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Review

‘Twisting the lion's tail’: Manipulationist tests of causation for psychological mechanisms in the occurrence of delusions and hallucinations

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HIGHLIGHTS

- Manipulationist-causal studies testing delusions and hallucinations are gathered.
- Forty-three studies manipulated psychological processes for psychotic experiences.
- Successful manipulation of a mechanism typically led to change in psychotic experiences.
- The studies potentially provide important treatment techniques.
- Causal tests are far too few, despite the potential for understanding and treatment.

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ABSTRACT

Over the past 20 years the importance of psychological processes in psychosis has gained increasing attention. However, it is key to determine the causal status of these processes in order to inform understanding and identify treatment targets. Studies that directly manipulate a psychological mechanism provide the most robust causal evidence. This review evaluates for the first time the extent of manipulationist causal evidence for the role of specific psychological mechanisms in delusions and hallucinations. A systematic search identified controlled experiments or targeted interventions that both manipulated a specific psychological mechanism and measured the effect on individual psychotic experiences. Forty-three manipulationist studies were found of which 40 measured paranoia, 11 measured hallucinations, and two measured grandiosity. Twenty-eight studies were experiments and 15 were targeted intervention trials. Only 18 used clinical samples. Manipulation of the specified psychological mechanism was demonstrated in 35 cases. Of these, 28 found a subsequent change in a psychotic experience. Negative affect and related psychological processing in relation to paranoia have been most tested. There is a small body of direct causal evidence for the role of psychological mechanisms in psychotic experiences – that highlight important novel treatment directions – but the manipulationist approach has been used too infrequently.

1. Introduction

1.1. The causal problem

‘The very essence of causation [is] the ability to predict the consequences of abnormal eventualities and new manipulations... Viewing causality this way explains why scientists pursue causal explanations with such zeal and why attaining a causal model is accompanied by a sense of gaining “deep understanding” and “being in control.”’ Pearl (2009, page 415).

‘Explanations and causal inference pervade our lives.’ Woodwood (2003, page 18).

‘[Francis Bacon] taught that not only must we observe nature in the raw, but that we must also ‘twist the lion's tail’, that is, manipulate our world in order to learn its secrets.’ Hacking (1983, page 149).

Causal explanations are central to our daily interactions, since they allow us to predict, comprehend, and interact with our environment. It is not surprising, therefore, that the idea of conducting experiments that manipulate an aspect of nature in order to discover an effect was embedded into the first articulations of the scientific method by Francis Bacon in his *Novum Organum Scientiarum* (Bacon, 1620). Shadish, Cook, and Campbell (2002) highlight that even as laypersons we often instinctively use manipulation to discover effects: “to see what happens to

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our blood pressure if we exercise more, to our weight if we diet less, to our behaviour if we read a self-help book” (page 3). The premise of the manipulationist approach to causality is simply that “Y is a cause of Z if we can change Z by manipulating Y” (Pearl, 2009, page 417). The consensus in the philosophy of science is that manipulation is the key approach to be taken, when possible, for testing causal relationships. A causal relationship can be inferred from a correlation, but it is typically impossible to have any certainty about conclusions made in this way. Causal conclusions are based on an accumulation of different types of evidence (Bradford Hill, 1965) or on a triangulation of methods, but the most convincing evidence is provided by manipulationist data. Indeed, Holland (1986) argues that there is ‘no causation without manipulation’ (page 959).

There are two main methodological routes in clinical psychology to achieving the kind of causal evidence that is the focus of this review. First, there are the traditional short-term randomised controlled experimental studies that manipulate a mechanism (e.g. attentional focus, worry) and measure the immediate change in a particular outcome (e.g. social anxiety, paranoia). Second, there are interventionist-causal (Kendler & Campbell, 2009) randomised controlled trials that use sustained treatment techniques focused on an individual mechanism to produce change in the primary clinical outcome. Kendler and Campbell (2009, page 881) note how defining causation in terms of “what would happen under interventions” aligns well with the practical interests in mental health research, namely preventing and treating disorders. Conclusions from both kinds of study can be further strengthened by the use of mediation analysis (Dunn et al., 2015). In this instance, mediation analysis serves as an additional check that the mechanism manipulated is the most likely explanation for the observed effect. In this review paper, we wish to consider the degree to which a manipulationist approach, ideally with tests of mediated effects, has been applied to the psychological understanding of delusions and hallucinations.

1.2. Psychosis

The manipulationist approach relies on predicting the effect of a particular manipulation on a particular outcome. Hence, the outcome needs to be precisely specified. Yet outcomes in schizophrenia research are all-too-often imprecise: a collection of very different experiences are commonly treated as one. Our favoured approach to achieve precision in this research area is to focus on individual psychotic experiences, such as paranoia, grandiosity, hallucinations, and anhedonia. There is a large body of empirical evidence showing that individual psychotic experiences load onto relatively independent factors (e.g. Peralta & Cuesta, 1999; Ronald et al., 2014; Vazquez-Barquero, Lastra, Cuesta Nunez, Herrera Castanedo, & Dunn, 1996; Wigman et al., 2011). Notably, there is evidence that different psychotic experiences have differing levels of genetic and environmental risk (Zavos et al., 2014).

Research on individual psychotic experiences has also highlighted that each is best conceptualised as a quantitative trait, existing on a spectrum of severity in the general population, just as is seen for common emotional problems such as anxiety and depression (Plomin, Haworth, & Davis, 2009). Although psychotic experiences are most commonly studied in the context of schizophrenia, they are also common in the general population. For example, a spectrum of severity of paranoia (unfounded ideas that others intend to harm you) exists in the general population, with persecutory delusions representing the most severe form of paranoia (e.g. Elahi, Perez Algorta, Varese, McIntyre, & Bentall, 2017; Freeman, Pugh, Vorontsova, Antley, & Slater, 2010). This review will therefore make use of studies of either clinical or non-clinical psychotic experiences (i.e. at any point in the continuum). Non-clinical studies have the advantage that increasing, in the very short term, a potential causal factor is ethically more possible than when working with clinical groups.

Increasingly over the last few decades there has been an emerging

psychological literature examining the causes of psychotic experiences. This has been largely provoked by the developing cognitive-behavioural therapy approaches for psychosis. Delusions (e.g. Bentall, Corcoran, Howard, Blackwood, & Kinderman, 2001; Freeman, 2016) and hallucinations (e.g. Morrison, Haddock, & Tarrier, 1995; Slade, 1976) have received the most psychological theorising and investigations, with less attention given to other psychotic experiences such as anhedonia (e.g. Strauss & Gold, 2012) or formal thought disorder (Goldberg & Weinberger, 2000). In the development of the new generation of psychological therapy for psychosis, The Feeling Safe Programme (Freeman et al., 2016) – a translational treatment for persecutory delusions – has been explicitly developed on the basis of a sustained programme of manipulationist studies. To date there has been no systematic assessment of how much of the supporting evidence overall cited for these wide variety of theoretical ideas comes from causal evidence provided by manipulation studies.

