

Cognitive Behaviour Therapy for Psychosis: Insights from Neuroimaging

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Abstract

Up to 40% of schizophrenia patients continue to suffer from distressing symptoms despite remaining compliant with their prescribed antipsychotic medication. Additional symptom reduction following cognitive behaviour therapy for psychosis (CBTp) has been shown, but only in about 50% of such patients. A clear understanding of the neural changes following CBTp (potential mediators of improvement in target outcomes) as well as neural predictors of CBTp-led improvement (possible moderators) may help to refine or develop it further and increase its effectiveness. We provide a review of studies published to date (9 in total) examining the neural effects and/or predictors of CBTp. The studies analysed comprised of one spectroscopic imaging study on pre- vs post-CBTp changes, five functional magnetic resonance imaging studies [two analysing pre- vs post-CBTp changes, two analysing pre-therapy brain properties as predictors of symptom reduction following CBTp, and one analysing pre- vs post-CBTp changes in functional connectivity as the predictors of long term (over 7 years) outcome following CBTp], and three structural magnetic resonance imaging studies [two on pre-therapy brain properties as predictors of symptom change following CBTp, and one analysing pre- vs post-CBTp changes]. The findings from pre- vs post-CBTp brain activation studies demonstrate that CBTp reduces fronto-limbic activation to social threat and normalises cortico-limbic functional connectivity, indicating improved affect regulation through top-down control after CBTp. Additionally, CBTp was found to reduce pituitary volume, potentially by lowering of symptom-related distress. The findings from studies analysing pre-therapy brain properties as predictors of symptom reduction following CBTp indicate that functional and structural properties of multiple brain areas that are implicated in a range of cognitive functions, particularly the dorsolateral (cognitive flexibility), medial (self-awareness) and inferior (verbal skills) frontal cortices, hippocampus (memory) and precuneus (self-awareness), predict symptom reduction following CBTp. These results suggest a role for cognitive enhancement in the context of CBTp.

Keywords

Schizophrenia, CBT, Threat, MRI, Brain activity, Functional connectivity

Introduction

Antipsychotic drugs reduce positive psychotic symptoms in the majority of acutely-ill schizophrenia patients [1, 2]. The long-term outcome, however, remains disappointing for up to 40% of patients who, despite remaining compliant with their prescribed antipsychotic medication, continue to experience one or more distressing symptoms [3-5]. A number of randomised control trials have

Table 1: Reviewed studies of the impact of CBTp (pre- vs post-CBTp) on brain structure and function as well as brain predictors of symptom reduction following CBTp in people with psychosis.

