trials are costly and currently rarely implemented in mental health research. The randomised controlled trial remains the conventional gold standard in assessing the efficacy of (mental) healthcare interventions.

A further related strength is the commitment undertaken to the careful assessment of methodological quality in the included research, alongside the utilisation of these assessments in sensitivity analyses to control for the potential effect of bias on outcome. Clear methods were developed and consistently implemented in all of the meta-analytic reviews included in this paper, which allowed the provision when possible of an effect size with minimal risk of bias due to exclusion of any RCTs in which risk of bias was demonstrated. These procedures help ensure the overall reliability and validity of the findings presented.

A final strength was the application of novel meta-analytical methods that provide an alternative perspective to that available in existing meta-analytic psychological therapy outcome research on psychosis, namely cumulative meta-analysis and individual-participant data meta-analysis. The inclusion in particular of cumulative meta-analysis methods allows a unique insight into the developmental stage of the evidence base.

Limitations

While the limitations of each individual contributory study are described within their respective chapters, it is relevant to consider the broader limitations of this body of research. One notable limitation is the relative lack of extended follow up data across the studies, both in meta-analytic comparisons and in the RCT. Furthermore, it was beyond the scope of the included RCT to include a follow up assessments due to time restrictions. This meant that the durability of the effects of the intervention was not assessed. Although CBTp has already been found as durable in both RCTs [35,36] and meta-analysis,[37]

this limitation means we cannot conclude whether the effects reported in the research included in this thesis were sustained in psychosis patients.

A further limitation regarding the pooling of effects in meta-analysis is the risk of comparing "apples and oranges," or in other words combining disparate interventions and outcomes across RCTs in a meaningless manner while interpreting the results of these comparisons as meaningful. In order to reduce the risk of such threats to validity in comparisons, heterogeneity between the included RCTs was assessed in all meta-analytic studies. Nevertheless, RCT selection and decisions upon comparisons in meta-analyses retain a degree of controversy due to different approaches between individual researchers and groups[1] since the human element of selection means that potential bias can be minimised but not wholly prevented. Similarly, there were additional sources of potential bias that were not assessed in all the included meta-analyses. Researcher allegiance- a source of potential bias discussed by Wampold[23] via which effect sizes risk being inflated in RCTs conducted by researchers who are invested in the intervention they are testing- was only assessed in **chapter 2**. Including additional such sensitivity analyses must always be balanced with loss of power in the relevant comparisons, which in itself may damage the validity of results. Nevertheless, the omission of researcher allegiance analyses in a proportion of the included meta-analytic research can be considered limiting. Furthermore, key limitations of the RCT in **chapter 6** included the therapist-therapy compound and lack of blinding, both of which may contribute to allowing researcher bias.

A further limitation is that the individual-participant data meta-analysis consisted of only *relative efficacy* comparisons of CBTp versus other interventions and therefore did not

compare CBTp or other psychological interventions to standard care in *absolute efficacy* comparisons. Comparison against standard care may provide further insight into the impact of moderator variables therefore this limitation acknowledges that conclusions from IPD are incomplete.

Also limiting to the wider validity of results is the relatively narrow focus of the meta-analytic studies in this thesis upon psychotic symptoms. While psychotic symptoms have been demonstrated as amenable to change and remain an important outcome measure in psychosis, many psychological interventions to not target symptom reduction as their primary outcome. For example, distress regarding voices is often prioritised in CBTp as opposed to positive symptom reduction per se.[44, 45] A narrow symptom-based focus also provides limited understanding of broader recovery in psychosis.

A final limitation is the acknowledgement that the comparative meta-analysis in **chapter 2** contains one study that should have been excluded due to implementing consecutive allocation of patients rather than a fully randomised design. The impact of this erroneous inclusion was however limited since this trial was omitted in more stringent sensitivity analyses via the risk of bias assessment.[43]

Future research

As indicated, there is great potential in further meta-analytic research with IPD. A comprehensive IPD meta-analysis that attempts to source data on all forms of RCT on psychological interventions for psychosis is warranted, although it should be acknowledged that obtaining all available RCTs presents challenges. Building a

comprehensive IPD database would allow closer examination of potential moderators of treatment outcome to extend the exploratory analyses included in **chapter 5**. Examination of such moderators provides the possibility that the impact of individual patient characteristics or experiences can be used to maximise the benefit of intervention and may help tailor interventions and services to specific groups. Collaboration between diverse research groups is essential in facilitating IPD database building, therefore the first steps toward allowing such research to flourish would involve developing appropriate networks and data sharing agreements.

A further future development would be the supplementation of the cumulative meta-analysis methodology applied in **chapter 4** to include follow up data. This update would help determine whether the *sufficient* and *stable* effects demonstrated were also durable. Furthermore, the application of cumulative meta-analysis methodology to a wider set of outcomes including broader positive, negative and general symptoms alongside other interventions such as social skills training and cognitive remediation would also benefit the field. Future meta-analytic work may also develop to better cover alternative outcome measures such as distress about voices or recovery-oriented measures.
Similarly, since the network meta-analysis included only total symptoms there is scope for integration of wider psychosis-related outcome measures including the broad categories of positive and negative symptoms alongside (depending on availability) more specific outcomes such as insight, distress about delusions, conviction in delusions or wider recovery-oriented outcomes.

Finally, it should be emphasised again that since the evidence base for CBTp has been demonstrated as *sufficient* and *stable,* the key focus of empirical research should be

oriented toward the development of new or improved approaches rather than perpetual examination of generic CBTp. Innovative recent developments included in the cumulative meta-analysis in **chapter 4** include interventions utilising virtual-reality methods (VR-CBTp)[38–40] and culturally-adapted CBTp.[41] The development of novel models of treatment that build on existing CBTp methods may allow effective use of often scarce resources. Similarly, there is the opportunity to implement factorial design in randomised trials in order to provide clearer insight into the effective elements and mechanisms at play in interventions such as CBTp, social skills training and cognitive remediation.[34] Alongside providing the opportunity for greater understanding and improved efficiency of interventions, examining which treatment elements are most effective may also help provide insight into the treatment response of specific psychosis sequelae themselves. This may in turn help improve theoretical understanding of the diagnosis and the responsiveness of specific presentations.

Final words

The beginning of the 2020s marks an important point in the historical development of psychological interventions for psychosis. Despite a controversial and at times brutal history, in many parts of the world those who suffer from psychosis have access to humane, scientifically developed psychological methods of intervention that have been demonstrated as efficacious in reducing its symptoms. While the research included in this thesis demonstrates efficacy of these interventions, the challenge now lies in widening access to these interventions while continuing to further develop efficient, cost-effective interventions that maintain or improve the beneficial effects that have been demonstrated. While this thesis has demonstrated the efficacy of psychological interventions for

psychosis from a scientific perspective, developing broader clinical applicability and cultural trust in these interventions worldwide remains of high importance for the field.

Table 1: *Author contribution to articles included in thesis manuscript*

Chapter & study topic	**Author contribution**
Chapter 2: Comparative meta-analysis	Primary investigator; design, data collection, analysis and write-up
Chapter 3: Network meta-analysis	Contribution of large dataset from previous meta-analysis and manuscript review only
Chapter 4: Cumulative meta-analysis	Primary investigator; design, data collection, analysis and write-up
Chapter 5: IPD meta-analysis	Primary investigator; design, data collection, analysis and write-up
Chapter 6: RCT of secondary data	Primary investigator; design, data collection, analysis and write-up

Chapter 8

Summary

Background

Psychological interventions for psychosis have a long and controversial history. Accumulating evidence over the past two to three decades for cognitive behavioural therapy for psychosis (CBTp) has challenged the traditional dominance of psychiatric, medical thinking in which psychosis is considered exclusively as an illness that requires medical treatment rather than psychological intervention. The challenge that psychological interventions pose to the established order has led to debate regarding the effectiveness of CBTp and whether or not it should be widely implemented in clinical practice.

Overview of research

This thesis consists of five studies investigating the effects of psychological interventions for psychosis patients. Each study utilises a different methodology allowing a variety conclusions to be drawn. **Chapter 1** provides a general introduction to the topic, including the background and history of psychological interventions for psychosis and their development in context to the dominant medical model, alongside an overview of the current evidence for psychological interventions. The critical questions that this thesis aims to address are also introduced.

Four of the five studies included in this thesis use meta-analytical methods. Meta-analysis is a statistical procedure that allows the comparison of multiple existing published studies to provide an overall estimate. When conducted carefully, meta-analyses can provide more information than individual trials alone and forms the basis of most guidelines on healthcare interventions. Meta-analyses typically include randomised controlled trials

(RCTs), which are scientific studies testing interventions against control conditions. These RCTs are conducted under strict conditions to improve the validity of results. The final study in this thesis uses RCT methodology to test a brief intervention. A general discussion is then provided which considers the implications of the findings alongside strengths, weaknesses and suggestions for future research.