1.3. This review

We set out to examine the manipulationist literature with regard to delusions and hallucinations and psychological processes. We wanted to determine the number, quality, and focus of such studies. In particular, which psychotic experiences were assessed, how many studies used clinical versus non-clinical samples, how many were experimental studies versus interventionist-causal studies, and how many included mediation tests. The interest was in causal studies that use a randomised controlled design and a manipulation or treatment intervention targeting a single psychological mechanism.

2. Method

A search was carried out in Medline, Embase, and PsychInfo for peer reviewed English language papers using the following search terms: (halluc* OR delus* OR paranoi* OR persecut* OR psychotic OR psychosis OR “ideas of reference” OR grandios*) AND (experiment* OR manipul* OR intervention* OR randomised OR randomized OR randomly) AND (mechanis* OR caus* OR maintenance OR maintaining) AND (emotion* OR cognit* OR social OR psychological*).

2.1. Inclusion criteria

Papers were required to have:

1. A manipulation of a specific psychological mechanism.
2. One or more individual psychotic experiences measured at outcome.
3. Random allocation to conditions.

2.2. Exclusion criteria

Papers were excluded if they were:

1. Case studies or case series.
2. Non-human studies.
3. Not available as a full text.

This search found 3618 papers (December 2018). Titles and abstracts were scanned and then full texts read as required. Citations and references of included papers were also checked. Fig. 1 presents a PRISMA diagram summary of the search process.

2.3. Quality assessment

The quality of included studies was assessed using a measure of methodological quality developed by Downs and Black (1998). This evaluates quality and risk in four areas: reporting, confounding, bias, and external validity. The measure was adapted to omit the final

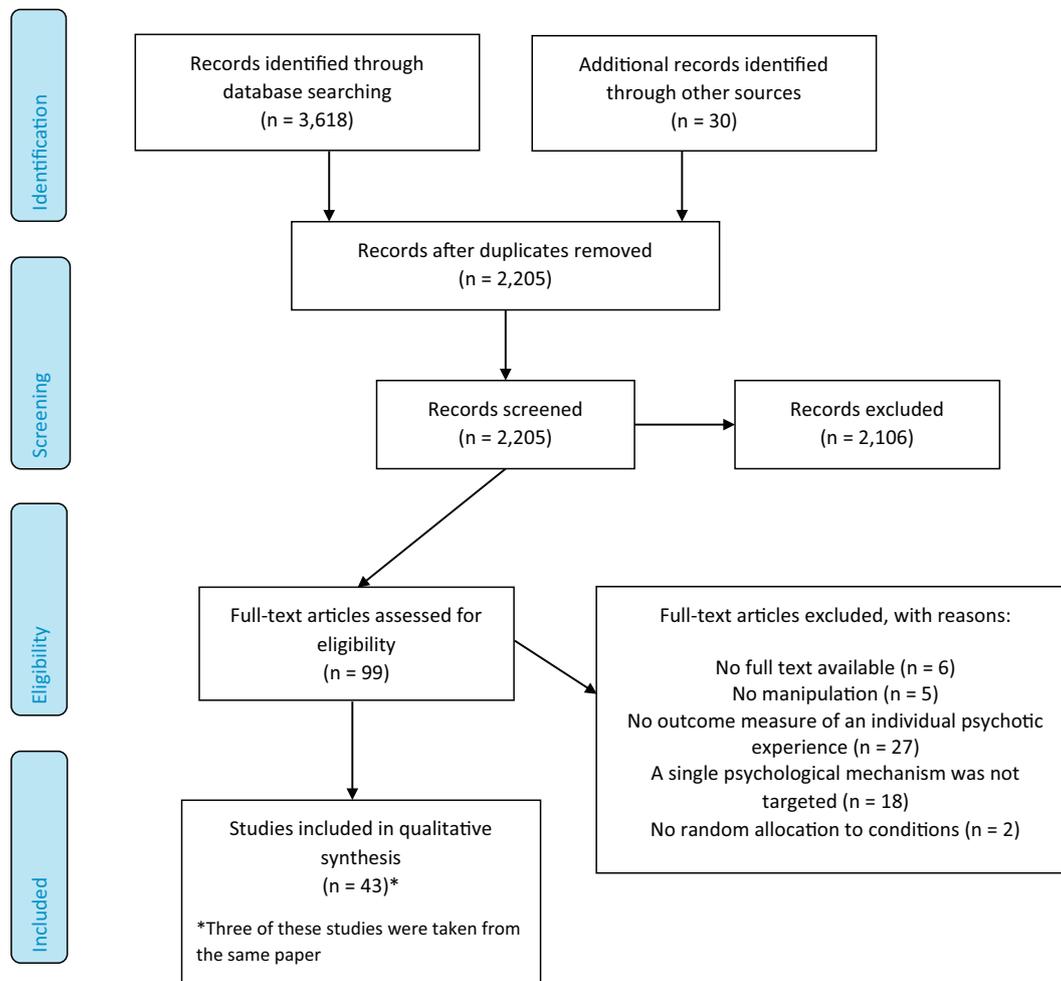


Fig. 1. PRISMA diagram of the search process.

question that assesses the power of a study, thereby allowing a maximum score of 27. Studies were assigned a grade according to their score: excellent (23–27), good (18–22), fair (13–17) or poor (0–12).

3. Results

A total of 43 manipulationist studies meeting the inclusion criteria were found. Just over half ($n = 25$) used non-clinical samples, and within these non-clinical studies the majority ($n = 15$) used student samples. There were only 18 studies on clinical populations. This gave a total of 5426 non-clinical participants (1671 when excluding one large-scale online trial by Freeman et al. (2017)) and 1509 clinical participants. Twenty-eight studies were experiments and 15 were targeted clinical intervention trials. Paranoia was measured at outcome in 40 studies, hallucinatory type experiences in 11 studies, and grandiosity in two studies. A total of 10 studies looked at multiple individual psychotic experiences at outcome. Summaries of the studies can be seen in Tables 1 and 2.

3.1. Studies of psychological mechanisms in non-clinical populations

3.1.1. Attention

The first manipulation studies conducted concerned attentional focus. If attention is frequently threat-focused then this may increase the frequency with which potential threats are identified, which in turn could increase future expectation of threat, and so have an effect on paranoid thoughts (Bentall & Kancy, 1989; Freeman, Garety, Kuipers, Fowler, & Bebbington, 2002; Freeman, Garety, & Phillips, 2000). Two

experiments manipulated participants to focus their attention towards a threat and measured paranoia as the outcome, but found contrasting results. Both studies used student samples with no requirement to have paranoid thinking and were rated as having somewhat poor methodological quality, however, suggesting caution may be required when drawing conclusions from the results.