Neural Changes: Pre- vs Post-CBTp				
Authors	Imaging Modality (Brain Regions Examined)	Participants and Design	Task [Contrast]	Main Findings
Premkumar et al. (2010) [24]	Spectroscopic imaging (anterior cingulate cortex)	24 outpatients, 11 of whom received 6-9 months of CBTp in addition to their usual treatment (CBTp+TAU; final n=7 with usable imaging data) and 13 received treatment-as-usual (TAU; final n=4). 15 healthy controls. Patients scanned and had their symptoms [33] assessed on two occasions: at baseline and 8-9 months later (follow-up). Healthy controls examined once only.	NA	Lower N-acetyl aspartate (NAA) concentration in the anterior cingulate cortex in patients at baseline relative to healthy controls. NAA concentration increased (trend-level), in parallel to a reduction in positive symptoms at follow-up relative to baseline in the CBTp+TAU group.
Kumari et al. (2011) [25]	fMRI (whole brain)	56 outpatients, of which 28 received CBTp+TAU (final n=22), and 28 received TAU (final n=16). All patients scanned and had their symptoms assessed on two occasions: at baseline and 6-8 months later.	Implicit facial affect processing task. Participants presented with facial expressions of fear, anger, happiness as well as neutral expressions (and required to indicate gender), in addition to a (no face) control condition (happy, fearful, angry and neutral expression vs control condition).	Significant reduction in PANSS symptoms, particularly in delusions and depression, in the CBTp+TAU group. No symptom change from baseline to follow-up in the TAU group. Reduced activity from baseline to follow-up in the threat processing neural network, namely in the inferior frontal, insula, thalamus, putamen and occipital areas during the viewing of fearful and angry facial expressions found in the CBTp+TAU group, but not the TAU group. Significant association between the degree of reduction of fMRI activity during angry expressions and symptom improvement.
Mason et al. (2016) [26]	fMRI (whole brain)	Patients: same sample and design as noted above [25]. In addition, 20 healthy controls scanned on one occasion.	Connectivity during the angry facial expressions assessed separately from left amygdala and right dorsolateral prefrontal cortex (DLPFC) seeds.	Symptom changes as above. Concerning functional connectivity patterns at baseline, greater amygdala connectivity with the insula and visual areas, but less connectivity with somatosensory areas in patients, relative to healthy controls. At follow-up, the CBTp+TAU group showed normalisation of the above differences (normal-like patterns). In addition, CBTp+TAU showed greater increases, relative to the TAU group, in amygdala connectivity with DLPFC and inferior parietal lobule. Latter associated with reduction in positive symptoms. From the DLPFC seed, significantly greater increase in DLPFC connectivity with other prefrontal regions including dorsal anterior cingulate and ventromedial prefrontal cortex in the CBT+TAU group, relative to the TAU group.
Premkumar et al. (2017) [27]	Structural MRI (pituitary volume)	40 outpatients, of which 24 received CBTp+TAU and 16 received TAU. All patients scanned and had their symptoms assessed on two occasions: at baseline and 6-9 months later.	NA	Symptom changes as above. Pituitary volume reduced at post-CBTp follow-up, relative to baseline, in the CBT+TAU group. No change in the TAU group.

Pre-therapy Brain Properties as Predictors of Post-CBTp Symptom Reduction				
Kumari et al. (2009) [28]	fMRI (whole brain)	52 outpatients, 26 of whom received CBTp+TAU (final n=19) and 26 continued with TAU alone (final n=17). 20 healthy controls. All patients and controls scanned at baseline. Symptoms in patients assessed on two occasions: at baseline and 6-8 months later.	Parametric n-back task. Block design. (0-back, 1-back, 2-back blocks vs rest; 1-back and 2-back vs 0-back).	No difference in working memory performance or symptoms between the CBT+TAU and TAU groups at baseline. Baseline to follow-up change in symptoms in only the CBT+TAU group. Stronger DLPFC activity (within the normal range) and DLPFC–cerebellum connectivity during the highest memory load condition (2-back > 0-back) correlated with post-CBT reduction in symptoms.
Kumari et al. (2010) [29]	fMRI (whole brain)	52 outpatients, 26 of whom received CBTp+TAU (final n=20) and 26 continued with TAU alone (final n=18). 20 healthy controls. All patients and controls scanned at baseline. Symptoms in patients assessed on two occasions: at baseline and 6-8 months later.	Verbal self-monitoring task (event-related design) requiring participants to read single words presented on screen and then decide based on verbal feedback relayed back to them whether the speech they heard was in their own voice or someone else's. The feedback was given in (a) their own voice (self-undistorted), (b) their own voice lowered in pitch by 4 semitones (self-distorted), (c) voice of another person matched on participant's sex (other-undistorted), or (d) another person's voice with the pitch lowered by 4 semitones (other-distorted).	No difference in performance or symptoms between the CBT+TAU and TAU groups at baseline. Baseline to follow-up change in symptoms in only the CBT+TAU group. Less inferior frontal gyrus and thalamic activation in patients, relative to controls. Post-CBT reduction in symptoms correlated with (i) greater left inferior frontal gyrus activation during accurate monitoring, especially of own voice, (ii) less inferior parietal deactivation with own, relative to other's voice, and (iii) less medial prefrontal deactivation and greater thalamic and precuneus activation during monitoring of distorted, relative to undistorted, voices.
Premkumar et al. (2009) [30]	Structural MRI (voxel-based-morphometry, whole brain)	60 outpatients, 30 of whom received CBTp+TAU (final n=25) and 30 received TAU (final n=19). 25 healthy controls. All patients and controls scanned at baseline. Symptoms in patients assessed on two occasions: at baseline and 6-8 months later.	NA	At baseline, no difference between the CBT+TAU and TAU groups in symptoms. Reduced symptoms at follow-up, relative to baseline, in only the CBTp+TAU group. In the CBTp+TAU group, reduction at follow-up in: (i) positive symptoms associated with greater right cerebellum grey matter volume (ii) negative symptoms associated with greater left precentral gyrus and right inferior parietal lobule grey matter volumes, and (iii) general psychopathology associated with greater right superior temporal gyrus, cuneus and cerebellum grey matter volumes.
Premkumar et al. (2014) [31]	Structural MRI (orbitofrontal cortex)	30 outpatients who received CBTp+TAU (final n=25) for 6-9 months and 25 healthy controls. All patients and controls scanned at baseline. Symptoms in patients assessed on two occasions: at baseline and 6-8 months later.	NA	Orbitofrontal grey matter volume not significantly different between the patients and control groups. Association between greater orbitofrontal grey matter volume (at baseline) and reduction in positive symptoms (at follow-up) in patients.
Neuroimaging Predictors of Long Term Outcome Following CBTp				
Mason et al. (2017) [32]	fMRI (whole brain)	22 CBT+TAU patients of Mason et al. [26]. Monthly ratings of psychotic and affective symptoms obtained retrospectively across 8 years since receiving CBTp. Additionally, self-reported recovery evaluated at final follow-up.	Task as noted above for Kumari et al. [25] Post-CBTp changes in connectivity during the angry, fearful and happy facial expressions assessed separately from left amygdala and right DLPFC seeds [26]. Examined as predictors of long term recovery.	Long-term psychotic symptoms predicted by changes in prefrontal connections during happy (prosocial) facial affect processing. Long-term affective symptoms predicted by amygdalo-inferior parietal lobule connectivity during threatening facial expressions. Higher subjective ratings of recovery at long-term follow-up predicted by in DLPFC connectivity with amygdala during threatening facial expressions.

