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Neural changes following cognitive behaviour therapy for psychosis: a longitudinal study

Veena Kumari,[1,2] Dominic Fannon,[1] Emmanuelle R. Peters,[1,2] Dominic H. ffytche,[3] Alexander L. Sumich,[1] Preethi Premkumar,[1] Anantha P. Anilkumar,[4] Christopher Andrew,[3] Mary L. Phillips,[5] Steven C. R. Williams[3] and Elizabeth Kuipers[1,2]

1 Department of Psychology, Institute of Psychiatry, King's College London, London SE5 8AF, UK
2 NIHR Biomedical Research Centre for Mental Health, South London and Maudsley NHS Foundation Trust, London SE5 8AZ, UK
3 Department of Neuroimaging, Institute of Psychiatry, King's College London, London SE5 8AF, UK
4 South London and Maudsley NHS Foundation Trust, London SE5 8AZ, UK
5 Department of Psychiatry, Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine, Pittsburgh, PA 15213, USA

Correspondence to: Veena Kumari,
Department of Psychology, P078,
Institute of Psychiatry,
King's College London,
De Crespigny Park,
London SE5 8AF, UK
E-mail: veena.kumari@kcl.ac.uk

A growing body of evidence demonstrates that persistent positive symptoms, particularly delusions, can be improved by cognitive behaviour therapy for psychosis. Heightened perception and processing of threat are believed to constitute the genesis of delusions. The present study aimed to examine functional brain changes following cognitive behaviour therapy for psychosis. The study involved 56 outpatients with one or more persistent positive distressing symptoms of schizophrenia. Twenty-eight patients receiving cognitive behaviour therapy for psychosis for 6–8 months in addition to their usual treatment were matched with 28 patients receiving treatment as usual. Patients' symptoms were assessed by a rater blind to treatment group, and they underwent functional magnetic resonance imaging during an affect processing task at baseline and end of treatment follow-up. The two groups were comparable at baseline in terms of clinical and demographic parameters and neural and behavioural responses to facial and control stimuli. The cognitive behaviour therapy for psychosis with treatment-as-usual group (22 subjects) showed significant clinical improvement compared with the treatment-as-usual group (16 subjects), which showed no change at follow-up. The cognitive behaviour therapy for psychosis with treatment-as-usual group, but not the treatment-as-usual group, showed decreased activation of the inferior frontal, insula, thalamus, putamen and occipital areas to fearful and angry expressions at treatment follow-up compared with baseline. Reduction of functional magnetic resonance imaging response during angry expressions correlated directly with symptom improvement. This study provides the first evidence that cognitive behaviour therapy for psychosis attenuates brain responses to threatening stimuli and suggests that cognitive behaviour therapy for psychosis may mediate symptom reduction by promoting processing of threats in a less distressing way.

Keywords: cognitive behaviour therapy; fMRI; schizophrenia; threat

Abbreviations: CBT = cognitive behaviour therapy; PANSS = Positive and Negative Syndrome Scale; TAU = treatment as usual

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Introduction

According to Beck's cognitive model of psychopathology (Beck, 1963), biased processing of external and/or internal events or stimuli distorts an individual's construction of experiences and leads to problematic behavioural and emotional responses. This model served as the basis for development of cognitive behaviour therapy (CBT) for depression >40 years ago (Beck, 2005). Numerous studies since then have established the effectiveness of CBT, applied in varied forms depending upon the cognitive formulation of a particular disorder, in reducing symptoms across a range of psychiatric disorders, including obsessive compulsive disorder, social phobia, panic disorder and psychosis (Butler *et al.*, 2006). The most common application of CBT for psychosis has been as an additional treatment to drug therapy for medication-resistant patients with schizophrenia, with its beneficial effects evident as a reduction in persistent positive symptoms, particularly delusions, and secondary disturbances such as depression (Pfammatter *et al.*, 2006; Wykes *et al.*, 2008; NICE, 2009).

The neuroscience of CBT is a novel area with important implications for our understanding of the mechanisms of maintenance of symptoms and of therapeutic change (Brenner *et al.*, 2006; van der Gaag, 2006). A number of studies have already documented significant neural changes following psychological therapies for depression (Martin *et al.*, 2001; Goldapple *et al.*, 2004; Fu *et al.*, 2008), obsessive compulsive disorder (Schwartz *et al.*, 1996), panic disorder (Prasko *et al.*, 2004) and social (Furmark *et al.*, 2002) and animal phobias (Paquette *et al.*, 2003; Straube *et al.*, 2006; Schienle *et al.*, 2009).

The aim of the present study was to examine, for the first time to our knowledge, what kind of functional brain changes, if any, might emerge following CBT for psychosis in patients with persistent and distressing positive symptom(s) of schizophrenia. To achieve this, we applied functional MRI during implicit processing of facial expressions denoting direct as well as indirect threat (Frijda, 1986; Fridlund, 1994). Angry expressions signal a direct and immediate threat, while fearful expressions indicate the presence of a significant, but uncertain, source of threat in the environment (Fridlund, 1994). Paranoia, a main symptom of psychosis, is fundamentally a threat response (Freeman *et al.*, 2002). Heightened perception and processing of social threat has been suggested to constitute the genesis of persecutory delusions (Green and Phillips, 2004), explained at least in part by inappropriate engagement of the brain's fear system (Corlett *et al.*, 2010). Both a pre-attentive bias for detection of threat-related information as well as difficulty disengaging threat-related emotional material from conscious awareness are considered to be involved in delusional beliefs (Green and Phillips, 2004).

Given consistent evidence for improvement in persistent positive symptoms, especially delusions, after CBT for psychosis (Pfammatter *et al.*, 2006; Wykes *et al.*, 2008; Rathod *et al.*, 2010), and the association between paranoia and aberrant processing of social threat (Green and Phillips, 2004), the present investigation tested the hypothesis that psychotic individuals with persistent positive symptoms of schizophrenia following a course of CBT for psychosis would display attenuated neural processing within the network of brain regions processing facial expressions, particularly those related to threat (i.e. fearful and angry expressions). The network of regions processing emotional facial expressions includes visual (fusiform gyrus, inferior and middle occipital gyrus, lingual gyrus), limbic (amygdala, parahippocampal gyrus), temporoparietal (middle–superior temporal gyrus, parietal lobule), prefrontal and subcortical areas (putamen), insula and the cerebellum (Fusar-Poli *et al.*, 2009). Of these regions, activation of the amygdala, which signifies fear processing (LeDoux, 2000), and of the insula, which is associated with anticipation and evaluation of potentially distressing cognitive and sensory information (Reiman *et al.*, 1997; Kumari *et al.*, 2009*a*), was hypothesized in particular to show reduced activation following a course of CBT for psychosis. No specific hypothesis was formulated with regard to neural response to happy expressions since enhancement of positive emotions is not a primary target of CBT for psychosis.