Locascio and Snyder (1975) randomised 60 undergraduates to selectively attend to threatening or non-threatening stimuli or to no attentional manipulation. They found no significant differences in reported paranoia between the conditions. However, there was no check as to whether the attention manipulation was successful. Conversely, Bodner and Mikulincer (1988), who used a sample of 177 undergraduates, did successfully manipulate attention either to be focused on a threatening agent (the experimenter) or on the self. They found that paranoia increased when attention was focused on the experimenter versus on the self, but only when participants had also been given negative feedback implicating personal failure. This might suggest that for attentional bias to affect paranoia some sort of negative event or emotion is required. The difference in results between the two studies could also be explained by the bespoke measure of paranoia used by Bodner and Mikulincer (1988) predominantly assessing ideas of reference rather than of harm.

Three further experiments within the same report examined the effects of self-focussed attention as opposed to threat-focussed (Ellett & Chadwick, 2007). It has been argued that self-consciousness increases directed attention towards the self, leading to the belief that other people are doing likewise, thus increasing paranoia (Fenigstein & Vanable, 1992). Ellett and Chadwick found in their three studies that

Table 1
Manipulationist studies assessing non-clinical samples.

Citation	Psychological Mechanism	N	Participant characteristics	Positive symptoms outcome	Comment on findings	Successful manipulation?	Significant effect on a psychotic experience?	Mediation analysis?	Risk of Bias score
Freeman, Dunn, Murray, et al. (2015)	Negative affect	121	Individuals reporting paranoid ideation	VASS, SSPS, PANSS suspiciousness subscale, CAPE, CAPS	THC administration increased paranoia, which was fully mediated by increased negative affect and anomalous experiences	Y	Y	Y	24, excellent
Lincoln et al. (2013)	Negative affect	71	Students	Paranoia checklist	Following a negative mood induction, a compassion focussed task led to fewer paranoid thoughts than a control condition. The effect was mediated by reduced negative emotion	Y	Y	Y	19, good
Lincoln et al. (2010)	Anxiety	90	Students	Paranoia checklist	Induced state anxiety resulted in increased state paranoia, partially mediated by an increased tendency to jump to conclusions	Y	Y	Y	20, good
Lincoln et al. (2009)	Anxiety	64	Undergraduates	Paranoia checklist	A stress induction caused a significant increase in paranoia, partially mediated by increased anxiety	Y	Y	Y	20, good
Martinelli et al. (2013)	Rumination	37	Students	SSPS	Following a paranoia induction, a distraction task significantly decreased paranoia where-as encouraging rumination led to maintained paranoia	Y	Y	N	22, good
McKie et al. (2017)	Rumination	32	Undergraduates	VAS measuring paranoia	Following a paranoia induction, a mindful self-focus task significantly decreased paranoia where-as ruminative self-focus maintained paranoia	Y	Y	N	18, good
Atherton et al. (2016)	Self-esteem	26	Males reporting paranoid ideation	SSPS	Compared to a high self-confidence manipulation, a low self-confidence manipulation led to significantly higher levels of paranoia	Y	Y	N	20, good
Ascone, Jaysa, and Lincoln (2016)	Self-esteem	172	Female students	Paranoia checklist	Giving participants an unfavourable online social profile versus a favourable one had no significant effect on paranoia	Y	N	N*	21, good
Freeman, Evans, et al. (2014)	Self-esteem	60	Females reporting paranoid ideation	SSPS	Reducing participants' height in virtual reality led to increased paranoia that was mediated by changes in social comparison	Y	Y	Y	22, good
Kesting et al. (2013)	Self-esteem	76	General population	Paranoia checklist	Being excluded from a virtual ball game and receiving negative feedback on a test led to increased paranoia, which was mediated by decreased self-esteem	Y	Y	Y	23, excellent
Butler et al. (2019)	Interpersonal stress	97	General population	PDS	Receiving critical comments increased paranoia but had no effect on self-esteem. Receiving warm comments increased self-esteem. Then being excluded from a virtual ball game reduced self-esteem and increased paranoia	Y	Y	N	19, good
Reeve et al. (2017)	Sleep	68	General population	SPEQ	Sleep loss increased paranoia and hallucinations, but not grandiosity. Changes in psychotic experiences were mediated by changes in negative affect	Y	Y	Y	19, good
Meyhöfer et al. (2017)	Sleep	32	General population	PSI	Sleep deprivation induced psychosis-like experiences mimicking hallucinations. No effect on paranoia	Y	Y	N	20, good
Petrovsky et al. (2014)	Sleep	24	General population	PSI	Sleep loss led to increased perceptual distortions but delusional thinking and paranoia did not increase	Y	Y	N	20, good
Freeman et al. (2017)	Sleep	3755		GPTS and SPEQ-H		Y	Y	Y	20, good

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Table 1 (continued)

Citation	Psychological Mechanism	N	Participant characteristics	Positive symptoms outcome	Comment on findings	Successful manipulation?	Significant effect on a psychotic experience?	Mediation analysis?	Risk of Bias score
Locascio and Snyder (1975)	Attention	60	Students with insomnia Undergraduates	Bespoke fear/malevolence questionnaire as an index of paranoia	CBT for insomnia reduced paranoia and hallucinations. Insomnia was the mediator of change in both cases Increasing attention to threat did not increase paranoia	No check	N	N	18, good
Bodner and Mikulincer (1998)	Attention	177	Undergraduates	Bespoke paranoia self-report questionnaire	Increasing attention to threat led to increased paranoia in those who received feedback implicating personal failure as compared to when attention was focussed elsewhere	Y	Y	N	19, good
Westermann et al. (2014)	Emotional regulation strategy	86	Undergraduates	VAS measuring state delusional ideation	Using a reappraisal strategy, a suppression strategy or no strategy following an anxiety induction had no significant effect on delusional ideation	No check	N	N	15, fair
Lanster et al. (2017)	Loneliness	60	General population	Paranoia checklist	Reducing loneliness led to a significant reduction in state paranoia, moderated by proneness to psychosis. Inducing loneliness led to increased paranoia though not significantly	Y	Y	N	22, good
Ellett and Chadwick (2007a)	Self-awareness	60	Undergraduates	PS, PDS	Inducing high self-awareness resulted in more paranoid self-cognitions following both a failure and a neutral task as compared to low self-awareness	No check	Y	N	18, good
Ellett and Chadwick (2007b)	Self-awareness	40	Undergraduates	PS, PDS	Inducing high self-awareness resulted in more paranoid self-cognitions following a neutral task as compared to low self-awareness	No check	Y	N	18, good
Ellett and Chadwick (2007c)	Self-cognitions	30	Undergraduates	PS, PDS	A negative prime resulted in more paranoid self-cognitions than a positive prime following a failure task completed under a high self-awareness condition	No check	Y	N	18, good
Hutton et al. (2017)	Attachment	60	Students	PDS	A secure attachment prime did not protect against paranoid thinking	No check	N	N	21, good
Zimbardo et al. (1981)	Awareness of anomalous experiences	18	Students susceptible to hypnosis	"A clinically derived" paranoia scale and the paranoia and grandiosity subscales of the MMPI	Those who were hypnotised to experience hearing loss without being aware of this manipulation experienced higher paranoia and grandiosity than those who were aware of the manipulation	Y	Y	N	14, fair
Kaltsi, Bucci, and Morrison (2018)	Metacognitive beliefs about paranoia	110	University staff and students	Paranoia checklist	Following social exclusion via a virtual ball game, frequency of paranoid thoughts increased in those who received a positive beliefs induction. Distress of paranoid thoughts decreased in those who received a negative belief induction	Y for positive beliefs group, N for negative beliefs group	Y	N	19, good