MRI: magnetic resonance imaging; fMRI: functional MRI; CBTp: cognitive behaviour therapy for psychosis; TAU: treatment-as-usual. DLPFC: dorsolateral prefrontal cortex

shown that persistent symptoms, particularly delusions and depression, can be reduced by cognitive behaviour therapy for psychosis (CBTp) in such patients with medication-refractory symptoms [6-8]. More recent studies also indicate a role for CBTp in the prevention of psychosis [9, 10].

Beck's cognitive model of psychopathology [11], which provided the framework for CBT for depression about 50 years ago, stipulates that problematic behavioural and emotional responses result from an individual's biased processing of external and/or internal information. Since then, CBT has been applied [12] in varied forms, depending upon the cognitive formulation of the disorder and target outcomes, to reduce symptoms in several psychiatric disorders, including psychosis [13]. Psychological models of CBT for psychosis, commonly referred to as CBTp [14, 15] propose that changes in patients' appraisal of their condition and psychotic experiences help ameliorate their symptoms. Key mechanisms of this approach include modifying patients' feelings of lack of control over their symptoms, diminishing their negative overall view of themselves and the world, and altering their exaggerated negative emotionality [14, 15]. The process of reappraising the distressing experiences of patients from their perspective seems relevant even in the context of effective antipsychotic treatment. It has been suggested [13] that antipsychotics may reduce acute psychotic symptoms (e.g. delusions) by "dampening the salience" of the abnormal experiences that caused or contributed to their formation, but they do not "erase" the symptoms. Symptom relief in the longer run may require the patients to "work through" and reappraise their experiences [16].