Materials and methods

Participants and design

The investigation involved 56 outpatients, 54 with paranoid schizophrenia and two with schizoaffective disorder diagnosed by a trained psychiatrist using the Structured Clinical Interview for DSM-IV (SCID; First *et al.*, 1995). All patients included in this study: (i) were right-handed; (ii) had no history of neurological conditions or head injury; (iii) had been on stable doses of antipsychotics for ⩾2 years, and on the present antipsychotic for >3 months; (iv) received a rating of ⩾60 on the Positive and Negative Syndrome scale (PANSS) (Kay *et al.*, 1987) and had at least one persistent positive symptom (a score of 3 or above on at least one of the positive symptoms items of the PANSS, which they experienced as distressing); and (v) were willing to receive 6–8 months of CBT for psychosis in addition to their usual treatment.

Of the 56 patients who participated in this study, 28 patients received CBT for psychosis for 6–8 months in addition to their usual treatment (CBT for psychosis + TAU group) and 28 continued to receive treatment as usual (TAU-alone group). The patients in the CBT for psychosis + TAU and TAU-alone groups were recruited from the same geographical area (South London, UK) and were identified by local psychiatric consultants as suitable for CBT for psychosis. The recruitment of patients into the study and the creation of study groups followed a cohort case-controlled design and involved the following steps: (i) a patient referred by his/her local consultant and accepted for CBT for psychosis by the Psychological Interventions Clinic for Outpatients with Psychosis (PICuP), South London and Maudsley NHS Foundation Trust; (ii) study introduced to the patient by PICuP staff; (iii) patient contacted by research team if interested in taking part in functional MRI study; (iv) if suitable clinically and functional MRI compatible (e.g. no metal in the body) patient recruited into the functional MRI study as part of the CBT for psychosis + TAU group; and (v) another patient with similar demographic and clinical characteristics (to that of the patient included in the CBT for psychosis + TAU group) recruited for the TAU-alone group via local consultants and studied over the same interval as the CBT for psychosis + TAU group. With the resources then available to the South London and Maudsley NHS Foundation Trust, out of all patients potentially eligible for CBT for psychosis, only ~10% patients were referred for CBT for psychosis at the time of patient recruitment (March 2003–June 2007).

There were no explicit biases in which patients received CBT for psychosis. Allocation of CBT for psychosis was driven by clinical resource limitations of the NHS Trust and not by patient characteristics. The researchers were independent of clinical decisions regarding which patients were referred for CBT for psychosis.

All patients underwent clinical assessment and functional MRI during the affect processing task at entry and follow-up (6–8 months later). TAU-alone patients were followed-up over the same period as CBT for psychosis + TAU patients in order to confirm CBT for psychosis led, rather than non-specific (time effect), symptom improvement and functional brain changes in the CBT for psychosis + TAU group.

Of 28 patients initially recruited in each group, 22 patients of the CBT for psychosis + TAU group and 16 patients of the TAU-alone group completed all assessments at baseline and follow-up and provided usable data. These patients had remained on the same type and dosage of antipsychotic medication during the follow-up period. Consent withdrawal, medication change or non-compliance and incomplete or unusable imaging data at baseline or follow-up were the primary reasons for patient drop-outs or exclusion from the study. Table 1 presents clinical and demographic characteristics of the final sample.

The study was approved by the research ethics committee of the Institute of Psychiatry and the South London and Maudsley NHS Foundation Trust (Ref 209/02). All participants provided written informed consent after the study procedures had been explained to them.

Cognitive behaviour therapy for psychosis and treatment-as-usual procedures

After baseline assessments, the CBT for psychosis + TAU group received 6–8 months of CBT for psychosis following a published manual (Fowler *et al.*, 1995) as described in our earlier studies (Kumari *et al.*, 2009*b*, 2010). Therapy sessions were conducted weekly or fortnightly, as preferred by the patient, for up to 1 h. Patients received an average of 16 sessions, as recommended by NICE guidelines in the UK (NICE, 2009). All CBT for psychosis interventions were formulation driven, and focused on the therapy goals of the patient. The Psychological Interventions Clinic for Outpatients with Psychosis (South London and Maudsley NHS Foundation Trust) has evidence of good therapy outcomes (Peters *et al.*, 2010). The therapists were supervised by one of the two investigators (E.K., E.R.P.) who have extensive experience of CBT for psychosis. The treatment adherence was recorded via fortnightly supervision. In addition, a small, random selection of therapy sessions ($n = 13$) were taped and sent to an independent, experienced CBT for psychosis therapist to be rated for fidelity of treatment using the Cognitive Therapy Scale for Psychosis (Haddock *et al.*, 2001). TAU provided to all patients prior to and during the study consisted of management offered by a case management team with a dedicated care coordinator who saw the patient on a regular basis, in addition to

Table 1 Demographics, task performance and clinical characteristics of participants