Key: VAS = Visual analogue scale; SSPS = Social State Paranoia Scale; PANSS = Positive And Negative Symptoms Scale; CAPE = Community Assessment of Psychic Experiences; CAPS = Cardiff Anomalous Perception Scale; SPEQ = Specific Psychotic Experiences Questionnaire; PSI = Psychotomimetic States Inventory; GPTS = Green Paranoid Thoughts Scale; PDS = Paranoia and Depression Scale; SPEQ-H = Psychotic Experiences Questionnaire – Hallucinations subscale; PS = Paranoia Scale; PDS = Paranoia and Depression Scale; MMPI = Minnesota Multiphasic Personality Inventory.

* Stated intention to include mediation analysis in the analysis plan but refrained due to lack of effect of the manipulation on the outcome.

Table 2
Manipulationist studies assessing clinical samples.

Citation	Psychological Mechanism	N	Participant characteristics	Positive symptoms outcome	Comment on findings	Successful manipulation?	Significant effect on a psychotic experience?	Mediation analysis?	Risk of Bias score
Freeman, Emsley, Dunn, et al. (2015)	Negative affect	59	Patients with current delusions	VASs for paranoia and hallucinations, SSPS	Exposure to an urban street scene led to increased paranoia and voice hearing, mediated by increased anxiety (45%), depression (38%) and negative beliefs about others (45%)	Y	Y	Y	22, good
Freeman et al. (2016)	Safety-seeking behaviours	30	Patients with current delusions	VAS measuring persecutory concerns	Encouraging the dropping of safety behaviours led to large reductions in delusional conviction	Y	Y	N	19, good
Freeman et al. (2013)	Worry	67	Patients with persecutory delusions	CAPS, CDS	A worry induction increased a range of anomalous experiences including feelings of unreality, perceptual alterations and temporal disintegration. There was no effect on hallucinations	Y	N for hallucinations, Y for feelings of unreality	N	20, good
Foster et al. (2010)	Worry	24	Patients with persistent persecutory delusions and high levels of worry	PSYRATS delusions subscale, GPTS	A worry intervention led to reduced delusional distress. Indication that it might have also reduced the frequency of paranoid thoughts, but this was not statistically significant	Y	Y	N	21, good
Freeman, Dunn, Startup, et al. (2015)	Worry	150	Patients with persistent persecutory delusions	PSYRATS delusions subscale	A worry intervention led to a reduction in persecutory delusions. Change in worry accounted for 66% of improvement in delusions	Y	Y	Y	22, good
Lecomte et al. (1999)	Self-esteem	95	Diagnosis of schizophrenia	PANSS	A 12-week empowerment module reduced scores on the PANSS delusion and paranoia items. The effect dissipated when treatment stopped	N (maybe due to lack of sensitivity of measure used)	Y	N	21, good
Freeman, Pugh, et al. (2014)	Self-esteem	30	Patients with persistent persecutory delusions	GPTS	A brief CBT intervention aimed at reducing negative self-cognitions led to small but not significant reduction in paranoia	N	N	N	23, excellent
Freeman, Waite, Startup, et al. (2015)	Sleep	50	Patients with persistent delusions or hallucinations	PSYRATS	Following CBT for insomnia, confidence intervals for the positive symptom outcomes were wide, suggesting in some patients delusions and hallucinations were reduced but in some patients they increased	Y	N	N*	21, good
Garety et al. (2015)	Reasoning	101	Patients with current delusions	VASs measuring paranoia and hallucinations	A brief intervention aimed at increasing belief flexibility and reducing jumping to conclusions led to significant improvements in state paranoia. Mediation analysis showed that changes in reasoning mediated changes in paranoia, though this did not quite reach significance after adjusting for baseline confounders. No significant changes in hallucinations were found	Y	Y	Y	21, good
Khazaal et al. (2015)	Reasoning	172	Outpatients with persistent psychotic symptoms	PDI	Training in the ability to generate alternative hypotheses led to reduced delusional conviction, distress and preoccupation, which was maintained at a 6 month follow up	Y	Y	N	22, good
Ross et al. (2011)	Reasoning	34	Patients with current delusions	Question assessing delusional conviction	Reasoning training led to less conviction and more flexibility in delusions for some patients, but the finding was not significant	Y	N	N	22, good
So et al. (2015)	Reasoning	44	Patients with current delusions	PANSS, PSYRATS	Training in reasoning (four modules of standard metacognitive training) led to reduced scores on the PANSS positive and delusions subscales and the PSYRATS delusions and conviction subscales, mediated by improved belief flexibility	Y	Y	Y	24, good
Moritz et al. (2015)	Reasoning	70		Paranoia checklist		Y	N	N	19, good

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Table 2 (continued)