CBTp is recommended for the treatment of psychosis both in the UK [17] and in the US [18]. However, not all patients respond equally well to it. Symptom reduction with CBTp is seen with modest effect sizes and found to a noticeable degree in only about 50% of patients who undergo this therapy [6-8]. Furthermore, according to a recent meta-analysis, the effect size for symptom reduction following CBTp may be even smaller when sources of potential bias, such as masking of outcome assessments, are controlled for [19]. However, the effect sizes for other target outcomes, such as diminished distress or decreased preoccupation with symptoms, reduced depression and emotional difficulties, heightened social and occupational functioning, and improved overall quality of life (which have not been systematically examined or included in meta-analytic reviews) may be larger [20, 21].

There is clearly a need for a better understanding of when and why CBTp works. It is reasonable to expect that neuroimaging studies identifying i) the impact of CBTp on brain structure or function, and ii) the (pre-CBTp) brain predictors of CBTp response would offer insight into possible mediators and moderators of CBTp effects. Specifically, the knowledge of which brain processes respond favourably to CBTp (possible mediators of improvement in target outcome) and which brain processes facilitate them (possible moderators of improvement) may help to develop and refine CBTp further to augment its efficacy.

The aim of this review is to appraise published studies that

have examined the neural effects and/or predictors of effective CBTp in schizophrenia and consider the implications of their findings for future developments of CBTp. Although there have been recent reviews of brain changes following psychological therapies more generally [22, 23], none have focused specifically on the brain correlates or predictors of CBTp effectiveness.

Literature Search

We conducted a comprehensive literature search of electronic databases (PubMed and Web of Science) using the search term ("psychosis" OR "psychotic" OR "schizophrenia" OR "schizophrenic") AND ("cognitive behav* therapy" OR "CBT") AND ("neuroimaging" OR "MRI" OR "Magnetic Resonance" OR "fMRI" OR "MRI"). The search was run on 12th May 2017 with no time range specified for the date of publication. Our search revealed 9 papers in total [24-32], all published within the last 10 years (see Table 1 for greater details).

Results

The main findings of the reviewed studies are summarised in Table 1.

Pre- vs post-CBTp changes

So far four reports [24-28], all published within the last 7 years and with overlapping samples from the same research group, have focused on pre- vs post-CBTp brain changes in psychosis. Of these, one study [24] used spectroscopic imaging, two studies used functional magnetic resonance imaging (fMRI) [25-26], and one study used structural magnetic resonance imaging (MRI) [27]. The findings of each of these are described and discussed below.

Spectroscopic imaging

Premkumar and colleagues [24] used spectroscopic imaging to investigate the changes following CBTp. Their study provided preliminary evidence for N-acetyl aspartate (NAA) concentration in the anterior cingulate cortex (ACC) to increase following 6-8 months of NICE (National Institute for Clinical Excellence, UK)-compliant CBTp [17], adjunct to treatment-as-usual, in a small group of medication-resistant schizophrenia patients. The increase in ACC NAA was concomitant with improvement in positive symptoms, as assessed by the positive and negative syndrome scale (PANSS) [33]. No change in ACC NAA was found in a matched group of patients who were also studied over the same time scale but did not receive CBTp. Furthermore, at baseline, ACC NAA concentration was lower in patients than matched healthy controls and correlated negatively with positive and general psychopathology symptoms scores. Although a neural change was observed in this study following CBTp, it may not tell us much about the specific mechanisms of CBTp action since the use of atypical (but not typical) antipsychotic drugs is also known to be accompanied with increased ACC NAA levels in both recent-onset cases and patients with chronic illness [34, 35].