Demographics	CBT for psychosis + TAU group ($n = 22$, 18 males)		TAU-alone group ($n = 16$, 14 males)	
	Mean (SD) Baseline	Mean (SD) Follow-up	Mean (SD) Baseline	Mean (SD) Follow-up
Age (years)	35.68 (7.82)		39.19 (9.37)	
Education (years)	13.90 (3.26)		13.56 (1.71)	
Predicted IQ[a]	109.38 (9.68)		106.64 (9.73)	
Age at illness onset (years)	24.77 (8.38)		25.81 (8.49)	
Duration of illness (years)	10.91 (7.70)		13.37 (10.16)	
Performance				
Gender discrimination accuracy (%)				
Neutral	92.62 (10.81)	91.76 (13.14)	88.28 (10.79)	90.04 (14.57)
Fear	90.48 (14.35)	91.36 (16.53)	87.89 (20.94)	87.89 (18.46)
Anger	88.63 (15.23)	88.92 (14.16)	84.77 (16.05)	87.30 (19.07)
Happy	94.74 (8.48)	93.32 (9.94)	92.38 (7.82)	90.82 (12.31)
Detection (%)				
No face	93.39 (12.39)	91.48 (16.42)	93.80 (13.72)	92.48 (18.12)
PANSS[b] symptoms				
Positive symptoms	18.09 (4.84)	14.86* (4.10)	18.56 (3.20)	18.06 (3.30)
Negative symptoms	17.73 (4.23)	15.59* (4.29)	19.13 (4.13)	20.31 (4.38)
General psychopathology	33.45 (7.24)	28.59* (7.40)	35.38 (4.41)	35.38 (6.49)
Total symptoms	69.27 (13.30)	59.04* (14.73)	73.06 (9.28)	73.75 (11.83)
Antipsychotic medication				
Type	20 patients on atypical; 2 on both atypical and typical antipsychotics	As baseline	14 patients on atypical; 2 on both atypical and typical antipsychotics	As baseline
Dose in chlorpromazine equivalents (mg)	543.00 (479.34)		448.92 (338.84)	

Duration of illness = current age minus age of illness onset.
a National Adult Reading Test (Nelson and Willison, 1991).
b Kay *et al.* (1987).
*Symptom reduction ($P < 0.05$) in the CBT for psychosis + TAU, relative to the TAU alone group (no significant change in TAU-alone group, $P > 0.05$), at follow-up relative to baseline.

a psychiatrist and other specialists, such as a benefits adviser or a vocational advisor, as needed.

Symptom assessment

Symptoms were rated in all patients, using the PANSS (Kay *et al.*, 1987), at entry (baseline) and then 6–8 months later (follow-up) by an experienced psychiatrist (D.F.), who had no role in clinical management and was blind to whether patients received CBT for psychosis or not. Appointments for these assessments were made by another member of the research team.

Functional magnetic resonance imaging paradigm and procedure

Participants were presented with black and white pictures depicting facial emotions (Ekman and Friesen, 1976). Three types of emotions (fear, anger, happiness; 100% expression) and relatively neutral expressions were shown in 30-s blocks of eight pictures each, with each picture presented for 3.75 s. There were 16 30-s blocks with facial expressions (four fear, four anger, four happy, four neutral), each followed by a 15-s control block during which an oval frame, as in facial expression trials and matched for luminance but without the face inside, appeared four times. We used this non-face condition, and not neutral facial expressions, as the control condition because individuals with schizophrenia (Horley *et al.*, 2001, Hall *et al.*, 2008) and those at a high risk of psychosis (Seiferth *et al.*, 2008) may respond to neutral expressions as if they were threatening and are reported to activate brain regions that are normally associated with fear processing while viewing neutral expressions (Hall *et al.*, 2008; Seiferth *et al.*, 2008). The sequence of presentation of fear, anger, happy and neutral blocks was counterbalanced over the 12-min experiment. On presentation of each facial expression, participants were required to indicate whether the face was male or female by pressing the left (female) or the right (male) button on a button box to ensure they were attending to the stimuli. During the 'no face' control condition, attention was monitored by asking participants to press either button (left or right) when the blank oval frame appeared. Patients underwent task familiarization in advance of the scan through practice of the gender discrimination task once on all identities used in the functional MRI experiment on a laptop computer and an identical button box device. They were requested to abstain from alcohol for at least 24 h prior to their scanning.

Image acquisition

Echoplanar magnetic resonance brain images were acquired using a 1.5 T GE Signa system (General Electric). In each of 16 near-axial non-contiguous planes parallel to the intercommissural plane, 240 T_2*-weighted magnetic resonance images depicting blood oxygen level-dependent contrast (echo time 40 ms, repetition time 3 s, flip angle 90°, field of view 240 mm, matrix 64 × 64, in-plane resolution 3.1 mm, slice thickness 7.0 mm, interslice gap 0.7 mm) were acquired over the experiment. In the same session, a high-resolution 3D inversion recovery prepared spoiled gradient recalled acquisition in the steady state volume data set was acquired with echo time = 5.3 ms, inversion time = 300 ms, repetition time = 12.2 ms, in-plane resolution = 0.94 mm, slice thickness = 1.5 mm.

Data analysis

Behavioural measures

The CBT for psychosis + TAU and TAU-alone groups were compared on age, education, predicted IQ (Nelson and Willison, 1991) and baseline PANSS symptoms using independent-sample *t*-tests.

The change in symptoms from baseline to follow-up was investigated using a Group (CBT for psychosis + TAU, TAU alone) × Time (baseline, follow-up) analysis of variance (ANOVA) with Group as the between-subjects factor and Time as the within-subjects factor. A significant Group × Time effect was followed-up by paired *t*-tests on total and subscale PANSS scores separately in the CBT for psychosis + TAU and TAU-alone groups. Following the observation of significant symptom reduction in the CBT for psychosis + TAU, but not in the TAU-alone group (refer to the 'Results' section), we examined potential associations between baseline symptom severity and symptom change (total baseline minus total follow-up) in the CBT for psychosis + TAU group using Pearson's correlations, and confirmed the effects of CBT for psychosis using ANCOVAs on symptom change scores after co-varying for baseline symptoms. We then calculated the symptom change data (baseline minus follow-up) on an item-to-item basis to find out which items showed the strongest improvement (top six) with CBT for psychosis and, given earlier findings of a positive relationship between persecutory delusions and depression in psychosis (e.g. Freeman *et al.*, 1998; Smith *et al.*, 2006), explored the interrelationships among these items at baseline across the whole sample using Spearman correlations.

Performance data (percentage of correct gender discrimination in facial expressions) were analysed by a Group (CBT for psychosis + TAU, TAU alone) × Time (baseline, follow-up) × Task (fear, anger, happy, neutral) ANOVA with Group as a between-subjects factor and Time and Task as the within-subjects factors, followed by analysis of lower order effects as appropriate. Performance data in 'no face' control trials (percentage of responses to control stimuli) were similarly analysed by Group × Time ANOVA.