Citation	Psychological Mechanism	N	Participant characteristics	Positive symptoms outcome	Comment on findings	Successful manipulation?	Significant effect on a psychotic experience?	Mediation analysis?	Risk of Bias score
Craig et al. (2018)	Beliefs about voices	150	Patients with schizophrenia Patients with persistent auditory/verbal hallucinations	PSYRATS-AH	Training in how to reduce 30 common cognitive biases led to a reduction in jumping to conclusions but not paranoia AVATAR therapy led to a significantly greater reduction in PSYRATS-AH total and subscale scores than did supporting counselling. By 24 weeks there were no differences	Y	Y	N	23, excellent
Birchwood et al. (2014)	Beliefs about voices	197	Patients with persistent command hallucinations	VCS, PANSS	Cognitive therapy to challenge perceived power of voices reduced compliance to voices at 18 month follow up but did not affect delusions or hallucinations	Y	N for delusions/hallucinations but Y for following commands	Y (separate paper,**)	20, good
Stinson et al. (2010)	Triggering cognitions	30	Patients with auditory hallucinations	PSYRATS-AH	No difference in severity of hallucinations following instruction to either focus on hallucination-triggering thoughts or on neutral thoughts	N	N	N	20, good
Ascone et al. (2017)	Compassion	51	Patients with paranoid ideation	Paranoia checklist	Following an induction of negative affect, a single session compassion focussed imagery intervention had no significant effect on paranoia as compared to a control imagery condition	Y for self-reassurance but N for self-compassion	N	N	22, good
Van den berg et al. (2016)	Trauma	155	Patients with a lifetime psychotic disorder and current PTSD	GPTS	Paranoia decreased significantly following the first session of trauma focussed therapy. At the end of the 8 sessions paranoia was lower in the treatment group compared to a waitlist group though the difference did not reach significance	Y	N	N	22, good

Key: VAS = Visual analogue scale; SSPS = Social State Paranoia Scale; CAPS = Cardiff Anomalous Perception Scale; CDS = Cambridge Depersonalisation Scale; PSYRATS = Psychotic Symptom Rating Scale; GPTS = Green Paranoid Thoughts Scale; PANSS = Positive And Negative Symptoms Scale; PDI = Peters Delusion Inventory; PSYRATS-AH = Psychotic Symptom Rating Scale – Auditory Hallucinations subscale; VCS = Voice Compliance Scale.

* Stated intention to include mediation analysis in the analysis plan but refrained due to lack of effect of the manipulation on the outcome.

** Birchwood et al. (2017).

paranoia increased in undergraduates following a manipulation to increase self-awareness e.g. via use of a camera and failure task. However, the lack of manipulation check means caution is needed with the interpretation of their results.

3.1.2. Self-esteem

Paranoia may build upon feelings that the self is vulnerable, arising from low self-esteem and viewing the self as inferior to others (Freeman, 2016). Four non-clinical studies successfully manipulated self-esteem, three of which saw the expected change in paranoia. Only two of the studies used populations selected for reporting paranoid ideation, but the methodological quality across all four studies was mostly strong. Various manipulations of self-esteem were used. Freeman et al. (2014) reduced the height (as a proxy for social rank and self-esteem) of 60 females reporting paranoid thoughts during an exposure to a social environment in virtual reality. This resulted in more negative self-esteem and a greater number of reported paranoid thoughts. The increase in paranoia was fully mediated by the changes in self-esteem. Atherton et al. (2016) used imagery and visualisation tasks to manipulate self-esteem, and Kesting, Bredenkopf, Klenke, Westermann, and Lincoln (2013) used exclusion from a virtual ball game, with both also finding significant change in paranoia at outcome. Conversely, Acone, Jaya and Lincoln, 2017 did not find a significant effect of manipulating self-esteem on paranoia, despite successfully altering participants' extent of social comparison. However, this study used a student sample who were not pre-selected for reporting paranoid thoughts, which might explain the absence of change in levels of paranoia.

A further study examined an important aspect of social environment (comments from others) on paranoia, and examined self-esteem as a moderator (Butler, Berry, Ellett, & Bucci, 2019). They randomised 97 individuals, predominately university students unselected for levels of paranoia, to receive critical, warm, or neutral comments. Self-esteem increased in those who received warm comments; no changes in the other groups were seen. However, those who received critical comments increased in state paranoia despite the lack of change in self-esteem. All groups were then subjected to social exclusion using a virtual ball game. Following exclusion, those who had received warm comments significantly decreased in self-esteem and increased in paranoia. No mediation analyses were included.

3.1.3. Rumination

Two experiments using student samples assessed whether changes in rumination led to changes in paranoia. Rumination may play a role in paranoia by increasing feelings of vulnerability, for example via perseverative appraisal of negative interpersonal experiences (Freeman, 2016; Freeman & Garety, 1999). This appraisal may also have effects by narrowing attention towards negative experiences and increasing anxiety. Martinelli, Cavanagh, and Dudley (2013) gave 37 participants a paranoia induction before randomising them to a task encouraging ruminative thinking or to a task encouraging distraction. They found that an increase in ruminative thinking led to the maintenance of paranoid thoughts whereas the distraction task decreased the experience of paranoid thoughts. This study scored highly on methodological rigour, and is supported by a similar experiment by McKie, Askew, and Dudley (2017). However, McKie et al. (2017) experiment was rated as having a high risk of bias due to a lack of blinding and no adjustment for potential confounders. Moreover, neither study included a mediation analysis.

3.1.4. Negative affect

Four studies examined negative affect as a putative causal mechanism in paranoia. All four studies found an alteration in negative affect led to a change in paranoia and were rated as having good methodological rigour, benefiting also from the use of mediation analysis. Lincoln, Peter, Schafer, and Moritz (2009) randomised 64

students to either a stress induction (via listening to building site noise) applied during a difficult question task or a control condition. Those in the stress condition experienced an increase in negative emotion and reported significantly more paranoid thoughts than those in the control condition, which was mediated by increased anxiety. This experiment is limited, however, by the use of a student sample not preselected for reporting paranoia, which is also the case for two of the other studies on negative affect (Lincoln, Hohenhaus, & Hartmann, 2013; Lincoln, Lange, Burau, Exner, & Moritz, 2010). Freeman et al. (2015) randomised 121 individuals reporting paranoid ideation to either the administration of THC, the active ingredient in cannabis, or a placebo. Those who received THC reported significantly more paranoid thoughts, and this was mediated by anxiety, depression, worry and negative thoughts about the self. This study was rated as having particularly high methodological quality and a low risk of bias.

3.1.5. Sleep

Disturbed sleep may contribute to the occurrence of psychotic experiences by increasing negative affect and anomalous perceptions (Freeman, 2016; Reeve, Sheaves, & Freeman, 2015). Unsurprisingly, sleep deprivation studies have only been carried out in non-clinical samples. It is also one of the few areas to give equal focus to hallucinations as well as to delusions. Three recent randomised controlled studies of sleep deprivation on the general population found that sleep loss increased perceptual distortions such as hallucinations (Reeve, Emsley, Sheaves, & Freeman, 2017; Meyhofer et al., 2017; Petrovsky et al., 2014). Out of these, only Reeve et al. (2017) also found an increase in paranoia. This was the most informative study as a number of psychotic experience outcomes were examined and mediation analyses were included. In a randomised order, 68 participants underwent three nights of restricted sleep and a control condition of three nights of normal sleep. Following sleep restriction, there were significant increases in both paranoia and hallucinations, but no significant changes in grandiosity. Mediation analysis revealed that changes in psychotic experiences were mediated by changes in negative affect and related processes. The effect of sleep deprivation on hallucinatory experiences is also supported by Meyhöfer, Kumari, Hill, Petrovsky, and Ettinger (2017) and Petrovsky et al. (2014). These studies did not find an increase in paranoia, however. This may have been due to the smaller sample size than in Reeve et al. (2017).