fMRI

In the first study using fMRI, Kumari and colleagues [25] examined 56 outpatients with one or more persistent distressing positive symptoms of schizophrenia, 28 of whom received CBTp for 6-8 months in addition to their usual treatment (CBTp+TAU), and 28 received treatment-as-usual (TAU). All patients underwent fMRI during an implicit affect processing task (gender discrimination) at baseline and the end-of-treatment follow-up. They had their symptoms assessed by a clinician blind to treatment group on both occasions (baseline and follow-up). The CBTp+TAU and TAU groups were comparable at baseline in terms of clinical and demographic characteristics and neural and behavioural responses to affective and neutral facial expressions. There was significant reduction in PANSS symptoms, particularly in delusions and depression, in the CBTp+TAU group, relative to the TAU group, which did not show significant symptom change from baseline to follow-up. The CBTp+TAU group, but not the TAU group, showed reduced activity from baseline to follow up in the threat processing neural network, namely in the inferior frontal, insula, thalamus, putamen and occipital areas during the viewing of fearful and angry facial expressions. The degree of reduction of fMRI activity during angry expressions correlated directly with symptom improvement. This study provided the first empirical evidence that effective CBTp reduces brain responses to social threat and most likely mediates symptom reduction by promoting processing of threats in a less distressing way. The areas showing reduced activation after CBTp are known to be involved in the detection and processing of threat [36] and can be expected to change following CBTp, possibly in association with a reduction in subjective experience of threat and distress following CBTp. Interestingly, post-CBT changes in many of the areas involved in threat processing have also been seen in depression and anxiety disorders [22]. This is perhaps not surprising given that CBT across disorders [12] aims to modify appraisals of physiological, cognitive and affective states and normalise (otherwise distorted) construction of experiences.

A later study [26] examined functional connectivity during social threat (angry expressions) separately from left amygdala and right dorsolateral prefrontal cortex (DLPFC) seeds in the sample reported earlier by Kumari et al. [25] to further examine the mechanisms underlying CBTp-led changes in threat processing and appraisal. The findings revealed that patients who received CBTp+TAU, but not those who received TAU, displayed normalised amygdala connectivity with the insula and visual areas (i.e. functional connectivity patterns showing amygdala connectivity with the insula and visual areas after, but not before, CBTp). They also showed greater increases in amygdala connectivity with DLPFC and inferior parietal lobule, with the latter associating with positive symptom improvements. From the DLPFC seed, the group which received CBTp+TAU showed a significantly greater increase in DLPFC connectivity with other prefrontal regions, including the dorsal anterior cingulate and ventromedial PFC, relative to the TAU group. These findings suggest that CBTp boosts connectivity between higher-order cognitive systems and those involved in threat and salience processing.

Furthermore, these results are in line with the suggestion that appropriate affect modulation requires the modulation of ventral and limbic regions by DLPFC through top-down connectivity [37].

Structural MRI

Very recently, Premkumar and colleagues [27] examined possible changes in pituitary volume in a subsample of patients who took part in the earlier study by Kumari and colleagues [25]. Pituitary volume was found to be reduced at post-CBTp follow-up, relative to baseline, in those who received CBTp in addition to their usual treatment but not in those who remained in treatment-as-usual. Since the pituitary is involved in stress regulation [38], this finding most likely reflects enhanced stress regulation and lowering of symptom-related distress.

Neuroimaging predictors: pre-therapy brain properties as predictors of symptom reduction following CBTp

The integrity of brain areas involved in the top-down processing of information is postulated to be associated with CBT responsiveness across disorders [39-41]. Most psychiatric disorders are associated with neurocognitive deficits to some degree. These deficits, despite skilled therapy adaptations to compensate for them, may hamper effective CBT by impeding patients' ability to remember information discussed during therapy sessions, to acquire new, more flexible thinking styles or coping strategies, or to generalise specific issues discussed during therapy session to other situations. Consistent with this notion, there is empirical evidence to suggest that pre-therapy level of cognitive function, in particular executive function [42-45] and the integrity of associated neural structures [46, 47], influence the response to CBT for anxiety and depression, particularly in older adults who are likely to be cognitively compromised at least to some degree. Pre-therapy level of neurocognitive function is likely to be an even stronger predictor of CBTp response in schizophrenia than the association seen in anxious, depressed or aged population, since this clinical population, on average, is known to be characterized by a range of neurocognitive deficits [48, 49].