Summary of research

Chapter 2 provides a comparative meta-analysis of psychological interventions, which includes any major form of psychological interventions for psychosis for which there was sufficient available research comparing them against other interventions to qualify. The meta-analysis therefore included randomised controlled trials on cognitive-behavioural therapy for psychosis (CBTp), social skills training, cognitive remediation, psycho-education, supportive therapy and befriending. A systematic search was conducted of four key databases resulting in the selection of 48 RCTs including 3,295 participants with psychosis. The data from all RCTs was analysed to pool the effect size from each study, which provided an aggregated statistic for each comparison. The quality of the RCTs was also assessed and the results of this assessment were used in further analyses to ensure the validity of results. Results showed that CBTp was more beneficial than other interventions for positive symptoms (which include key psychosis symptoms such as hallucinations and delusions) while social skills training was more beneficial for negative symptoms (which include apathy and lack of motivation). Cognitive remediation also showed a beneficial effect for overall symptoms, as did CBTp, although these findings did not survive the extra 'sensitivity analyses' we conducted based on methodological

quality of the included RCTs. Based on these results, it was concluded that there are small but reliable differences between psychological interventions for psychosis.

Chapter 3 provides a network meta-analysis focused on the impact of psychological interventions on psychotic symptoms. Network meta-analysis is an alternative methodology which allows researchers to draw statistical conclusions not only from direct comparisons between interventions but also indirect evidence using the network model. A systematic search was conducted resulting in the inclusion of 90 RCTs and 8,440 randomised participants with psychosis. Network meta-analysis was used to examine direct and indirect evidence for 'total symptoms' of psychosis, which is an overall measure including all relevant psychotic symptoms. Study quality was again assessed to help ensure validity of results. Results demonstrated that psychological interventions were of significant benefit compared to control groups. Mindfulness-based psycho-education was shown as the intervention most likely to reduce total symptoms. However, all included RCTs for this intervention were from China, meaning that future research investigating the efficacy of mindfulness-based psycho-education in a variety of cultural contexts may help determine whether these findings generalise to other international settings.

While the previous chapters apply conventional meta-analytic techniques, **chapter 4** provides a cumulative meta-analysis investigating the impact of individualised, case-formulation based CBTp on hallucinations and delusions, which are the key features of positive symptoms. Case formulation refers to an essential technique in CBT that helps to individualise a patient's treatment and allows a close conceptual link between research and clinical practice. Cumulative meta-analysis is a novel technique that, alongside

providing information on the effectiveness of a treatment, can also help us determine whether the evidence base for that treatment is *sufficient* and *stable*. A systematic search resulted in the inclusion of 35 RCTs and 2407 participants with psychosis. Meta-analyses were conducted and study quality was again assessed to help determine the validity of results. Results demonstrated that the evidence base for CBTp has been sufficient and stable since 2016 for hallucinations and 2015 for delusions. CBTp was demonstrated as beneficial for hallucinations compared to any control, treatment as usual and active controls. For delusions, CBTp was beneficial when compared to any control and treatment as usual, but did not demonstrate significant benefit against active controls although there were a limited number of RCTs included in this comparison, which may limit validity. The effects of CBTp were also shown as stronger when case-formulation was used and also when the primary focus of the study was the reduction of hallucinations or delusions instead of other outcomes. The fact that the evidence for CBTp has been shown as sufficient and stable means that there may be limited worth in continuing to spend vital resources on similar RCTs testing 'generic' CBTp and resources may better be directed into developing new or improved variants.

Chapter 5 utilises another novel meta-analytic technique allowing the application of individual-participant data (IPD). In this approach, the original databases from published RCTs are requested from authors meaning that the individual data for each participant can be used in analyses rather than relying on the summary effect size data available in published manuscripts. The IPD approach allows a more precise estimation of effects and allows the investigation of 'moderator' variables, which refer to demographic or clinical variables at the individual level that may impact who benefits most from treatment. This study was initially developed as follow-on from chapter 1 and attempted to source

databases all the included CBTp RCTs alongside conducting a new systematic search to determine whether any new RCTs were eligible. After contacting relevant authors, databases for 14 of 23 eligible RCTs were included resulting in the data for 898 participants with psychosis being included. CBTp was demonstrated as beneficial for total psychotic symptoms and general symptoms, although not for positive symptoms. This finding contrasts results from the previous chapters, although may be explained by the exclusion of a proportion of eligible RCTs due to failure to obtain these databases from original authors. The moderator analysis did not show any demographic or clinical variables as influencing treatment outcome although the number of therapy sessions a patient received had impact on outcome. The results of this IPD meta-analysis suggest that patient characteristics, including severity of psychotic symptoms, do not significantly influence treatment outcome while sufficient 'dosage' of CBTp is important.

Finally, **chapter 6** reports on a secondary analysis of an RCT conducted in a clinical setting in the UK National Health Service (NHS). This study examined the effects of a brief psychological intervention aiming to address overconfidence in perceptual decision-making among patients diagnosed with psychosis. 31 patients aged 16-65 were randomly assigned to one of two groups; 1) a brief intervention based on 'metacognitive training' which aimed to address a common thinking bias called the "jumping-to-conclusions" bias, or 2) an attention-control condition designed to account for therapist time and attention. Participants completed outcome measures assessing overconfidence and the "jumping-to-conclusions" bias. Results demonstrated that those receiving meta-cognitive training experienced a significant reduction in overconfident reasoning when compared to those receiving the control condition. This RCT provides preliminary evidence that meta-cognitive training is a worthwhile method by which to address overconfident reasoning in

psychosis. There were however methodological limitations of this RCT due to limited resources. A larger RCT with stronger methodology is therefore warranted.

Conclusions

When considered collectively, the findings from the body of research included in this thesis provide strong evidence for the validity of psychological interventions for psychosis. The evidence base for CBTp was demonstrated as *sufficient and stable,* while social skills training was demonstrated as an effective intervention for negative symptoms. The results for CBTp are important in the on-going debate about effectiveness and whether or not it has been "oversold." In light of the accumulated evidence, future research on psychological interventions for psychosis may best focus on the development of new or improved approaches and move on from the debate on whether psychological intervention "works" or not.

Overzicht van onderzoek

Dit proefschrift bestaat uit vijf studies die de effecten van psychologische interventies voor psychosepatiënten onderzoeken. Elke studie maakt gebruik van een verschillende methodologie waardoor verschillende conclusies kunnen worden getrokken. Hoofdstuk 1 geeft een algemene inleiding tot het onderwerp, inclusief de achtergrond en geschiedenis van psychologische interventies voor psychose en hun ontwikkeling in de context van het dominante medische model, naast een overzicht van het huidige bewijs voor psychologische interventies. De kritische vragen die dit proefschrift wil beantwoorden, worden ook geïntroduceerd.

Vier van de vijf studies die in dit proefschrift zijn opgenomen, gebruiken meta-analytische methoden. Meta-analyse is een statistische procedure waarmee meerdere bestaande gepubliceerde onderzoeken kunnen worden vergeleken om een algemene schatting te geven. Als ze zorgvuldig worden uitgevoerd, kunnen meta-analyses meer informatie opleveren dan individuele studies alleen en vormen ze de basis van de meeste richtlijnen voor interventies in de gezondheidszorg. Meta-analyses omvatten doorgaans *randomised controlled trials* (RCT's). Dit type studie test het effect van een interventie door deze af te zetten tegen een controleconditie en wordt uitgevoerd onder strikte voorwaarden om de validiteit van de resultaten te waarborgen. De eerste vier studies in dit proefschrift zijn meta-analyses en de laatste studie gebruikt RCT-methodologie om een korte interventie te testen. Vervolgens wordt een algemene discussie gegeven waarin de implicaties van de bevindingen worden besproken, naast de sterke en zwakke punten en suggesties voor toekomstig onderzoek.

Samenvatting van onderzoek

Hoofdstuk 2 beschrijft een vergelijkende meta-analyse waarmee zes vormen van psychologische interventies gericht op psychose worden vergeleken. De meta-analyse omvatte RCT's naar CGTp, sociale vaardigheidstraining (SOVA), cognitieve remediëring, psycho-educatie, ondersteunende therapie en *befriending* (vergelijkbaar met Maatjesprojecten in Nederland). De zoektocht in vier belangrijke databases resulteerde in een selectie van 48 RCT's met 3295 deelnemers met psychose. De gegevens van alle RCT's werden geanalyseerd om de effectgrootte van elk studie samen te voegen, wat een geaggregeerde statistiek voor elke vergelijking opleverde. Vervolgens werd de kwaliteit van de RCT's beoordeeld om daarmee de validiteit van de meta-analytische resultaten te kunnen beoordelen. De meta-analyse toonde aan dat CGTp beter was dan andere interventies voor de behandeling van positieve symptomen (waaronder belangrijke psychosesymptomen zoals hallucinaties en wanen), terwijl sociale vaardigheidstraining beter was voor negatieve symptomen (waaronder apathie en gebrek aan motivatie). Cognitieve remediëring toonde ook een gunstig effect op algemene symptomen, net als CGTp, hoewel deze bevindingen de extra sensitiviteitsanalyses die we hebben uitgevoerd op basis van de methodologische kwaliteit van de geïncludeerde RCT's niet overleefden. Op basis van deze resultaten werd geconcludeerd dat er kleine maar betrouwbare verschillen zijn tussen psychologische interventies voor psychose.