All analyses were performed using Statistical Package for Social Sciences (version 16). Alpha level for testing significance of effects was maintained at $P < 0.05$.

Functional magnetic resonance imaging

For preprocessing, the 240 volume functional time series of each participant was motion corrected, transformed into stereotactic space (Montreal Neurological Institute, MNI), smoothed with a 8-mm full width at half maximum Gaussian filter and band pass filtered using statistical parametric mapping software (SPM5; http://www.fil.ion.ucl.ac.uk/spm).

Models and statistical inferences

Data were analysed using a random effect procedure (Friston *et al.*, 1999). Subject-specific activations were identified with a factorial model consisting of four facial expression conditions, and no face control condition serving as an implicit baseline. The boxcar for each 30-s epoch was convolved with the haemodynamic response function. Motion parameters were included as covariates at this stage. Generic task-related activations across all patients at baseline were identified (height threshold $P < 0.005$; cluster corrected $P \leqslant 0.05$) for each facial expression condition using one-sample *t*-tests. The effect of CBT for psychosis was investigated within a series of Group (CBT for psychosis + TAU, TAU alone) × Time (baseline, follow-up) ANOVAs for each of: fearful, angry, happy and neutral expressions versus control T-image contrasts to identify regions with significant Group, Time

and Group × Time effects (height threshold $P < 0.005$; cluster corrected $P \leqslant 0.05$). Both CBT for psychosis + TAU > TAU alone and TAU alone > CBT for psychosis + TAU sides of the interaction were examined. We also examined one sample and ANOVA analyses for individual voxels surviving family-wise error correction at the voxel level ($P < 0.05$) to identify effects in small regions (e.g. the amygdala or thalamic nuclei), which might be missed using a test of significance based on the extent of activation (i.e. cluster level correction for multiple comparisons—none found, thus not reported further).

Next, subject-specific mean blood oxygen level-dependant signal at baseline and follow-up from each of the clusters that showed a change at follow-up in the CBT for psychosis group (no cluster showed a change in the TAU-alone group; see 'Results' section) were extracted using the MarsBaR toolbox (http://marsbar.sourceforge.net/projects/marsbar). A difference in signal from baseline to follow-up was calculated for each subject and correlated (Pearson's r) with change from baseline to follow-up in (total and subscale) PANSS scores. These additional analyses allowed us to address the question of how brain changes at follow-up were associated with the change in symptoms. Such correlations were first performed in the CBT for psychosis + TAU-alone group, and then across the whole sample. Given the lack of change in symptoms and brain activity from baseline to follow-up in the TAU-alone group (see 'Results' section), there was insufficient power for this analysis in the TAU-alone group on its own.

Results

Demographic, clinical and behavioural measures: baseline comparisons

The final CBT for psychosis + TAU and TAU-alone groups were comparable in age, education, predicted IQ, symptoms, age at illness onset, illness duration and task performance at baseline ($P > 0.05$) (Table 1).

Effects of cognitive behaviour therapy for psychosis

The CBT for psychosis + TAU, but not the TAU-alone, group showed changes in symptoms from baseline to follow-up [Group × Time: total PANSS scores, $F(1,36) = 7.23$, $P = 0.011$; positive symptoms, $F(1,36) = 4.45$, $P = 0.042$; negative symptoms, $F(1,36) = 5.84$, $P = 0.021$; general psychopathology: $F(1,36) = 4.42$, $P = 0.043$] (Table 1). Only the CBT for psychosis + TAU group showed reduced symptoms at follow-up [total PANSS scores: $t(21) = 3.72$, $P = 0.001$; positive symptoms: $t(21) = 3.90$, $P = 0.001$; negative symptoms: $t(21) = 2.61$, $P = 0.016$; general psychopathology: $t(21) = 2.97$, $P = 0.007$].

Baseline symptoms were not associated with CBT for psychosis responsiveness ($P > 0.30$). Thus, as can be expected, Group effects in symptom change scores (indicating symptom improvement in CBT for psychosis + TAU relative to the TAU alone) remained significant after co-varying for baseline symptoms [total PANSS scores, $F(1,35) = 10.17$, $P = 0.003$; positive symptoms, $F(1,35) = 7.66$, $P = 0.009$; negative symptoms, $F(1,35) = 10.08$, $P = 0.003$; general psychopathology: $F(1,35) = 7.46$, $P = 0.01$].

Of 30 individual PANSS items, the strongest effects of CBT for psychosis were found on PANSS-P1 (delusions), PANSS-P6 (persecution), PANSS-N2 (emotional withdrawal), PANSS-N4 (passive social avoidance), PANSS-G6 (depression) and PANNS-G16 (active social avoidance) ratings. Correlational analyses of baseline symptom ratings across the whole sample revealed that the patients rated highly on the persecution item (PANSS-P6) were also rated highly on delusions (PANSS-P1, $\rho = 0.363$, $P = 0.04$) and active social avoidance (PANNS-G16, $\rho = 0.505$, $P = 0.001$). Furthermore, those who were rated highly on active social avoidance were rated highly on emotional withdrawal (PANSS-N2, $\rho = 0.331$, $P = 0.04$), passive social withdrawal ($\rho = 0.329$, $P = 0.04$) and depression items ($\rho = 0.386$, $P = 0.020$).

Task performance

Patients showed a high level of gender discrimination accuracy across all conditions (Table 1); this was expected given the easy task demands, implemented simply to ensure patients' attention to task stimuli and not place cognitive demands on them. The CBT for psychosis + TAU and TAU-alone groups displayed similar performance during all conditions on both occasions ($F < 1$ for Group, Group × Time, Group × Task and Group × Time × Task effects).