Functional MRI

Of the two studies that used fMRI to examine neural predictors of CBTp responsiveness, the first study [28] examined the association between pre-therapy brain activity within the working memory neural network and clinical response to CBTp. Stronger bilateral DLPFC activation (but within the normal range) during the memory load condition was found to be positively associated with post-CBTp clinical improvement. In addition, positive connectivity between the left DLPFC and cerebellum and reduced deactivation of the default network regions were strongly associated with a favourable response to CBTp. Of various fronto-parietal regions normally activated by the n-back task (see Table 1 for task details), the DLPFC contributes primarily to executive processes such as noting the contents of working memory [50, 51] and executive control of maintenance and manipulation [52]. The DLPFC is also critical for relational processing in

decision-making [53] and top-down control [54]. It can be inferred from these results that patients with relatively intact DLPFC function were more capable of schema induction (facilitating transfer of learning from one situation to other, similar situations), reasoning, and relational processing (pooling together and comparing decision-relevant information), and thus they benefited the most from CBTp. An interesting observation of this study was, although DLPFC activity of both hemispheres was associated with a favourable response to CBTp, the left DLPFC showed a more robust pattern of activity and connectivity with the cerebellum in association with CBTp responsiveness. This finding suggests that left hemisphere resources (verbal processing) may be crucial for a beneficial outcome of CBTp, as reported previously for CBT for depression [55]. This potential association between the left DLPFC-cerebellum connectivity and a favourable CBTp response may reflect cerebellar contributions to executive control [56–58]. Furthermore, the relationship between reduced deactivation of the default network regions (which are normally engaged in ‘default mind-wandering states’) and poor response to CBTp possibly indicates a reduced ability to focus on and/or switch to the task-at-hand in poor CBTp responders.

The second fMRI study [29] investigated whether pre-therapy brain activity during a verbal self-monitoring task [59] predicts a favourable response to CBTp. The task involved monitoring self- and externally-generated speech, which were either normal or distorted (see Table 1 for further task details). The use of various forms of speech for this investigation was motivated by the role of left hemisphere-based language processes in responsiveness to CBT for depression [55], language pathway abnormalities in psychosis [60, 61], and the earlier finding concerning the left DLPFC response associating somewhat more strongly than the right DLPFC response with CBTp effectiveness [28]. The findings revealed positive associations between a favourable response to CBTp and greater left inferior frontal gyrus activity during accurate monitoring, especially of own voice. The results also showed less inferior parietal deactivation/slight activation with monitoring own voice relative to someone else’s and less medial prefrontal deactivation and greater thalamic and precuneus activation with monitoring of distorted voices relative to undistorted voices. All greater activations were within the normal range (i.e. not hyper-activated in patients relative to healthy participants). The left inferior frontal gyrus-CBTp response association observed in this study was in line with earlier findings in the context of CBT for depression [55] and well explained by known involvement of the left inferior frontal gyrus (Broca’s area) in speech and language processing [62] and verbal working memory [50]. The thalamus is involved in attention [63] while the medial prefrontal, inferior parietal and precuneus regions are implicated in self-awareness, self-representation and reflection of own experiences [64–66]. Given these functions, the findings can be taken to suggest that patients with relatively preserved language processing (left inferior frontal gyrus), attention (thalamus), and insight and self-awareness (medial prefrontal, inferior parietal, precuneus) benefitted most from CBTp.

Structural MRI

Of the two structural MRI studies, the first study [30] used voxel-based morphometry to examine the association between pre-therapy grey matter volume across the whole brain and reduction in symptoms following CBTp. The findings showed positive associations between CBTp-led improvement in symptoms and grey matter volume in a number of localised regions, particularly in the cerebellum, superior temporal gyrus and the parietal lobe. Although this study was exploratory in that it examined CBTp associations with voxels across the whole brain, the observed grey matter volume-CBTp response associations appear meaningful. Disruption in the cortico-cerebellar-thalamo-cortical circuitry has been theorised to result in deficient processing, prioritising, retrieval, coordination, and responding to information in schizophrenia [67]. Several studies have confirmed cerebellar contributions to higher order cognitive functions, such as task management and multi-tasking components of executive processing [56, 57]. There is evidence for the involvement of the parietal lobe in both working and episodic memory [68]. GMV of the superior temporal gyrus is positively associated with abstraction ability [69] and awareness of symptoms and attributing them to illness in patients with schizophrenia [70]. Perhaps the most interesting finding of this study was that CBTp+TAU responders (11/25 showing >20% improvement from baseline on total PANSS scores) had greater hippocampal volume relative to CBTp+TAU non-responders. Hippocampal volume is known to correlate positively with verbal learning and memory in schizophrenia [71] and there is evidence from another research group for impaired verbal memory to be a limiting factor in the context of CBTp [72]. Patients with greater grey matter volume in the areas associated with a good CBTp response were perhaps relatively better at coordination of mental activity, cognitive flexibility, verbal learning, and memory, all of which can be expected to facilitate CBTp. A more recent study [31], using a region-of-interest approach and the same sample reported previously by Premkumar and colleagues [30], demonstrated an association between larger grey matter volume of the orbitofrontal cortex and symptom reduction following CBTp. This association is most likely explained by the role of orbitofrontal cortex in emotional decision-making and cognitive flexibility [73].