Hoofdstuk 3 beschrijft een netwerk meta-analyse gericht op psychologische interventies voor psychose. Netwerk meta-analyse is een alternatieve methodologie waarmee onderzoekers statistische conclusies kunnen trekken, niet alleen uit

directe vergelijkingen tussen interventies, maar ook uit indirect bewijs met behulp van het netwerkmodel. Zoals hierboven werd een systematische zoektocht uitgevoerd die resulteerde in de inclusie van 90 RCT's en 8440 deelnemers met psychose. Netwerk meta-analyse werd gebruikt om direct en indirect bewijs voor 'totale symptomen' van psychose te onderzoeken. De studiekwaliteit werd opnieuw beoordeeld om de validiteit van de resultaten te begrijpen. Resultaten toonden aan dat psychologische interventies zijn meer effectief in vergelijking met controlegroepen. Mindfulness-gebaseerde psychoeducatie werd getoond als de interventie die het meest waarschijnlijk de totale symptomen vermindert. Alle RCT's voor deze interventie waren in China gepubliceerd, wat betekent dat toekomstig onderzoek naar mindfulness-gebaseerde psycho-educatie in verschillende culturele contexten kan helpen bepalen of deze bevindingen naar andere internationale omgevingen zou generaliseren.

Terwijl de vorige hoofdstukken conventionele meta-analytische technieken toepassen, beschrijft **hoofdstuk 4** een cumulatieve meta-analyse die de impact van geïndividualiseerde, casusformulering-gebaseerde CGTp op hallucinaties en wanen onderzoekt. Casusformulering verwijst naar een essentiële techniek in CGT die helpt de behandeling van een patiënt te individualiseren en een nauwe conceptuele link tussen onderzoek en klinische praktijk mogelijk maakt. Cumulatieve meta-analyse is een nieuwe techniek die ons, naast het verstrekken van informatie over de effectiviteit van een behandeling, ook kan helpen bepalen of het bewijs voor die behandeling voldoende en stabiel is. Een systematische zoektocht resulteerde in de inclusie van 35 RCT's en 2407 deelnemers met psychose. Er werden meta-analyses uitgevoerd en de kwaliteit van het onderzoek werd opnieuw beoordeeld om de

validiteit van de resultaten te helpen bepalen. De resultaten toonden aan dat de bewijsbasis voor CGTp sinds 2016 “afdoende” en “stabiel” is voor hallucinaties en sinds 2015 voor wanen. Van CGTp werd aangetoond dat het effectiever is in de behandeling van hallucinaties in vergelijking met elke controle, standaard zorg en actieve controles. Voor wanen was CGTp beter in vergelijking met de standaard zorg, maar vertoonde geen significant voordeel ten opzichte van actieve controles, hoewel er een beperkt aantal RCT's in deze vergelijking was geïncludeerd, wat de geldigheid kan beperken. De effecten van CGTp bleken ook sterker te zijn wanneer casusformulering werd gebruikt en als de primaire focus van het onderzoek de vermindering van hallucinaties of wanen was in plaats van andere doelen. Het feit dat het bewijs voor CGTp is aangetoond als afdoende en stabiel, betekent dat het van beperkte waarde is om essentiële middelen te blijven besteden aan RCT's die de effectiviteit van generieke CBTp testen. Deze middelen kunnen beter worden gericht op het ontwikkelen van nieuwe of verbeterde varianten.

Hoofdstuk 5 maakt gebruik van een andere nieuwe meta-analytische techniek die de toepassing van gegevens van individuele deelnemers (IPD) mogelijk maakt. In deze benadering worden de originele databases van gepubliceerde RCT's opgevraagd bij de auteurs van geselecteerde studies. Dit zorgt ervoor dat de individuele data van elke deelnemer kunnen worden gebruikt in de analyses in plaats van te vertrouwen op de samenvattende effect groottes die beschikbaar zijn in gepubliceerde manuscripten. De IPD-benadering maakt een nauwkeurigere schatting van effecten mogelijk en maakt het mogelijke moderatoren te onderzoeken, die verwijzen naar demografische of klinische variabelen die van invloed kunnen zijn op wie het meeste baat heeft bij behandeling. Deze studie is een

vervolg op de studie in hoofdstuk 2. Daarom zijn dezelfde CGTp RCT's opgenomen in de huidige studie en is er een nieuwe systematische zoektocht uitgevoerd om te bepalen of er nieuwe RCT's in aanmerking kwamen. Na contact met relevante auteurs werden databases voor 14 van de 23 in aanmerking komende RCT's geïncludeerd, waardoor de data van 898 deelnemers met psychose werden gebruikt. Uit de resultaten blijkt dat CGTp effectiever is voor de behandeling van psychose symptomen en de bredere algemene psychiatrische symptomen, behalve voor positieve symptomen. Deze bevinding staat in contrast met de resultaten van de voorgaande hoofdstukken, hoewel dit kan worden verklaard door de exclusie van een deel van de geselecteerde RCT's omdat deze databases niet van de oorspronkelijke auteurs zijn verkregen. Uit de moderatie-analyse bleek dat demografische of klinische variabelen de uitkomst van de behandeling niet beïnvloeden maar dat het aantal therapiesessies dat een patiënt ontving wel een impact heeft op de uitkomst. De resultaten van deze IPD-meta-analyse suggereren dat patiëntkenmerken, waaronder de ernst van psychose symptomen, de behandelresultaten niet significant beïnvloeden, terwijl voldoende dosering van het aantal behandelsessies bij CGTp wel belangrijk is.

Tenslotte rapporteert **hoofdstuk 6** over een secundair analyse van een RCT uitgevoerd in een klinische setting in de UK National Health Service (NHS). Deze studie onderzocht de effecten van een korte psychologische interventie voor patiënten met een psychotische stoornis, met als doel om te zelfverzekerde perceptuele besluitvorming te verminderen. 31 patiënten van 16-65 jaar werden willekeurig toegewezen aan een van de twee groepen; 1) een korte interventie genaamd 'metacognitieve training die gericht is op het aanpakken van een algemene

cognitieve bias, de '*jumping to conclusions'*-bias, of 2) een aandachtscontroleconditie die is ontworpen om te controleren voor de tijd en aandacht van de therapeut. De deelnemers voltooiden uitkomstmaten om te zelfverzekerde perceptuele besluitvorming en de JTC-bias te meten. De resultaten toonden aan dat degenen die meta-cognitieve training kregen beduidende vermindering in te zelfverzekerde besluitvorming in vergelijking met degenen in de controleconditie. Deze RCT levert daarom preliminaire bewijs voor dat het verminderen van de JTC bias via metacognitieve training een effectieve methode is om te zelfverzekerde perceptuele besluitvorming in psychose te verminderen. Bij het interpreteren van de resultaten moeten methodologische beperkingen van deze RCT in acht worden genomen. Een grotere RCT met een sterkere methodologie is daarom gerechtvaardigd.

Conclusies

Al met al leveren de bevindingen van de onderzoeksgroep die in dit proefschrift zijn opgenomen sterk bewijs voor de validiteit van psychologische interventies voor psychose. De bewijsbasis voor CGTp werd aangetoond als afdoende en stabiel, terwijl SOVA werd aangetoond als een effectieve interventie voor negatieve symptomen. De resultaten voor CGTp zijn belangrijk in het lopende debat over effectiviteit en of het al dan niet 'oversold' is. In het licht van het verzamelde bewijs kan toekomstig onderzoek naar psychologische interventies voor psychose zich het best richten op de ontwikkeling van nieuwe of verbeterde benaderingen in plaats van verder te gaan met het debat over de vraag of psychologische interventie 'werken' of niet.