The most convincing causal test is provided by a large interventionist-causal model trial testing the effects of a sleep improvement programme on paranoia and hallucinations (Freeman et al., 2017). 3755 students with insomnia were randomised to either receive digital cognitive behavioural therapy (CBT) for insomnia or usual care. There was a large improvement in sleep and small improvements in paranoia and hallucinations in those who received the sleep intervention. Mediation analysis showed that improvements in sleep accounted for nearly 60% of the change in paranoia after treatment, with a similar effect found for hallucinations. This indicates that, at least in the specific population of young adults, disrupted sleep plays a contributory causal role in the occurrence of psychotic experiences.

3.1.6. Further psychological mechanisms

A number of further studies on different psychological mechanisms were also found, though these studies were generally rated as having a slightly higher risk of bias than most others included. The experience of internal anomalous experiences, such as unexplained anxious arousal, could be a causal mechanism in paranoia as misinterpretation of these experiences can lead to incorrect conclusions about the external world (e.g. that there is an external threat) (Freeman, 2016; Garety, Kuipers, Fowler, Freeman, & Bebbington, 2001; Maher, 1974). Zimbardo et al. (1981) examined this mechanism, though it was rated as having a high risk of bias. Twelve students were hypnotised to experience hearing loss and randomised to either being made aware of the cause of this experience or to not being told about the cause, with a further six students

included in a control group. All participants then completed an anagram task in a social setting. Being unaware of the cause of the anomalous experience led to participants perceiving themselves as more irritated, hostile and unfriendly than the group who were made aware of the cause. They also reported greater paranoia and grandiosity than those in the awareness group.

Kaltsi, Bucci, and Morrison (2018) aimed to test specifically the causal role of metacognitive beliefs concerning paranoia in 110 university staff and students. They induced either positive or negative beliefs about paranoia i.e. that paranoia is productive in promoting safety vs. it is negative and promotes distress, before exposing participants to social exclusion via a virtual ball game. Frequency of paranoid thoughts increased significantly following exclusion in those who underwent the manipulation to induce positive beliefs. Distress concerning paranoid thoughts decreased in those who had the negative induction. However, the manipulation check showed that only the positive beliefs induction was successful; the negative beliefs induction did not successfully alter metacognitive beliefs, so caution is needed with the interpretation of this result.

The effects of attachment style are perhaps difficult to investigate experimentally. Attachment style might be expected to have an effect on psychotic experiences given its importance in the development of affect regulation, self-esteem, and understanding of interpersonal experiences (Sitko, Bentall, Shevlin, O'Sullivan, & Sellwood, 2014; MacBeth, Schwannauer, & Gumley, 2008). Hutton, Ellett, and Berry (2017) randomised 60 students (unselected for levels of paranoia) to experience a secure attachment prime, a positive affect prime or a neutral control condition. All participants then underwent a paranoia induction. Despite expectations that a secure attachment prime might buffer against paranoid thinking following a paranoia induction, no such differences were observed. Whether this is because attachment style does not causally affect paranoia or whether priming feelings of attachment style is not comparable to real attachment style is unclear. It is also possible that the attachment primes and/or the paranoia induction were unsuccessful.

There is also evidence from a non-clinical study that loneliness affects paranoia. Feeling distanced from people and lacking meaningful relations that make one feel valued might plausibly be expected to increase paranoia (Lamster, Lincoln, Nittel, Rief, & Mehl, 2017). Lamster, Nittel, Rief, Mehl, and Lincoln (2017) randomised 60 individuals to a high loneliness condition, a low loneliness condition, or a control group. The inductions did successfully alter feelings of loneliness, and it was also found that reducing loneliness significantly reduced paranoia, and increasing loneliness increased paranoia, although the differences were not statistically significant.

Lastly, a study by Westermann, Rief, and Lincoln (2014) instructed 86 undergraduates, unselected for paranoia, to respond to anxiety-provoking stimuli with a reappraisal strategy, expressive suppression strategy, or no strategy. Adaptive reappraisal of anxiety provoking situations has been shown to protect against psychopathology (Aldao, Nolen-Hoeksema, & Schweizer, 2010) but has not, aside from this study, been tested in relation to paranoia. However, state delusional ideation at outcome was not significantly different between those using each strategy. On the other hand, while the anxiety induction was successful, there was no check on strategy use meaning the extent to which each strategy was truly used by participants cannot be determined.

3.2. Studies of psychological mechanisms in clinical populations

3.2.1. Self-esteem

Two clinical intervention studies rated as having high methodological quality and low risk of bias found that increasing self-esteem reduced paranoia. Freeman et al. (2014) successfully increased self-esteem in 30 patients with persecutory delusions and found a moderate reduction in paranoia post-treatment. Lecomte et al. (1999) randomised 95 patients with a diagnosis of schizophrenia to receive either a 12-

week empowerment module aimed at increasing self-esteem or treatment as usual (TAU). No increase in self-esteem was seen, although the authors suggest this may have been due to their self-esteem measure looking predominantly at global features of self-worth rather than more specific constructs that might be more relevant for the patient group. On the other hand, scores on both the paranoia and delusion items of the Positive and Negative Symptom Scale (PANSS) significantly decreased in the intervention group whereas they increased in the TAU group.

3.2.2. Worry and rumination

Three studies with good methodological rigour examined the role of worry in the occurrence of psychotic experiences. A worry induction on 67 patients with persecutory delusions led to an increase in anomalous experiences but not hallucinations (Freeman et al., 2013), and two interventions targeting worry also showed significant effects at outcome (Foster, Startup, Potts, & Freeman, 2010; Freeman et al., 2015). The strongest study randomised 150 patients with persistent persecutory delusions to receive either six sessions of a CBT worry treatment in addition to standard care or standard care alone (Freeman, Dunn, Startup, et al., 2015). It was found that the intervention significantly reduced both worry and persecutory delusions. Moreover, mediation analysis showed that change in worry accounted for 66% of the change in the persecutory delusions.