Baseline functional magnetic resonance imaging patterns

The areas showing increases during individual facial expressions across all patients at baseline are described in Table 2. The comparison relates to the control blank oval stimuli and thus will also reveal activity related to low-level visual aspects of the face stimuli such as spatial variations in contrast. The activated regions at baseline identified across all patients for fearful expressions, relative to the control condition, included the inferior frontal gyrus, insula, thalamus, amygdala, parahippocampal gyrus, putamen (all right sided) and cerebellum (left) along with robust bilateral activation in the inferior–middle occipital and fusiform gyri. The activated regions identified for angry expressions included the inferior frontal gyrus (bilateral), thalamus (bilateral), anterior insula (right), amygdala (right), putamen (bilateral), cerebellum (right) and robust bilateral activation of the inferior–middle occipital and fusiform gyri. Many of these areas were also activated for neutral expressions. Happy expressions robustly activated only the right visual areas. CBT for psychosis + TAU and TAU-alone groups did not differ significantly in baseline activation of these areas.

Functional magnetic resonance imaging changes following cognitive behaviour therapy for psychosis in addition to usual treatment versus usual treatment alone

Group × Time effects at a stringent threshold of significance ($P < 0.05$ cluster corrected) were found in the bilateral inferior frontal gyrus, right insula, bilateral putamen, left thalamus and left occipital areas during the processing of fearful expressions (Table 3). The CBT for psychosis + TAU group showed a greater

Table 2 Activation increases to individual facial expressions compared with non-face control stimuli across all patients at baseline (voxel threshold $P < 0.005$ uncorrected)

Brain area	Brodmann area	Voxels (*n*)	Side	MNI Coordinates			Voxel *T*	Cluster-corrected, *P*-value
				x	*y*	*z*		
Fearful								
Inferior–middle occipital gyrus	19	2196	Right	38	−80	−8	10.61	<0.001
	19		Right	44	−68	−14	8.63	
Fusiform gyrus	37		Right	38	−46	−24	8.59	
Fusiform gyrus	37	993	Left	−38	−64	−20	8.23	<0.001
Culmen			Left	−38	−48	−26	7.25	
Middle occipital gyrus	18		Right	20	−92	0	5.87	
Parahippocampal gyrus	27	1274	Right	20	−32	−4	5.11	0.001
Insula—extends to inferior frontal gyrus, amygdala and putamen			Right	42	−10	10	4.25	
			Right	34	−8	−8	3.82	
Angry								
Inferior occipital gyrus	18/19	3175	Right	42	−72	−8	10.24	<0.001
Culmen			Right	38	−50	−26	9.64	
Middle occipital gyrus	18		Right	28	−92	0	9.38	
Fusiform gyrus	37	922	Left	−42	−64	−20	8.47	0.009
Culmen			Left	−36	−48	−26	6.43	
Middle occipital gyrus	19		Left	−38	−68	−10	6.04	
Amygdala		3637	Right	20	−2	−18	5.91	<0.001
Thalamus—extends to putamen			Right	14	−32	2	5.75	
			Left	−12	−22	0	5.64	
Inferior frontal gyrus	44	873	Left	−46	16	22	5.47	0.011
	45		Left	−46	30	8	4.35	
	47		Left	−48	40	0	3.25	
Inferior frontal gyrus—extends to part of anterior insula	44	1369	Right	46	8	44	4.65	0.001
	45		Right	50	32	12	4.62	
	44		Right	42	8	32	4.05	
Neutral								
Middle–inferior occipital gyrus	18	2059	Right	28	−92	0	8.84	<0.001
	19		Right	42	−70	−12	8.61	
	18		Right	34	−84	−8	7.30	
Fusiform gyrus	37	1009	Left	−42	−64	−20	7.77	0.012
Inferior occipital gyrus	19		Left	−38	−74	−8	6.23	
Culmen			Left	−36	−48	−26	6.08	
Parahippocampal gyrus	27	4685	Right	18	−32	−4	6.65	<0.001
Transverse temporal gyrus	41		Left	−48	−22	12	4.50	
Post-central gyrus	6		Left	−46	−10	−2	4.39	
Putamen		1062	Right	30	−4	−2	5.02	0.01
Insula			Right	44	0	12	3.59	
Thalamus			Right	22	−12	18	3.18	
Happy								
Middle–inferior occipital gyrus	18	1823	Right	28	−92	0	8.23	<0.001
	18		Right	40	−74	−12	6.71	
	18/19		Right	34	−84	−8	5.96	

activity decrease in these areas at follow-up (relative to baseline) (Fig. 1A), compared with the activity decrease at follow-up (relative to baseline) in the TAU-alone group (i.e. difference of the differences). No Group × Time effects were found at the same level of significance during the processing of angry expressions. However, at a lower threshold ($P < 0.05$ uncorrected cluster), effects were found in the left inferior frontal gyrus, left anterior insula, bilateral putamen and left occipital areas during the processing of angry expressions (Table 3). These indicated a greater activity decrease in the CBT for psychosis + TAU group in these areas at follow-up (relative to baseline), compared with the activity decrease at follow-up (relative to baseline) in the TAU-alone group (Fig. 1D).

We did not find any regions in which the TAU-alone group showed significantly greater activity increases or decreases from baseline to follow-up than the CBT for psychosis + TAU group.

Group × Time effects were not found at a corrected or uncorrected cluster level of significance for happy or neutral expressions. Also, no area showed a significant Time [i.e. change from baseline to follow–up (6–8 months later) across both groups] or a Group

Table 3 Significant decreases after CBT for psychosis + TAU, compared with TAU alone (no significant change), during fearful and angry facial expressions (voxel threshold $P < 0.005$ uncorrected)

Brain area	Brodmann area	Voxels (*n*)	Side	MNI Coordinates			Voxel *T*	Cluster, *P*-value
				x	*y*	*z*		
Fearful								
Inferior frontal gyrus	45	1567	Left	−50	20	10	4.74	<0.001
	45		Left	−44	30	8	4.35	
	45		Left	−52	12	−2	4.02	
Inferior frontal gyrus	45	2863	Right	40	22	4	4.54	<0.001
	45		Right	60	14	6	4.24	
Precentral gyrus	6		Right	50	0	10	4.08	
Putamen (lentiform nucleus)			Right	28	−2	10	4.06	
Insula	13		Right	42	−14	4	3.29	
Lingual gyrus	19	1047	Left	−24	−74	−8	3.95	0.003
	19		Left	−8	−76	−2	3.78	
	19		Left	−6	−66	−2	3.66	
Putamen (lentiform nucleus)		559	Left	−26	0	6	3.80	0.05
Claustrum			Left	−32	−14	10	3.66	
Thalamus			Left	−12	−8	8	3.01	
Angry								
Inferior frontal gyrus—extends to anterior insula	47	255	Left	−42	42	0	3.73	0.048
	45		Left	−32	34	4	3.45	
	45		Left	−44	24	4	3.07	
Caudate		248	Left	−18	−12	20	3.95	0.05
Putamen (lentiform nucleus)			Left	−18	−12	12	2.91	
Putamen (lentiform nucleus)		349	Right	26	−12	10	3.74	0.024
Cuneus/lingual gyrus	17/18	305	Left	−4	−78	12	4.10	0.033
Middle occipital gyrus	19		Left	−20	−88	14	3.43	
Cuneus	18		Left	−16	−72	12	3.35	