Appendices

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Chapter 1

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Appendix 2. Components of 1-hour MTC-JTC intervention

1. An introduction to the jumping-to-conclusions bias in psychosis
2. Inferences without 100% proof; examples from daily life (2 examples)
3. Jumping-to-conclusions "in action;" examples from politics and medicine of the pitfalls of using jumping-to-conclusions in decision-making (4 examples)
4. How jumping-to-conclusions promotes misinterpretation; discussion and examples including a worksheet for personal experiences and alternative interpretation
5. Jumping-to-conclusion and it's role in conspiracy theories; illustration via the moon landing conspiracy theory
6. Worksheet exercise; providing evidence for and against personal delusional beliefs including conviction rating
7. Picture-identification tasks (3 tasks); participants were required to identify all possible interpretations of images as progressive detail was revealed and state their confidence in their interpretation
8. Face illusion tasks (3 tasks); participants were required to identify all details or alternative interpretations when presented with images, for example the old woman/young woman/old man face illusion
9. Scene identification from cut-out (4 tasks); four tasks in which a cut-out image from a larger scene was provided from which participants were required to infer the correct wider context from four options using evidence in the picture and state confidence
10. Misfits task (5 tasks): presentation of five classic paintings in which participants were required to identify the correct title from four options based upon clues within the painting and state confidence
11. Summary of jumping-to-conclusions session and suggested tactics

Chapter 7

General discussion

Introduction

This thesis attempted to help further develop the knowledge and evidence base for psychological interventions for psychosis. A key objective was the provision of a comprehensive and contemporary overview of the meta-analytic evidence for psychosocial interventions for psychosis, including a deliberate focus on methodological stringency to help estimate the quality of the included outcome research and assist confidence in the validity of findings. Related to this objective was the aim to use these findings to conclude on the current 'state of the evidence' for psychological interventions in light of on-going debate regarding their efficacy.[1] The inclusion of novel methodological techniques and approaches allowed the consideration of important contextual questions. Firstly, the application of cumulative meta-analysis provided the possibility to assess the development of the evidence base from a longitudinal perspective and comment on stability and sufficiency. Secondly, the exploratory application of individual-participant data meta-analysis allowed a preliminary investigation of what factors influence treatment outcome. Similarly, the inclusion of network meta-analysis methodology allowed evidence to be drawn from a broad range of indirect comparisons alongside those direct comparisons examined in conventional meta-analysis. Finally, the application of a brief psychological intervention to improve overconfident perceptual decision-making among psychosis patients allowed investigation of the potential for psychological interventions to improve a common deficit in psychosis patients.

This general discussion section will begin with a brief recap on the key findings of the studies included in the previous chapters before focusing on the broader implications of these findings from both research and clinical perspectives. The strengths and limitations of this thesis will then be considered before outlining relevant potential developments for

future research. Finally, overall conclusions will be drawn by utilising the somewhat unique opportunity provided by this compilation of psychosis intervention outcome research.

Summary of the main findings

CBTp outperforms other psychological intervention for positive symptoms

Chapter 2 reported on a comparative meta-analysis of six psychological interventions for psychosis, namely CBTp, cognitive remediation, psycho-education, supportive counselling and befriending. This review demonstrated that CBTp consistently outperformed other psychological interventions in reducing the positive symptoms of psychosis by a small effect size of $g = 0.16$ when all eligible RCTs were included and $g = 0.14$ when including only RCTs with minimal risk of bias. It should be noted that this effect size denotes *relative efficacy* (i.e. comparison between active intervention conditions) whereas *absolute efficacy* effect sizes compared to treatment-as-usual are typically of higher magnitude. This was demonstrated in **chapter 4** in our meta-analysis investigating the effects of CBTp on the more specific positive symptom outcome measures of hallucinations and delusions. CBTp was consistently beneficial for hallucinations across comparisons against treatment as usual and active interventions. Effect sizes ranged from $g = 0.3$ for broad 'inclusive' comparisons in which all eligible trials were included, to a high of $g = 0.6$ when including only case-formulation based CBTp trials with primary outcome focus assessed as having minimal risk of bias. CBTp was also consistently beneficial versus treatment as usual for delusions and when including any form of control for delusions with effect sizes ranging from $g = 0.3 – 0.4$. These effect sizes were robust when including only trials with minimal bias risk, although

were non-significant in comparisons against active interventions, which suffered from limited power.

SST outperforms other psychological intervention for negative symptoms

The comparative meta-analysis in **chapter 2** also demonstrated consistent superiority of social skills training compared to other psychological interventions for negative symptoms, with effect sizes ranging from $g = 0.3$ when including all eligible trials and $g = 0.6$ when reducing risk of bias.

The evidence is less clear regarding the effects of psychological intervention on 'overall' psychotic symptoms

While the comparative meta-analysis in **chapter 2** demonstrated superiority of CBTp for overall symptoms in the less stringent comparisons, no significant effect was demonstrated when removing trials assessed as having risk of bias. The network meta-analysis in **chapter 3** demonstrated superiority of mindfulness-based psycho-education compared to other interventions for overall symptoms, although all studies in this comparison originated from one country and therefore leads to critical questions regarding cultural generalisability and broader validity.

The evidence base for CBTp for positive symptoms (hallucinations and delusions) is stable and sufficient

The inclusion of cumulative meta-analysis procedures in **chapter 4** as part of the meta-analysis investigating the effects of CBTp in reducing hallucinations and delusions demonstrated that, according to the procedures set out by Muellerleile and Mullen,[2] the evidence base for CBTp in reducing hallucinations has been *sufficient* and *stable* since

2016. This effect was consistent when considering only trials with minimal risk of bias. The evidence base for delusions was shown as sufficient and stable since 2015, although when considering only trials with minimal risk of bias sufficiency and stability was demonstrated in 2017.

Exploratory utilisation of individual-participant data in meta-analysis does not indicate that demographic or clinical characteristics influence treatment outcome

Conventional meta-analysis methodology does not allow the investigation of moderator variables that vary at the participant level on treatment outcome. This therefore means that it is not possible to determine which individual patient profiles most benefit from particular interventions. **Chapter 5** presented the first individual-participant data meta-analysis on psychological interventions for psychosis outcome trials, which provides the best-available statistical power to investigate the impact of demographic and clinical variables on psychosis patient treatment outcome. Results suggested that demographic and clinical variables do not significantly impact treatment outcome although the number of sessions (or "dosage" of CBTp) significantly moderates treatment outcome.

Brief psychological intervention has the potential to improve overconfident perceptual decision-making in psychosis patients

Chapter 6 reported the results of a randomised controlled trial assessing a brief metacognitive training intervention targeting the "jumping-to-conclusions" reasoning bias as a means of improving overconfident perceptual decision-making among psychosis patients. Results demonstrated that the brief intervention was significantly beneficial in reducing overconfidence ($d = 0.97$) alongside the "jumping to conclusions bias" ($d = 1.16$) although the latter comparison violated the necessary data assumptions for

ANCOVA. A non-parametric sensitivity analysis was applied post-hoc and demonstrated consistent results. Limitations in this trial mean results should be interpreted as preliminary.

Discussion

Efficacy of CBTp

When considered broadly, the research included in this thesis provides clear support for the premise that psychological intervention is a valid treatment option for psychosis patients. Discussion of psychological interventions for psychosis in contemporary terms most often refers to CBTp or its variants and derivatives. Despite the widespread implementation of CBTp in European healthcare systems including the UK and the Netherlands, the premise that CBTp for psychosis "works" is not yet taken for granted due to the on-going debate regarding whether CBTp is in fact ineffective and has been "oversold."[1,3]

Importantly, the meta-analytical comparisons in **chapter 4** in which the effect of CBTp on hallucinations and delusions were examined address a key aspect of this debate. While one recent meta-analysis reported that the beneficial effects of CBTp specifically targeted toward positive symptoms were maintained when limiting inclusion to only blinded RCTs,[4] another, notably with broader overall study inclusion criteria, found no effect when including only blinded RCTs.[5] **Chapter 4** however reported that CBTp continued to demonstrate superiority when including only blinded RCTs both when all eligible RCTs were included and when including only RCTs implementing individualised case-

formulation with primary outcome focus. This finding was valid in both the hallucinations and delusions comparisons. These findings therefore add weight to the argument that CBTp is an effective means of reducing hallucinations and delusions and therefore positive symptoms. This premise is strengthened by the finding that the effects of CBTp were robust to various sensitivity analyses for blinding and methodological quality overall.

A potential explanation for diverging findings in comparison to previous negative meta-analytic studies or those which demonstrated a less reliable effect of CBTp[3, 5] may lie in study selection; the categorisation of the therapies delivered in RCTs can often be complex and controversial[1] as can the selection of outcome variables. Notably, the cumulative meta-analysis in **chapter 4** focused intentionally on hallucinations and delusions as outcome measures, alongside RCTs implementing case-formulation driven CBTp with the relevant symptoms as primary outcome. In this sense, the RCTs that were included utilised the form of CBTp designed most specifically to target the core positive symptoms of psychosis while other meta-analyses have included interventions such as cognitive-behavioural social skills training in the positive symptoms category,[5] despite such interventions not specifically targeting positive symptoms. Studies implementing case-formulation and primary outcome focus provided stronger effect sizes in sensitivity analysis in the cumulative meta-analysis. A further possible reason for diverging findings is statistical power, since as more RCTs have become available, the availability of RCTs especially in the more stringent sensitivity bias categories for risk of bias or primary outcome focus has improved. The ability to detect effects in such categories may therefore be improved in the more recent meta-analysis in **chapter 4**. Furthermore, previous negative meta-analyses[5,42] have focused primarily on assessor blinding in risk of

bias sensitivity analyses rather than employing the broader Cochrane risk of bias assessments which are accepted as standard. This may also have impact on results.