Neuroimaging predictors of long term outcome following CBTp

CBTp has been reported to produce continued improvements at a longer follow-up (e.g. 9 months after the end of CBTp) [74] and reported to be associated with better longer term outcomes (e.g. lower symptom levels 5 years after the end of CBTp) [75]. Very recently, Mason and colleagues [32] examined and detected a positive association between some of the cortico-limbic connectivity changes observed immediately following CBTp [27] and clinical outcomes over a 7 year period. These findings highlighted the importance of neuroimaging in the context of improved longer term outcome in schizophrenia and perhaps other psychiatric disorders.

Implications: future research and therapeutic avenues

All published studies examining the neural effects and

predictors of CBTp so far arise from an overlapping sample of outpatients with fully or partially medication resistant symptoms. Nonetheless, their findings have important implications both at the theory level and clinical practice level. At the theory level, the findings concerning the effects of CBTp on brain functions [25-27] agree with current psychological models of CBTp [14, 15], which state CBTp aims for a reappraisal of, and a reduction in distress in response to, signals of potential direct threat (e.g. distressing voices or eye contact from strangers). To further elucidate the mechanisms of CBTp, future studies should aim to clarify whether CBTp normalises fronto-limbic activations to threatening stimuli via its effect on conscious processing of emotional information (help patients re-interpret and disengage from threat-related information), early unconscious emotion processing (addressing hyper-vigilance, pre-attentive bias to threat), or both. Such a distinction is important because both a pre-attentive bias for detection of threat-related information as well as difficulty disengaging threat-related emotional material from conscious awareness have been implicated in delusional beliefs [76]. It would also be valuable to examine emotion regulation and worry management as possible mechanisms of CBTp [77, 78]. Finally, future studies need to examine the neural mechanisms, especially the involvement of brain systems implicated in cognitive reappraisal of emotions [37] and recently found to predict longer term outcome [32], underlying CBTp effects on specific symptoms, such as depression and delusions [79, 80], and those that might explain improvements in other target outcomes such as reduced symptom-related distress, increased social and occupational functioning and higher well-being [20, 21].

The findings concerning the neural predictors of CBTp suggest novel avenues for future development and modification of CBTp at the clinical practice level for schizophrenia patients who appear relatively less responsive to current versions of the routine CBTp. For example, targeting insight and self-monitoring skills very early during the course of CBTp may improve the clinical benefits of CBTp. CBTp may need to be further modulated for patients with impaired executive function, memory and language processing skills. A formal pre-therapy assessment of relevant cognitive functions followed by targeted cognitive remediation therapies [81] may be helpful. There are promising data showing that cognitive remediation therapies can normalise activity in many brain areas, including the prefrontal and cingulate regions that commonly show activation deficits during working memory and affect processing paradigms in schizophrenia [82] and also found predict CBTp response [24-32].

Conclusion

Neuroimaging studies have helped to elucidate the mechanisms of effective CBTp by showing that it reduces or normalises brain response to social threat. They also highlight the importance of pre-therapy level of brain function in the context of effective CBTp. Addressing relevant brain and cognitive deficits prior to or during CBTp with cognitive enhancement therapies may improve the efficacy of CBTp.

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Conflict of Interest

The author reports no conflict of interest.

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