P-values for Fearful are cluster-corrected, whilst those for Angry are cluster-uncorrected.

effect (i.e. higher/lower in one group at both time points) during any facial expressions.

Relationship between functional magnetic resonance imaging changes and symptom improvement

For each region showing a significant (fearful expressions—corrected cluster threshold) or nominally significant (angry expressions—uncorrected cluster threshold) Group × Time effect, we extracted parameter estimates for each subject and explored their relationship with change in PANSS total and subscale scores. For fearful expressions, no region correlated with any of the PANSS change scores (Table 4). In contrast, for angry expressions, reduction in all regions correlated positively with symptom improvement (Table 5). These relationships were generally weaker for negative symptoms, possibly because this symptom dimension also showed the least change (of all PANSS dimensions) following CBT for psychosis (Table 1).

Discussion

This study investigated neural changes following 6–8 months of CBT for psychosis in patients with schizophrenia using functional MRI and an implicit affective processing task.

Clinical and behavioural findings

The final CBT for psychosis + TAU and TAU-alone groups, after loss of some patients from the study, were matched with no evidence of differences between the two groups in demographic or clinical characteristics. The two patient groups were also equally attentive to the simple task requirements, as shown by their performance level, both at baseline and follow-up.

As expected, based on the findings of meta-analyses of randomized controlled trials of CBT for psychosis (Pfammatter *et al.*, 2006; Wykes *et al.*, 2008; NICE, 2009), the CBT for psychosis + TAU group, on average showed significantly reduced symptom severity at follow-up, relative to the TAU-alone group. The clinical improvement following CBT for psychosis in the present study was of similar magnitude to that observed by several randomized controlled trials (Butler *et al.*, 2006; Pfammatter *et al.*, 2006; Wykes *et al.*, 2008) and confirms that well-designed studies with a cohort- or case-control design do not systematically overestimate treatment effects (Concato *et al.*, 2000). Of 30 PANSS items, the effect of CBT for psychosis were most pronounced on persecution, delusions (positive symptoms), emotional withdrawal, passive social withdrawal (negative symptoms), and depression and active social avoidance (general psychopathology). In line with earlier findings of a positive relationship between persecutory delusions and depression in psychosis (Freeman *et al.*, 1998; Smith *et al.*, 2006), baseline ratings on these individual symptoms across