Furthermore, the cumulative meta-analysis in **chapter 4** demonstrates that the evidence base for CBTp for psychosis is *sufficient* and *stable* when measuring the effect on hallucinations and delusions. It can be hypothesised that broader measures of positive symptoms may also be approximated by this analysis, although cumulative techniques have not yet been applied to positive symptom outcomes such as the Positive and Negative Syndromes Scale (PANSS).[6] When considered alongside the finding of superiority of CBTp compared to other psychological interventions, this conclusion on the cumulative progression of the evidence base may mitigate reservations regarding the validity of CBTp.

Efficacy of other psychological interventions for psychosis

As a result of it's more widespread implementation in research and practice, the majority of meta-analytical findings in this thesis are in relation to CBTp. **Chapter 2** concluded through comparative meta-analysis that social skills training represents an efficacious means of reducing the negative symptoms of psychosis. Negative symptoms in psychosis are recognised as a key element of the psychopathology,[7] although there are comparatively fewer tailored intervention packages available attempting to reduce them. Negative symptoms have been a primary outcome focus within a small number of CBTp RCTs[8] and quasi-experimental studies.[9] There also exist cognitive-behavioral social skills training (CB-SST) trials integrating the approaches.[10,11] The further development of

interventions focusing on negative symptoms has the potential to influence significant improvement in quality of life of many psychosis patients.

This thesis only provided brief coverage of cognitive remediation, psycho-education and befriending in the comparative meta-analysis in **chapter 2**. Supportive counselling was included in a number of comparisons throughout the included studies although primarily as a comparative control accounting for 'common factors,' with no specific focus on its own merits out with **chapter 2**. This thesis therefore adds little to the understanding of these interventions other than the demonstration of their relative inferiority to CBTp for positive symptoms and SST for negative symptoms, although cognitive remediation did demonstrate a significant effect small effect (g=0.2) versus other interventions pooled. This effect was not robust against sensitivity analyses for risk of bias, but due to the risk of Type 2 error as a consequence of reduced power it is too early to rule out efficacy. Cognitive remediation is however well studied in comparison with the other aforementioned interventions and boasts a considerable meta-analytical evidence base. Cognitive remediation has been demonstrated as an efficacious intervention for negative symptoms; a recent network meta-analysis focusing specifically on this intervention demonstrated a similar pattern to many comparisons in this thesis in that effect sizes increased (g = 0.4) when including only trials with more robust methodology.[12] In combination with the above finding, the results from the network meta-analysis and other reviews[13–15] therefore bolster confidence in this intervention. There is also meta-analytic evidence that social cognition training, commonly a variant of cognitive remediation, may improve social performance although no significant benefit was found for psychotic symptoms.[16]

Also noteworthy is the omission of some well-known forms of psychological intervention for psychosis from this thesis, including family therapy,[17] psychodynamic therapy[18] and art therapy.[19] The reason for omission was our commitment to producing meta-analytical evidence and drawing conclusions in a firmly evidence-based manner, rather than drawing conclusions from a) individual randomised controlled trials, which have more potential to suffer from Type I "false positive" errors, or b) running low powered meta-analysis with an insufficient number of RCTs and therefore providing results of limited validity.[20] The lack of RCTs comparing these forms of intervention against other active treatments therefore resulted in their exclusion from the comparative efficacy meta-analysis in **chapter 2**. The network meta-analysis in **chapter 3** suggested that family therapy was, when including direct and indirect comparisons, one of the least effective interventions for total symptoms psychosis. Family therapy has previously indicated favourable meta-analytic results in reducing relapse when compared to any form of control[21] and continues to be recommended in the UK National Institute for Clinical and Care Excellence (NICE) guidelines[22] while to date no detailed meta-analytical evidence exists for art therapy or psychodynamic therapy.

Related topics

Moderators of outcome in psychological interventions for psychosis

Although the individual-participant data meta-analysis in **chapter 5** concluded that no demographic or clinical variables moderated treatment outcome, it must be recognised that this evidence is at present preliminary. The moderator analysis was conducted from an exploratory angle, which introduces potential bias due to the absence of clearly defined

hypothesis testing. Also of note is that this was a relative efficacy meta-analysis as opposed to an absolute efficacy meta-analysis, therefore examination of moderators against all forms of control conditions (including treatment as usual) has the potential to find different results.

The Dodo verdict

The meta-analytic reviews contained in this thesis most commonly provide support for effects of specific factors as operating in psychological interventions in psychosis, although it is too early to comment conclusively on whether the effects of the interventions assessed are achieved primarily by common or specific factors.[23] **Chapters 2 and 4** demonstrated that when compared to control conditions specifically designed to account for the common factors present in all talking therapies (most commonly supportive counselling without the 'specific' ingredients of any psychological model), CBTp was superior in reducing positive symptoms (g = 0.23 versus supportive counselling) and hallucinations (g = 0.3-0.4 versus active treatments). This effect was not however observed for delusions. It is possible that the absence of an effect for delusions may be attributed to limited power; the comparison in which CBTp was compared to active interventions in trials with minimal bias risk contained only three RCTs. However, one of Wampold's[23] key arguments is that outcome research, via the presence of various research biases, often inflates true effect sizes therefore despite the effects noted above, the evidence provided remains preliminary.

An attempt was made to address these biases within the scope of the included reviews. The effects of publication bias were investigated using the appropriate analyses; minimal

impact on results was noted. **Chapter 2** also included an attempt to assess the impact of *researcher allegiance,* another key consideration noted by Wampold. What is often however problematic with such comparisons is that in meta-analyses which often already suffer from limited RCT availability and hence low power, dichotomising RCTs into those demonstrating researcher allegiance and those not further limits power and risks Type II errors. This is demonstrated in **chapter 1** in the researcher allegiance sensitivity analysis for positive symptoms in which the non-allegiance comparison contained only three RCTs, which falls below the minimum recommended for meaningful meta-analytic comparisons.[20] Due to such on-going issues with power, alongside the absence of complex and costly dismantling studies, definitive comment on whether psychological interventions for psychosis have their key impact via specific effects awaits further clarification.

Overconfidence in perceptual decision-making in psychosis

The preliminary finding in **chapter 6** that a brief adapted metacognitive training intervention addressing the "jumping-to-conclusions" bias improved overconfident decision-making in psychosis patients represents an interesting developmental step in this area. The potential to address cognitive biases and impaired decision making in a brief, modular manner has the potential for implementation in acute settings in which it is challenging to provide lengthier, more comprehensive psychological interventions for psychosis.

Implications for clinical practice

The assessment of the evidence base for CBTp for hallucinations and delusions as *stable* and *sufficient* helps counter the previously noted doubts regarding the value of the widespread implementation in mental health services, for example in the UK National Health Service (NHS). It has been recommended that CBTp is offered as a treatment option for all patients diagnosed with psychosis[26] although in practice access to CBTp for all patients has been reported as lacking.[27–29] The findings add weight to the existing recommendation of CBTp by, among others, NICE (UK), the US National Guidelines Clearing House (NGC)[30] and the Dutch multidisciplinary guidelines for schizophrenia.[31] Findings from cumulative meta-analysis in **chapter 4** counter those utilised by the Cochrane Collaboration by providing robust evidence that CBTp is a worthy intervention for hallucinations and delusions and therefore is suitable for wide clinical implementation.

As previously discussed, **chapter 2** demonstrated that social skills training represents the best available psychological intervention for the negative symptoms of psychosis. There exists little clinical culture of social skills training provision in Europe (for example in the UK or the Netherlands) in comparison to the United States despite CBTp being comparatively widely implemented for positive symptoms. Attempts to further the implementation of social skills training in European clinical settings therefore has potential as a means of improving wider life functioning than a narrower positive symptoms focus. Intervention packages combining cognitive-behavioural and social skills methods already exist although primarily apply group[10] rather than individual[32] format. Adaptation of such programmes for a European context may be of benefit. The results from the cumulative meta-analysis suggest greater strength of individualised, case-formulation driven interventions when targeting positive symptoms although this may be

less valid for social skills training due to the potential impact of group sessions when targeting social skills and negative symptoms.

On a broader note, the various findings reported in this thesis firmly support the clinical application of psychological interventions for patients with psychosis. Most of the evidence presented is from RCTs in which psychological therapies have been provided primarily as adjunctive to anti-psychotic treatment, although there is initial evidence that CBTp is also efficacious in patients not taking medication.[33] These findings may help overcome some remaining scepticism in clinical psychiatry regarding psychological interventions.