3.2.3. Negative affect

Three clinical studies investigated the causal relationship between negative affect, predominantly anxiety, and paranoia. An experiment by Freeman et al. (2015) was rated as having particularly good methodological quality. They found that upon randomising 59 patients with persecutory delusions to either go outside into a busy urban street or to stay inside, those in the former condition reported significantly more anxiety and negative thoughts about the self. Paranoid thoughts and voice hearing also significantly increased in this group. The increase in paranoia was mediated by increased anxiety, depression, and negative thoughts about others.

The second study concerned the anxiety-related psychological process of safety behaviours. Safety behaviours are actions designed to prevent certain feared catastrophes from occurring (Salkovskis, 1991). Such behaviours prevent individuals from receiving and processing evidence that goes against delusional beliefs, as they believe their feared catastrophe has not happened due to the use of safety behaviours rather than because their belief is inaccurate. Freeman et al. (2016) randomised 30 patients with persecutory delusions to enter a virtual reality social environment and either receive instruction to try to drop their usual safety behaviours or to keep using them. While it was not possible to ascertain the extent to which safety behaviours were fully dropped (although there were expected differences in objective movement in virtual reality), there were large reductions in the conviction with which persecutory delusions were held for the group instructed to reduce the use of safety behaviours.

It might be expected that increasing self-compassion in a clinical sample would reduce paranoia via a reduction in negative affect, as in Lincoln et al.'s (2013) non-clinical experiment. The only experiment to investigate this was by Ascone, Sundag, Schlier, and Lincoln (2017). 51 patients with paranoid ideation received a negative emotion induction via in sensu exposure to a recent distressing social situation and were then randomly assigned to a single session intervention using either compassionate imagery or control imagery. Skin conductance levels increased following the negative affect induction, suggesting the negative emotion induction increased physical stress, though no measure of subjective emotional distress was used. The compassionate imagery intervention significantly improved self-reassurance and happiness, but not self-compassion, and there was no change in paranoia at outcome.

3.2.4. Sleep

Only one intervention study targeting the improvement of sleep was found that used a clinical sample. Freeman et al. (2015) randomised 50 patients with persistent persecutory delusions or hallucinations to receive 12 weeks of CBT for insomnia in addition to standard care, or standard care alone. CBT was found to lead to significant reductions in insomnia as compared to standard care. However, the trial was insufficiently powered to determine with sufficient precision the effects of sleep improvement on hallucinations and delusions, which led to the subsequent OASIS trial (Freeman et al., 2017).

3.2.5. Reasoning biases

Six interventions, all having strong methodological quality, have successfully manipulated reasoning biases in clinical samples, with four out of the six finding a resultant change in paranoia. Reasoning biases may distort the appraisal or reappraisal of negative interpersonal events or anomalous experiences, thus increasing paranoia (Garety, Hemsley, & Wessely, 1991). Encouraging flexibility in belief formation might plausibly help reduce the impact of reasoning biases. The largest study was by Khazaal et al. (2015) who randomised 172 patients with psychosis to either a waitlist control or to an intervention using a card game targeting the ability to generalise alternative hypotheses. Belief flexibility improved following the intervention, and this group also reported significant decreases in delusion conviction, distress, and preoccupation, which was maintained at a six-month follow up. So et al. (2015) similarly demonstrated in their study of 44 patients with delusions that improved belief flexibility mediated reduced delusional conviction. A similar type of reasoning intervention by Garety et al. (2015) randomised 101 patients to receive brief computerised reasoning training to increase belief flexibility and reduce jumping to conclusions or an active control group involving basic computer activities. Belief flexibility improved and state paranoia reduced in those who received training. Mediation analysis showed that changes in reasoning mediated changes in paranoia. However, this effect did fall outside of conventional levels of statistical significance following adjustment for baseline confounders. Garety et al. (2015) also looked at the effect of training in belief flexibility on hallucinations, but found no improvements.

Two of the interventions examined the effects of reasoning training on the jumping to conclusions bias that is often seen in patients with delusions (Dudley, Taylor, Wickham, & Hutton, 2016). Moritz et al. (2015) randomised 70 patients with schizophrenia to receive six online presentations that taught about cognitive biases or to a waitlist control group. Although the teaching led to improvements in the jumping to conclusion bias, no significant changes in paranoia were seen. Similarly, Ross, Freeman, Dunn, and Garety (2011) found that a single session of reasoning training reduced jumping to conclusions, but it did not reduce delusional conviction significantly as compared to an attention control condition.

3.2.6. Beliefs about voices

Two interventionist-causal type trials attempted to change patients' beliefs about the voices that they hear. Both studies had good ratings of methodological quality. Craig et al. (2018) randomised 150 patients to receive AVATAR therapy or supportive counselling for 12 weeks. AVATAR therapy involved patients creating a computer screen avatar of their hallucination, and a therapist helping the person develop and practice a more helpful relationship with the avatar in order to facilitate change in beliefs about the actual voices. AVATAR therapy was successful in reducing patients' perceived omnipotence of voices, and also led to significant improvements in auditory hallucinations immediately post-treatment as compared to the supportive counselling group. Differences between the two randomised groups were not maintained at follow-up.

The COMMAND trial by Birchwood et al. (2014) randomised 197 patients who heard voices that they complied with to either receive

treatment as usual or a cognitive behavioural therapy targeting beliefs about the voices. The intervention reduced compliance with command hallucinations and a mediation analysis showed that a reduction in voice omnipotence was the main mediator of change (Birchwood et al., 2017).

3.2.7. Further psychological mechanisms

One intervention was found that examined the effect of trauma-focused treatment on patients with a lifetime psychotic disorder and current PTSD. Trauma may contribute to the occurrence of paranoia in a number of ways, for example leading to negative schemas concerning the self and others (Bentall et al., 2001; Garety et al., 2001). Van Den Berg et al. (2016) randomised 155 patients to receive eight sessions of trauma focused therapy or to a waitlist control group. PTSD symptoms significantly decreased in the treatment group after 8 weeks. Paranoia also decreased significantly after the first session of treatment as compared to the control group. At the end of all eight treatment sessions paranoia was still lower in the treatment group than the waitlist group, though the difference did not reach statistical significance.

Finally, Stinson, Valmaggia, Antley, Slater, and Freeman (2010) argue that certain cognitions may be important for triggering auditory hallucinations. They therefore instructed 30 patients with persecutory delusions to either focus on their (previously identified) cognitive antecedents to auditory hallucinations, or to focus on neutral cognitions unrelated to their hallucinations while they entered a tube train ride in virtual reality. However, the occurrence of auditory hallucinations in VR was the same for both groups, thus not providing evidence that antecedent cognitions trigger auditory hallucinations.