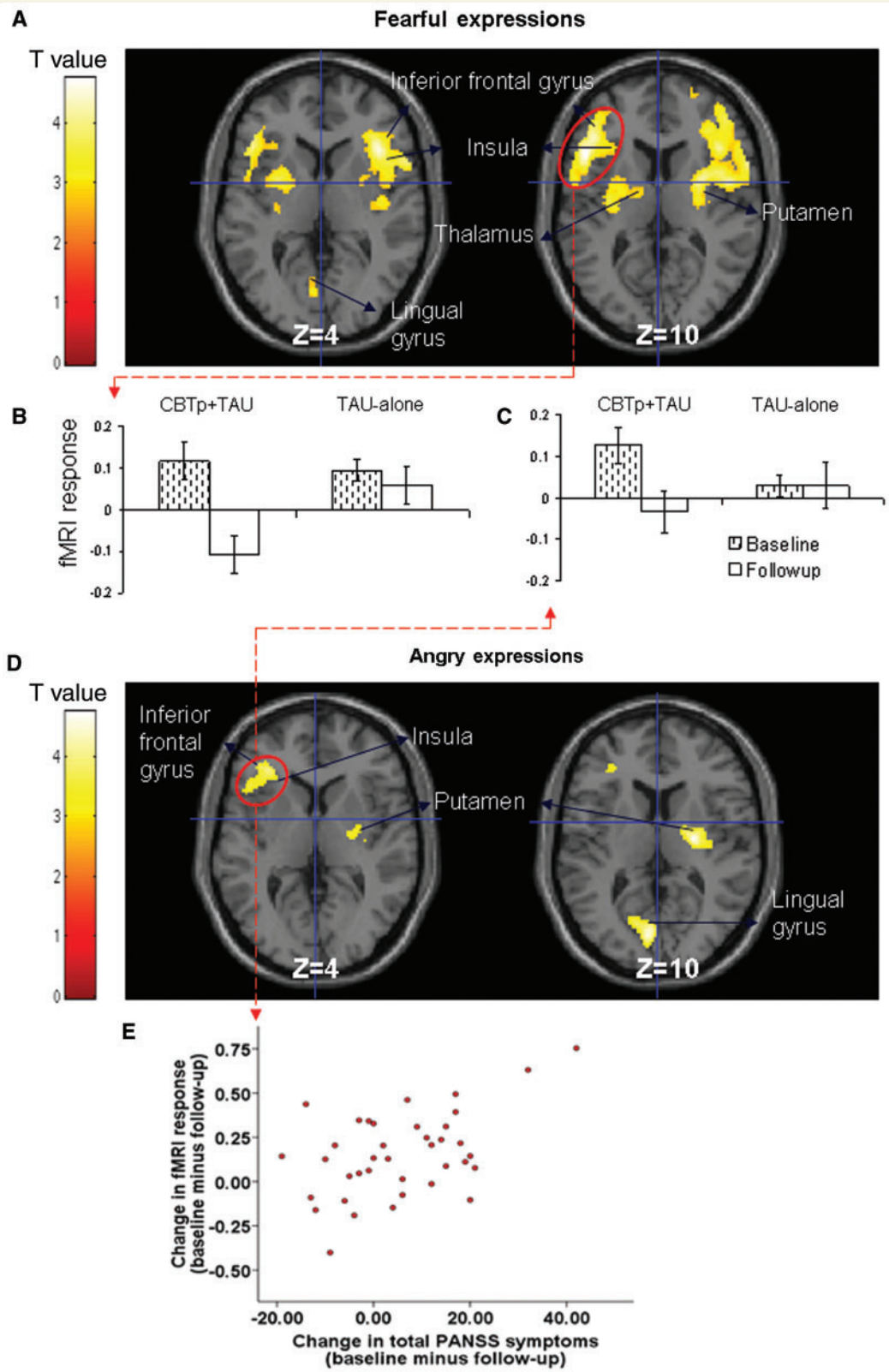

Figure 1 (**A** and **D**) Areas of reduced brain activity following CBT for psychosis + TAU (CBTp) (but not following TAU alone) to fearful and angry facial expressions (voxel threshold $P < 0.005$ uncorrected) in axial views with associated MNI *z* co-ordinates. Left hemisphere is shown on the left. (**B**) Mean functional MRI response in the left inferior frontal–insula cluster in each group at baseline and follow-up to fearful expressions. (**C**) Mean functional MRI response in the left inferior frontal cluster in each group at baseline and follow-up to angry expressions. (**E**) Scatter plot of decreases in activity from baseline to follow-up in the left inferior frontal region during angry expressions against the change in symptoms from baseline to follow-up across the whole sample.

Table 4 Correlations (none significant) between change in brain activity during fearful expressions and change in PANSS total and subscale scores

Cluster	CBT for psychosis + TAU group ($n = 22$)				Whole sample ($n = 38$)			
	Total *r* (*P*)	Positive symptoms *r* (*P*)	Negative symptoms *r* (*P*)	General psychopathology *r* (*P*)	Total *r* (*P*)	Positive symptoms *r* (*P*)	Negative symptoms *r* (*P*)	General psychopathology *r* (*P*)
Left inferior frontal gyrus	0.080 (0.724)	0.045 (0.843)	0.044 (0.846)	0.133 (0.554)	0.205 (0.216)	0.203 (0.222)	0.049 (0.722)	0.229 (0.166)
Right inferior frontal gyrus–precentral gyrus–putamen–insula	0.121 (0.593)	0.012 (0.959)	−0.001 (0.996)	0.197 (0.380)	0.209 (0.207)	0.171 (0.305)	0.042 (0.804)	0.259 (0.117)
Left lingual gyrus	0.218 (0.329)	0.030 (0.896)	0.229 (0.305)	0.237 (0.288)	0.124 (0.457)	0.113 (0.500)	0.078 (0.640)	0.115 (0.493)
Left putamen–claustrum–thalamus	0.128 (0.570)	0.011 (0.960)	0.073 (0.747)	0.184 (0.412)	0.068 (0.687)	0.032 (0.850)	0.061 (0.718)	0.103 (0.537)

Table 5 Correlations between change in brain activity during angry expressions and change in PANSS total and subscale scores

Cluster	CBT for psychosis + TAU group ($n = 22$)				Whole sample ($n = 38$)			
	Total *r* (*P*)	Positive symptoms *r* (*P*)	Negative symptoms *r* (*P*)	General psychopathology *r* (*P*)	Total *r* (*P*)	Positive symptoms *r* (*P*)	Negative symptoms *r* (*P*)	General psychopathology *r* (*P*)
Left inferior frontal–anterior insula	0.551 **(0.008)**	0.549 **(0.008)**	0.197 (0.379)	0.549 **(0.008)**	0.482 **(0.002)**	0.320 **(0.05)**	0.347 **(0.033)**	0.492 **(0.002)**
Left caudate–putamen	0.422 (0.051)	0.327 (0.137)	0.242 (0.277)	0.421 **(0.051)**	0.483 **(0.002)**	0.395 **(0.014)**	0.247 (0.134)	0.504 **(0.001)**
Right putamen	0.165 (0.464)	0.208 (0.354)	0.147 (0.515)	0.245 (0.273)	0.267 (0.105)	0.267 (0.105)	0.271 (0.099)	0.356 **(0.028)**
Left lingual gyrus–middle occipital gyrus–cuneus	0.527 **(0.012)**	0.439 **(0.041)**	0.192 (0.392)	0.567 **(0.006)**	0.493 **(0.002)**	0.349 **(0.032)**	0.253 (0.125)	0.545 **(0.001)**

Numbers in bold represent significance level.

the whole sample were correlated positively with each other. The effect of CBT for psychosis on negative (emotional withdrawal, passive social withdrawal) and general psychopathology (depression, active social avoidance) symptom dimensions is thus likely to be related to its effect on positive symptoms (persecution and delusions), as suggested previously by Kuipers and colleagues (2006), and to share common neural correlates (our functional MRI findings). The meta-analysis by Wykes *et al*. (2008) not only confirmed beneficial effects of CBT for psychosis on positive symptoms, negative symptoms, functioning, mood and social anxiety (effect sizes ranging from 0.35 to 0.44) but also found that improvements in one domain correlated with improvements in others.

Our TAU-alone group, although limited by a smaller sample size ($n = 16$), showed no change in symptoms from baseline to follow-up. This was expected given that our inclusion criteria required all patients to have stable (although distressing) symptom(s), to be on the same medication for a minimum of three months prior to study entry, and no change in their medication during the course of this investigation.

Baseline functional magnetic resonance imaging patterns

There were no significant differences at baseline between the CBT for psychosis + TAU and TAU-alone groups in brain response to emotive and neutral facial expressions. The activations observed across all patients at baseline, i.e. activation of the amygdala, insula, thalamus, putamen, inferior frontal gyrus, parahippocampal gyrus and cerebellum, along with robust activation of fusiform gyrus, are consistent with results of previous studies using facial stimuli (Phillips *et al.*, 2003; Phan *et al.*, 2004; Britton *et al.*, 2006; Gur *et al.*, 2007; Fusar-Poli *et al.*, 2009). As confirmed by a recent meta-analysis (Fusar-Poli *et al.*, 2009), the processing of facial emotions reliably produces increased activation in a number of brain areas including the visual (fusiform gyrus, inferior and middle occipital gyrus, lingual gyrus), limbic (amygdala, parahippocampal gyrus), temporoparietal (middle–superior temporal gyrus, parietal lobule), prefrontal and subcortical areas (putamen), insula and the cerebellum. Although the exact functional interplay among these regions remains to be established, the occipital and temporal areas are thought to contribute primarily to early perceptual processing of faces, with the remaining areas acting to associate perceptual representation of the face to the generation of the knowledge about the displayed emotion in the face (Adolphs, 2002).