Strengths

The research collated in this thesis has a number of collective strengths. A key strength shared by all the included studies is a commitment to utilising the best available methods to facilitate the contribution of reliable data to supplement the evidence base. This includes the utilisation of meta-analytic methods that capitalise on high-quality existing data from published randomised controlled trials in four of the studies alongside the implementation of a randomised controlled trial in the final study. Although alternatives to the standard randomised controlled trial have been developed including factorial approaches,[34] such trials are costly and currently rarely implemented in mental health research. The randomised controlled trial remains the conventional gold standard in assessing the efficacy of (mental) healthcare interventions.

A further related strength is the commitment undertaken to the careful assessment of methodological quality in the included research, alongside the utilisation of these assessments in sensitivity analyses to control for the potential effect of bias on outcome. Clear methods were developed and consistently implemented in all of the meta-analytic reviews included in this paper, which allowed the provision when possible of an effect size with minimal risk of bias due to exclusion of any RCTs in which risk of bias was demonstrated. These procedures help ensure the overall reliability and validity of the findings presented.

A final strength was the application of novel meta-analytical methods that provide an alternative perspective to that available in existing meta-analytic psychological therapy outcome research on psychosis, namely cumulative meta-analysis and individual-participant data meta-analysis. The inclusion in particular of cumulative meta-analysis methods allows a unique insight into the developmental stage of the evidence base.

Limitations

While the limitations of each individual contributory study are described within their respective chapters, it is relevant to consider the broader limitations of this body of research. One notable limitation is the relative lack of extended follow up data across the studies, both in meta-analytic comparisons and in the RCT. Furthermore, it was beyond the scope of the included RCT to include a follow up assessments due to time restrictions. This meant that the durability of the effects of the intervention was not assessed. Although CBTp has already been found as durable in both RCTs [35,36] and meta-analysis,[37]

this limitation means we cannot conclude whether the effects reported in the research included in this thesis were sustained in psychosis patients.

A further limitation regarding the pooling of effects in meta-analysis is the risk of comparing "apples and oranges," or in other words combining disparate interventions and outcomes across RCTs in a meaningless manner while interpreting the results of these comparisons as meaningful. In order to reduce the risk of such threats to validity in comparisons, heterogeneity between the included RCTs was assessed in all meta-analytic studies. Nevertheless, RCT selection and decisions upon comparisons in meta-analyses retain a degree of controversy due to different approaches between individual researchers and groups[1] since the human element of selection means that potential bias can be minimised but not wholly prevented. Similarly, there were additional sources of potential bias that were not assessed in all the included meta-analyses. Researcher allegiance- a source of potential bias discussed by Wampold[23] via which effect sizes risk being inflated in RCTs conducted by researchers who are invested in the intervention they are testing- was only assessed in **chapter 2**. Including additional such sensitivity analyses must always be balanced with loss of power in the relevant comparisons, which in itself may damage the validity of results. Nevertheless, the omission of researcher allegiance analyses in a proportion of the included meta-analytic research can be considered limiting. Furthermore, key limitations of the RCT in **chapter 6** included the therapist-therapy compound and lack of blinding, both of which may contribute to allowing researcher bias.

A further limitation is that the individual-participant data meta-analysis consisted of only *relative efficacy* comparisons of CBTp versus other interventions and therefore did not

compare CBTp or other psychological interventions to standard care in *absolute efficacy* comparisons. Comparison against standard care may provide further insight into the impact of moderator variables therefore this limitation acknowledges that conclusions from IPD are incomplete.

Also limiting to the wider validity of results is the relatively narrow focus of the meta-analytic studies in this thesis upon psychotic symptoms. While psychotic symptoms have been demonstrated as amenable to change and remain an important outcome measure in psychosis, many psychological interventions to not target symptom reduction as their primary outcome. For example, distress regarding voices is often prioritised in CBTp as opposed to positive symptom reduction per se.[44, 45] A narrow symptom-based focus also provides limited understanding of broader recovery in psychosis.

A final limitation is the acknowledgement that the comparative meta-analysis in **chapter 2** contains one study that should have been excluded due to implementing consecutive allocation of patients rather than a fully randomised design. The impact of this erroneous inclusion was however limited since this trial was omitted in more stringent sensitivity analyses via the risk of bias assessment.[43]

Future research

As indicated, there is great potential in further meta-analytic research with IPD. A comprehensive IPD meta-analysis that attempts to source data on all forms of RCT on psychological interventions for psychosis is warranted, although it should be acknowledged that obtaining all available RCTs presents challenges. Building a

comprehensive IPD database would allow closer examination of potential moderators of treatment outcome to extend the exploratory analyses included in **chapter 5**. Examination of such moderators provides the possibility that the impact of individual patient characteristics or experiences can be used to maximise the benefit of intervention and may help tailor interventions and services to specific groups. Collaboration between diverse research groups is essential in facilitating IPD database building, therefore the first steps toward allowing such research to flourish would involve developing appropriate networks and data sharing agreements.

A further future development would be the supplementation of the cumulative meta-analysis methodology applied in **chapter 4** to include follow up data. This update would help determine whether the *sufficient* and *stable* effects demonstrated were also durable. Furthermore, the application of cumulative meta-analysis methodology to a wider set of outcomes including broader positive, negative and general symptoms alongside other interventions such as social skills training and cognitive remediation would also benefit the field. Future meta-analytic work may also develop to better cover alternative outcome measures such as distress about voices or recovery-oriented measures.
Similarly, since the network meta-analysis included only total symptoms there is scope for integration of wider psychosis-related outcome measures including the broad categories of positive and negative symptoms alongside (depending on availability) more specific outcomes such as insight, distress about delusions, conviction in delusions or wider recovery-oriented outcomes.

Finally, it should be emphasised again that since the evidence base for CBTp has been demonstrated as *sufficient* and *stable,* the key focus of empirical research should be

oriented toward the development of new or improved approaches rather than perpetual examination of generic CBTp. Innovative recent developments included in the cumulative meta-analysis in **chapter 4** include interventions utilising virtual-reality methods (VR-CBTp)[38–40] and culturally-adapted CBTp.[41] The development of novel models of treatment that build on existing CBTp methods may allow effective use of often scarce resources. Similarly, there is the opportunity to implement factorial design in randomised trials in order to provide clearer insight into the effective elements and mechanisms at play in interventions such as CBTp, social skills training and cognitive remediation.[34] Alongside providing the opportunity for greater understanding and improved efficiency of interventions, examining which treatment elements are most effective may also help provide insight into the treatment response of specific psychosis sequelae themselves. This may in turn help improve theoretical understanding of the diagnosis and the responsiveness of specific presentations.

Final words

The beginning of the 2020s marks an important point in the historical development of psychological interventions for psychosis. Despite a controversial and at times brutal history, in many parts of the world those who suffer from psychosis have access to humane, scientifically developed psychological methods of intervention that have been demonstrated as efficacious in reducing its symptoms. While the research included in this thesis demonstrates efficacy of these interventions, the challenge now lies in widening access to these interventions while continuing to further develop efficient, cost-effective interventions that maintain or improve the beneficial effects that have been demonstrated. While this thesis has demonstrated the efficacy of psychological interventions for

psychosis from a scientific perspective, developing broader clinical applicability and cultural trust in these interventions worldwide remains of high importance for the field.

Table 1: *Author contribution to articles included in thesis manuscript*

Chapter & study topic	**Author contribution**
Chapter 2: Comparative meta-analysis	Primary investigator; design, data collection, analysis and write-up
Chapter 3: Network meta-analysis	Contribution of large dataset from previous meta-analysis and manuscript review only
Chapter 4: Cumulative meta-analysis	Primary investigator; design, data collection, analysis and write-up
Chapter 5: IPD meta-analysis	Primary investigator; design, data collection, analysis and write-up
Chapter 6: RCT of secondary data	Primary investigator; design, data collection, analysis and write-up

Chapter 8

Summary

Background

Psychological interventions for psychosis have a long and controversial history. Accumulating evidence over the past two to three decades for cognitive behavioural therapy for psychosis (CBTp) has challenged the traditional dominance of psychiatric, medical thinking in which psychosis is considered exclusively as an illness that requires medical treatment rather than psychological intervention. The challenge that psychological interventions pose to the established order has led to debate regarding the effectiveness of CBTp and whether or not it should be widely implemented in clinical practice.

Overview of research

This thesis consists of five studies investigating the effects of psychological interventions for psychosis patients. Each study utilises a different methodology allowing a variety conclusions to be drawn. **Chapter 1** provides a general introduction to the topic, including the background and history of psychological interventions for psychosis and their development in context to the dominant medical model, alongside an overview of the current evidence for psychological interventions. The critical questions that this thesis aims to address are also introduced.