4. Discussion

We searched the empirical literature, with no date restriction, for studies manipulating psychological mechanisms potentially involved in psychotic experiences. Only 43 manipulationist studies were found. Just 18 of these studies were with people being seen in clinical services for psychosis. For one of the most severe mental health problems, this is a very small number of causal research studies. Hence, arguably the key point highlighted by the review is the limited number of studies that have directly tested causal roles for psychological processes in psychosis. Interestingly, all but four of the included experiments and interventions were conducted in the last decade, with over two-thirds conducted in the last five years. This perhaps reflects an increasing awareness of the importance of the approach and its neglect hitherto in psychosis research.

Notably, nearly all of the manipulationist studies were on paranoia. This particularly follows an endeavour by Freeman and colleagues to build a much more efficacious treatment for persecutory delusions by explicitly using manipulationist studies chosen on the basis of a theoretical model (Freeman et al., 2016). In this work, persecutory delusions are conceptualised as threat beliefs, developed in the context of genetic and environmental risk (Zavos et al., 2014), that are maintained by several psychological processes including anxious avoidance (safety-seeking behaviours), excessive worry, low self-confidence, poor sleep, anomalous experiences, and reasoning biases (Freeman, 2016). The causal mechanisms of maintenance are set out in this theoretical account: safety-seeking behaviours prevents the receipt of disconfirmatory evidence that the person is safe; worry brings implausible ideas to mind, keeps them there, and exacerbates the distress; low self-esteem (negative self-beliefs and low positive self-beliefs) lead the person to feel inferior and vulnerable to harm from others; subjectively anomalous internal states (e.g. hallucinations) provoke fearful and unusual explanations; disrupted sleep increases anxiety, worry, low self-esteem and the anomalous internal states; and reasoning biases prevent the processing of alternative explanations. Hence numerous different manipulationist tests are identifiable. Each main aspect of the model has been tested in a manipulationist design, and, most notably,

typically in a targeted interventionist treatment trial that has directly tested a treatment innovation. There has also been a valuable strand of manipulationist studies focussed on treatment development that have followed the repeated identification from the late 1980's onwards of reasoning biases such as jumping to conclusions in patients with delusions (Garety et al., 2015). Overall, the findings provide consistent evidence for the potential benefit of clinical interventions in the treatment of persecutory delusions that target worry, self-esteem, and negative affect. Treatment studies focussing on reasoning biases have had more variable results, though those targeting belief flexibility in particular do seem especially promising. Given that the effect sizes for first generation cognitive behavioural therapy are small (Bighelli et al., 2018), the argument is that successfully targeting specific mechanisms (i.e. translational research) has the potential to build better treatments. The interventionist-causal trials covered in this review have begun to demonstrate this promise. In interventionist-treatment trials there is a valuable combination of causal test and clinical test of specific treatment techniques.

Other than the literature on sleep – which itself still requires further work in clinical samples – only two intervention studies tried to reduce hallucinations via targeting key psychological mechanisms (appraisals) (Birchwood et al., 2014; Craig et al., 2018). These appraisal-focussed hallucination trials have shown clinical benefits. No interventions have specifically targeted grandiosity. The file-drawer problem might contribute to the lack of experimental manipulation studies, but this is far less likely to be the case with clinical interventions, given that the pre-registration of clinical trials now decreases the likelihood of such publication bias. More significant, therefore, is likely to be the time and difficulty involved in conducting such clinical intervention studies.

It is important to recognise that there are no single causes of psychotic experiences. Most causes are likely to be ‘in-us conditions’ – an *insufficient* but *non-redundant* part of an *unnecessary* but *sufficient* condition’ (Mackie, 1974). Each causal factor therefore only increases the probability of a particular psychotic experience occurring. A consequence of this is that the causal role of a mechanism can be difficult to detect without using a large sample size. Given this caveat, it is interesting that replicated findings are nonetheless seen in several areas, namely self-esteem, worry, negative affect, belief flexibility, and sleep, all in relation to paranoia.

It seems that when the psychological processes hypothesised in the psychological models of have been successfully manipulated then effects on psychotic experiences are seen. This is encouraging for the model and for the development of intervention. However, the findings in this review also perhaps indicate that research has been focused only on mechanisms in which there is a good deal of confidence in the relationship. As the field matures, we would hope to see novel mechanisms being successfully manipulated that are not found to have any effects on psychotic experiences, as would be expected in any well researched area.

Although in most cases methodological quality was strong, with risk of bias therefore being low, the included literature did have a number of limitations. Less than half of the included studies used mediation analysis, thus limiting to a degree the strength of causal inferences that are made. Moreover, six of the studies did not include a manipulation check. In cases where no effect on a psychotic experience was then found, it is unclear whether this was because the manipulation was unsuccessful or because the mechanism had no causal relationship to the outcome. Additionally, although the majority of samples included more than 50 participants, few included more than 100. Over half (15) of the non-clinical studies used student samples, making conclusions from these studies somewhat limited in their generalisability. Replications across different samples and with greater statistical power are needed, with a stronger focus on examining moderators and mediators of relationships.

4.1. Limitations of the review

There are number of limitations of the review. First, it cannot be guaranteed that the search strategy identified every study that would meet the inclusion criteria. While three different databases were searched, any study not including one word from each search string would not have been identified. Our scanning of citations and reference lists of included studies would have reduced the likelihood of this problem, but a number of studies may still not have been found. Second, the file-drawer problem means there may be unpublished studies that would have met criteria for inclusion in this review but have been missed. Fortunately, this is less of a problem for clinical trials given that they now need to be registered. Third, this review was limited to the positive symptoms of psychosis, specifically delusions and hallucinations. Negative symptoms of psychosis, such as anhedonia, were not examined. Finally, we chose to use Downs and Black (1998) scale of methodological quality, which has its limitations. The value of totalling a score for each study based on a wide variety of methodological questions, and giving it a rating based on this score, is rather questionable. Some aspects of method are more important than others, yet this method assigns equal weight to every aspect. Moreover, some of the questions within this tool are more appropriate for cohort studies than randomised controlled designs. To our knowledge there is no existing tool that focuses on the study design included in this review. Most tools are either solely for observational studies or for clinical trials.

4.2. Conclusion

As Shadish, Cook and Campbell (2002, page xv) state: “the rewards associated with being correct in identifying causal relationships can be high, and the costs of misidentification can be tremendous.”. Conducting manipulation experiments and therapeutic interventions serves an important theoretical and clinical purpose. The results of the studies included in this review indicate that these methods have the potential to be informative, but have been insufficiently applied to the psychological understanding of psychosis.

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PB conducted the systematic review of the literature and wrote a first draft of the manuscript under the supervision of DF and FW. DF and FW edited the text and contributed to the writing.

Conflict of interest

None.

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