Functional magnetic resonance imaging changes following cognitive behaviour therapy for psychosis with usual treatment versus usual treatment alone

Confirming our hypothesis, CBT for psychosis + TAU group at follow-up compared with baseline showed attenuation of functional MRI response to fearful and angry expressions. This response attenuation was present in the inferior frontal gyrus, (anterior) insula, putamen, thalamus and visual areas. The inferior frontal gyrus is an established part of the brain system that processes facial expressions (Haxby *et al.*, 2002) and is found to be more active during explicit, relative to implicit, processing of facial emotions (Scheuerecker *et al.*, 2007). The insula integrates internal and external information (Mesulam and Mufson, 1982) and is believed to play a role in processing of potentially distressing information (Reiman *et al.*, 1997). Increased insula activation also occurs when participants attempt to suppress their emotions, with an opposite effect for reappraisal (Goldin *et al.*, 2008). Delusional information processing has been suggested to involve an initial vigilance for threat, followed by active avoidance of threat during later controlled information processing stages (Green and Phillips, 2004). It is plausible that this active avoidance includes suppression of response to threat. Activation of the inferior frontal–anterior insula area is also observed during high anticipatory fear in both healthy and schizophrenia groups (Kumari *et al.*, 2009*a*), and this activation is attenuated after the administration of anxiolytic drug lorazapam in healthy subjects (Schunck *et al.*, 2010). Recent studies demonstrate basal ganglia response to stress (Scott *et al.*, 2006). The thalamus, with projections to the amygdala, modulates arousal (Van der Werf *et al.*, 2002; Li and Kirouac, 2008) and is involved in processing of threat in facial expressions (Luo *et al.*, 2007). The areas of reduced activation after 6–8 months of CBT for psychosis in this study included visual (occipital) areas, which are suggested to be recruited primarily for early perceptual processing (Adolphs, 2002) and receive feedback from areas processing visual emotion (Catani *et al.*, 2003). It is possible that CBT for psychosis achieves some of its clinical benefit by acting on psychological processes involved in early perceptual processing through feed-back from higher areas as well as by modulating conscious and explicit processing of threat-related emotional materials in the inferior frontal gyrus and other regions.

Contrary to our hypothesis, we did not observe a significant change in amygdala activation following a course of CBT for psychosis. The reason for this is unclear. It is plausible that CBT for psychosis in paranoid schizophrenia patients has a relatively weaker effect on brain regions involved implicitly in generating emotional responses to simple and perceptual associative aspects of stimuli (Izard, 1993). This, however, needs to be confirmed using event-related paradigms and specific image acquisition and analytical techniques that allow the temporal course of activation to be quantified given that activation of the amygdala may show a rapid attenuation (Buchel *et al.*, 1998) and functional activity within this structure is more difficult to image than within other cortical structures.

Relationship between functional magnetic resonance imaging changes and symptom improvement

Attenuation of functional MRI activity at follow-up relative to baseline during angry expressions was correlated directly with a reduction in symptoms following CBT for psychosis. This may explain why the Group × Time effects were less significant for this expression as the size of the attenuation varied for different participants. We did not show direct correlations with immediate reductions in PANSS symptoms and brain changes with exposure to fearful faces. It is plausible that some PANSS symptom items are more relevant to signals of direct threat (angry faces with direct eye contact) than signals of danger with uncertain source (fearful faces). Therapists may also have a better defined symptom target when aiming for a reduction in distress in response to signals of

potential direct threat (e.g. eye contact from strangers) than signals of indirect threat. Furthermore, PANSS fails to capture subjective qualities of symptoms and thus is not ideal for measuring the range of clinical effects of CBT for psychosis (Birchwood and Trower, 2006). The effect of CBT for psychosis on threat processing observed in this study may also relate to the continued improvements that can be seen at a longer follow-up (i.e. 9 months after the end of CBT for psychosis) (Sensky *et al*., 2000).

Study limitations

The study was not designed to test the efficacy of CBT for psychosis but to observe changes in brain activity over the course of CBT for psychosis. As such we did not attempt to randomize patients into different treatment arms but used a cohort case-controlled design to compare brain activity in patients accepted for CBT for psychosis by the clinical service with those continuing to receive standard treatment. It is possible there were differences in the type of patient accepted for CBT for psychosis compared with those remaining on standard treatment; however, such differences are not apparent in any of the clinical or demographic measures included in the study. Importantly, brain response at baseline was equivalent in the two groups making it unlikely the Group × Time effects described could be attributed to biases introduced by our recruitment method. Another limitation is that we did not include a measure of anxiety. Anxiety is known to play a key role in threat perception and paranoia (Green and Phillips, 2004; Freeman, 2007) and may have been directly associated with symptomatic improvement and attenuation of functional MRI activity at follow-up relative to baseline during exposure to threatening facial expressions. However, PANSS anxiety item (PANSS-G2) was not one of the items showing the strongest effects of CBT for psychosis suggesting that the neural effects of CBT for psychosis found in this study are unlikely to be explained simply by a general reduction in anxiety.

Conclusion

This study provides the first evidence that a course of 6–8 months of NICE guideline compliant CBT for psychosis attenuates brain responses to threatening socially relevant stimuli in people with psychosis. The demonstration of CBT for psychosis-induced changes in social cognition at the neural level is an important development in the field. Further studies are required to examine neural changes accompanying CBT for psychosis-led improvement on specific symptoms of schizophrenia, using multidimensional measures of behavioural change and sophisticated experimental paradigms with multimodal imaging sensitive to temporal aspects of brain changes, allowing the effects to be quantified precisely during the early processing of threat detection, as well as conscious processing of threatening materials.

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