Four of the five studies included in this thesis use meta-analytical methods. Meta-analysis is a statistical procedure that allows the comparison of multiple existing published studies to provide an overall estimate. When conducted carefully, meta-analyses can provide more information than individual trials alone and forms the basis of most guidelines on healthcare interventions. Meta-analyses typically include randomised controlled trials

(RCTs), which are scientific studies testing interventions against control conditions. These RCTs are conducted under strict conditions to improve the validity of results. The final study in this thesis uses RCT methodology to test a brief intervention. A general discussion is then provided which considers the implications of the findings alongside strengths, weaknesses and suggestions for future research.

Summary of research

Chapter 2 provides a comparative meta-analysis of psychological interventions, which includes any major form of psychological interventions for psychosis for which there was sufficient available research comparing them against other interventions to qualify. The meta-analysis therefore included randomised controlled trials on cognitive-behavioural therapy for psychosis (CBTp), social skills training, cognitive remediation, psycho-education, supportive therapy and befriending. A systematic search was conducted of four key databases resulting in the selection of 48 RCTs including 3,295 participants with psychosis. The data from all RCTs was analysed to pool the effect size from each study, which provided an aggregated statistic for each comparison. The quality of the RCTs was also assessed and the results of this assessment were used in further analyses to ensure the validity of results. Results showed that CBTp was more beneficial than other interventions for positive symptoms (which include key psychosis symptoms such as hallucinations and delusions) while social skills training was more beneficial for negative symptoms (which include apathy and lack of motivation). Cognitive remediation also showed a beneficial effect for overall symptoms, as did CBTp, although these findings did not survive the extra 'sensitivity analyses' we conducted based on methodological

quality of the included RCTs. Based on these results, it was concluded that there are small but reliable differences between psychological interventions for psychosis.

Chapter 3 provides a network meta-analysis focused on the impact of psychological interventions on psychotic symptoms. Network meta-analysis is an alternative methodology which allows researchers to draw statistical conclusions not only from direct comparisons between interventions but also indirect evidence using the network model. A systematic search was conducted resulting in the inclusion of 90 RCTs and 8,440 randomised participants with psychosis. Network meta-analysis was used to examine direct and indirect evidence for 'total symptoms' of psychosis, which is an overall measure including all relevant psychotic symptoms. Study quality was again assessed to help ensure validity of results. Results demonstrated that psychological interventions were of significant benefit compared to control groups. Mindfulness-based psycho-education was shown as the intervention most likely to reduce total symptoms. However, all included RCTs for this intervention were from China, meaning that future research investigating the efficacy of mindfulness-based psycho-education in a variety of cultural contexts may help determine whether these findings generalise to other international settings.

While the previous chapters apply conventional meta-analytic techniques, **chapter 4** provides a cumulative meta-analysis investigating the impact of individualised, case-formulation based CBTp on hallucinations and delusions, which are the key features of positive symptoms. Case formulation refers to an essential technique in CBT that helps to individualise a patient's treatment and allows a close conceptual link between research and clinical practice. Cumulative meta-analysis is a novel technique that, alongside

providing information on the effectiveness of a treatment, can also help us determine whether the evidence base for that treatment is *sufficient* and *stable*. A systematic search resulted in the inclusion of 35 RCTs and 2407 participants with psychosis. Meta-analyses were conducted and study quality was again assessed to help determine the validity of results. Results demonstrated that the evidence base for CBTp has been sufficient and stable since 2016 for hallucinations and 2015 for delusions. CBTp was demonstrated as beneficial for hallucinations compared to any control, treatment as usual and active controls. For delusions, CBTp was beneficial when compared to any control and treatment as usual, but did not demonstrate significant benefit against active controls although there were a limited number of RCTs included in this comparison, which may limit validity. The effects of CBTp were also shown as stronger when case-formulation was used and also when the primary focus of the study was the reduction of hallucinations or delusions instead of other outcomes. The fact that the evidence for CBTp has been shown as sufficient and stable means that there may be limited worth in continuing to spend vital resources on similar RCTs testing 'generic' CBTp and resources may better be directed into developing new or improved variants.

Chapter 5 utilises another novel meta-analytic technique allowing the application of individual-participant data (IPD). In this approach, the original databases from published RCTs are requested from authors meaning that the individual data for each participant can be used in analyses rather than relying on the summary effect size data available in published manuscripts. The IPD approach allows a more precise estimation of effects and allows the investigation of 'moderator' variables, which refer to demographic or clinical variables at the individual level that may impact who benefits most from treatment. This study was initially developed as follow-on from chapter 1 and attempted to source

databases all the included CBTp RCTs alongside conducting a new systematic search to determine whether any new RCTs were eligible. After contacting relevant authors, databases for 14 of 23 eligible RCTs were included resulting in the data for 898 participants with psychosis being included. CBTp was demonstrated as beneficial for total psychotic symptoms and general symptoms, although not for positive symptoms. This finding contrasts results from the previous chapters, although may be explained by the exclusion of a proportion of eligible RCTs due to failure to obtain these databases from original authors. The moderator analysis did not show any demographic or clinical variables as influencing treatment outcome although the number of therapy sessions a patient received had impact on outcome. The results of this IPD meta-analysis suggest that patient characteristics, including severity of psychotic symptoms, do not significantly influence treatment outcome while sufficient 'dosage' of CBTp is important.

Finally, **chapter 6** reports on a secondary analysis of an RCT conducted in a clinical setting in the UK National Health Service (NHS). This study examined the effects of a brief psychological intervention aiming to address overconfidence in perceptual decision-making among patients diagnosed with psychosis. 31 patients aged 16-65 were randomly assigned to one of two groups; 1) a brief intervention based on 'metacognitive training' which aimed to address a common thinking bias called the "jumping-to-conclusions" bias, or 2) an attention-control condition designed to account for therapist time and attention. Participants completed outcome measures assessing overconfidence and the "jumping-to-conclusions" bias. Results demonstrated that those receiving meta-cognitive training experienced a significant reduction in overconfident reasoning when compared to those receiving the control condition. This RCT provides preliminary evidence that meta-cognitive training is a worthwhile method by which to address overconfident reasoning in

psychosis. There were however methodological limitations of this RCT due to limited resources. A larger RCT with stronger methodology is therefore warranted.

Conclusions

When considered collectively, the findings from the body of research included in this thesis provide strong evidence for the validity of psychological interventions for psychosis. The evidence base for CBTp was demonstrated as *sufficient and stable,* while social skills training was demonstrated as an effective intervention for negative symptoms. The results for CBTp are important in the on-going debate about effectiveness and whether or not it has been "oversold." In light of the accumulated evidence, future research on psychological interventions for psychosis may best focus on the development of new or improved approaches and move on from the debate on whether psychological intervention "works" or not.

Overzicht van onderzoek

Dit proefschrift bestaat uit vijf studies die de effecten van psychologische interventies voor psychosepatiënten onderzoeken. Elke studie maakt gebruik van een verschillende methodologie waardoor verschillende conclusies kunnen worden getrokken. Hoofdstuk 1 geeft een algemene inleiding tot het onderwerp, inclusief de achtergrond en geschiedenis van psychologische interventies voor psychose en hun ontwikkeling in de context van het dominante medische model, naast een overzicht van het huidige bewijs voor psychologische interventies. De kritische vragen die dit proefschrift wil beantwoorden, worden ook geïntroduceerd.

Vier van de vijf studies die in dit proefschrift zijn opgenomen, gebruiken meta-analytische methoden. Meta-analyse is een statistische procedure waarmee meerdere bestaande gepubliceerde onderzoeken kunnen worden vergeleken om een algemene schatting te geven. Als ze zorgvuldig worden uitgevoerd, kunnen meta-analyses meer informatie opleveren dan individuele studies alleen en vormen ze de basis van de meeste richtlijnen voor interventies in de gezondheidszorg. Meta-analyses omvatten doorgaans *randomised controlled trials* (RCT's). Dit type studie test het effect van een interventie door deze af te zetten tegen een controleconditie en wordt uitgevoerd onder strikte voorwaarden om de validiteit van de resultaten te waarborgen. De eerste vier studies in dit proefschrift zijn meta-analyses en de laatste studie gebruikt RCT-methodologie om een korte interventie te testen. Vervolgens wordt een algemene discussie gegeven waarin de implicaties van de bevindingen worden besproken, naast de sterke en zwakke punten en suggesties voor toekomstig onderzoek.

Samenvatting van onderzoek

Hoofdstuk 2 beschrijft een vergelijkende meta-analyse waarmee zes vormen van psychologische interventies gericht op psychose worden vergeleken. De meta-analyse omvatte RCT's naar CGTp, sociale vaardigheidstraining (SOVA), cognitieve remediëring, psycho-educatie, ondersteunende therapie en *befriending* (vergelijkbaar met Maatjesprojecten in Nederland). De zoektocht in vier belangrijke databases resulteerde in een selectie van 48 RCT's met 3295 deelnemers met psychose. De gegevens van alle RCT's werden geanalyseerd om de effectgrootte van elk studie samen te voegen, wat een geaggregeerde statistiek voor elke vergelijking opleverde. Vervolgens werd de kwaliteit van de RCT's beoordeeld om daarmee de validiteit van de meta-analytische resultaten te kunnen beoordelen. De meta-analyse toonde aan dat CGTp beter was dan andere interventies voor de behandeling van positieve symptomen (waaronder belangrijke psychosesymptomen zoals hallucinaties en wanen), terwijl sociale vaardigheidstraining beter was voor negatieve symptomen (waaronder apathie en gebrek aan motivatie). Cognitieve remediëring toonde ook een gunstig effect op algemene symptomen, net als CGTp, hoewel deze bevindingen de extra sensitiviteitsanalyses die we hebben uitgevoerd op basis van de methodologische kwaliteit van de geïncludeerde RCT's niet overleefden. Op basis van deze resultaten werd geconcludeerd dat er kleine maar betrouwbare verschillen zijn tussen psychologische interventies voor psychose.

Hoofdstuk 3 beschrijft een netwerk meta-analyse gericht op psychologische interventies voor psychose. Netwerk meta-analyse is een alternatieve methodologie waarmee onderzoekers statistische conclusies kunnen trekken, niet alleen uit

directe vergelijkingen tussen interventies, maar ook uit indirect bewijs met behulp van het netwerkmodel. Zoals hierboven werd een systematische zoektocht uitgevoerd die resulteerde in de inclusie van 90 RCT's en 8440 deelnemers met psychose. Netwerk meta-analyse werd gebruikt om direct en indirect bewijs voor 'totale symptomen' van psychose te onderzoeken. De studiekwaliteit werd opnieuw beoordeeld om de validiteit van de resultaten te begrijpen. Resultaten toonden aan dat psychologische interventies zijn meer effectief in vergelijking met controlegroepen. Mindfulness-gebaseerde psychoeducatie werd getoond als de interventie die het meest waarschijnlijk de totale symptomen vermindert. Alle RCT's voor deze interventie waren in China gepubliceerd, wat betekent dat toekomstig onderzoek naar mindfulness-gebaseerde psycho-educatie in verschillende culturele contexten kan helpen bepalen of deze bevindingen naar andere internationale omgevingen zou generaliseren.

Terwijl de vorige hoofdstukken conventionele meta-analytische technieken toepassen, beschrijft **hoofdstuk 4** een cumulatieve meta-analyse die de impact van geïndividualiseerde, casusformulering-gebaseerde CGTp op hallucinaties en wanen onderzoekt. Casusformulering verwijst naar een essentiële techniek in CGT die helpt de behandeling van een patiënt te individualiseren en een nauwe conceptuele link tussen onderzoek en klinische praktijk mogelijk maakt. Cumulatieve meta-analyse is een nieuwe techniek die ons, naast het verstrekken van informatie over de effectiviteit van een behandeling, ook kan helpen bepalen of het bewijs voor die behandeling voldoende en stabiel is. Een systematische zoektocht resulteerde in de inclusie van 35 RCT's en 2407 deelnemers met psychose. Er werden meta-analyses uitgevoerd en de kwaliteit van het onderzoek werd opnieuw beoordeeld om de

validiteit van de resultaten te helpen bepalen. De resultaten toonden aan dat de bewijsbasis voor CGTp sinds 2016 “afdoende” en “stabiel” is voor hallucinaties en sinds 2015 voor wanen. Van CGTp werd aangetoond dat het effectiever is in de behandeling van hallucinaties in vergelijking met elke controle, standaard zorg en actieve controles. Voor wanen was CGTp beter in vergelijking met de standaard zorg, maar vertoonde geen significant voordeel ten opzichte van actieve controles, hoewel er een beperkt aantal RCT's in deze vergelijking was geïncludeerd, wat de geldigheid kan beperken. De effecten van CGTp bleken ook sterker te zijn wanneer casusformulering werd gebruikt en als de primaire focus van het onderzoek de vermindering van hallucinaties of wanen was in plaats van andere doelen. Het feit dat het bewijs voor CGTp is aangetoond als afdoende en stabiel, betekent dat het van beperkte waarde is om essentiële middelen te blijven besteden aan RCT's die de effectiviteit van generieke CBTp testen. Deze middelen kunnen beter worden gericht op het ontwikkelen van nieuwe of verbeterde varianten.

Hoofdstuk 5 maakt gebruik van een andere nieuwe meta-analytische techniek die de toepassing van gegevens van individuele deelnemers (IPD) mogelijk maakt. In deze benadering worden de originele databases van gepubliceerde RCT's opgevraagd bij de auteurs van geselecteerde studies. Dit zorgt ervoor dat de individuele data van elke deelnemer kunnen worden gebruikt in de analyses in plaats van te vertrouwen op de samenvattende effect groottes die beschikbaar zijn in gepubliceerde manuscripten. De IPD-benadering maakt een nauwkeurigere schatting van effecten mogelijk en maakt het mogelijke moderatoren te onderzoeken, die verwijzen naar demografische of klinische variabelen die van invloed kunnen zijn op wie het meeste baat heeft bij behandeling. Deze studie is een

vervolg op de studie in hoofdstuk 2. Daarom zijn dezelfde CGTp RCT's opgenomen in de huidige studie en is er een nieuwe systematische zoektocht uitgevoerd om te bepalen of er nieuwe RCT's in aanmerking kwamen. Na contact met relevante auteurs werden databases voor 14 van de 23 in aanmerking komende RCT's geïncludeerd, waardoor de data van 898 deelnemers met psychose werden gebruikt. Uit de resultaten blijkt dat CGTp effectiever is voor de behandeling van psychose symptomen en de bredere algemene psychiatrische symptomen, behalve voor positieve symptomen. Deze bevinding staat in contrast met de resultaten van de voorgaande hoofdstukken, hoewel dit kan worden verklaard door de exclusie van een deel van de geselecteerde RCT's omdat deze databases niet van de oorspronkelijke auteurs zijn verkregen. Uit de moderatie-analyse bleek dat demografische of klinische variabelen de uitkomst van de behandeling niet beïnvloeden maar dat het aantal therapiesessies dat een patiënt ontving wel een impact heeft op de uitkomst. De resultaten van deze IPD-meta-analyse suggereren dat patiëntkenmerken, waaronder de ernst van psychose symptomen, de behandelresultaten niet significant beïnvloeden, terwijl voldoende dosering van het aantal behandelsessies bij CGTp wel belangrijk is.

Tenslotte rapporteert **hoofdstuk 6** over een secundair analyse van een RCT uitgevoerd in een klinische setting in de UK National Health Service (NHS). Deze studie onderzocht de effecten van een korte psychologische interventie voor patiënten met een psychotische stoornis, met als doel om te zelfverzekerde perceptuele besluitvorming te verminderen. 31 patiënten van 16-65 jaar werden willekeurig toegewezen aan een van de twee groepen; 1) een korte interventie genaamd 'metacognitieve training die gericht is op het aanpakken van een algemene

cognitieve bias, de '*jumping to conclusions'*-bias, of 2) een aandachtscontroleconditie die is ontworpen om te controleren voor de tijd en aandacht van de therapeut. De deelnemers voltooiden uitkomstmaten om te zelfverzekerde perceptuele besluitvorming en de JTC-bias te meten. De resultaten toonden aan dat degenen die meta-cognitieve training kregen beduidende vermindering in te zelfverzekerde besluitvorming in vergelijking met degenen in de controleconditie. Deze RCT levert daarom preliminaire bewijs voor dat het verminderen van de JTC bias via metacognitieve training een effectieve methode is om te zelfverzekerde perceptuele besluitvorming in psychose te verminderen. Bij het interpreteren van de resultaten moeten methodologische beperkingen van deze RCT in acht worden genomen. Een grotere RCT met een sterkere methodologie is daarom gerechtvaardigd.

Conclusies

Al met al leveren de bevindingen van de onderzoeksgroep die in dit proefschrift zijn opgenomen sterk bewijs voor de validiteit van psychologische interventies voor psychose. De bewijsbasis voor CGTp werd aangetoond als afdoende en stabiel, terwijl SOVA werd aangetoond als een effectieve interventie voor negatieve symptomen. De resultaten voor CGTp zijn belangrijk in het lopende debat over effectiviteit en of het al dan niet 'oversold' is. In het licht van het verzamelde bewijs kan toekomstig onderzoek naar psychologische interventies voor psychose zich het best richten op de ontwikkeling van nieuwe of verbeterde benaderingen in plaats van verder te gaan met het debat over de vraag of psychologische interventie 'werken' of niet.

Appendices

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Chapter 1

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