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ORIGINAL ARTICLE

Amygdala and ventral anterior cingulate activation predicts treatment response to cognitive behaviour therapy for post-traumatic stress disorder

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Background. Although cognitive behaviour therapy (CBT) is the treatment of choice for post-traumatic stress disorder (PTSD), approximately half of patients do not respond to CBT. No studies have investigated the capacity for neural responses during fear processing to predict treatment response in PTSD.

Method. Functional magnetic resonance imaging (fMRI) responses of the brain were examined in individuals with PTSD ($n=14$). fMRI was examined in response to fearful and neutral facial expressions presented rapidly in a backwards masking paradigm adapted for a 1.5 T scanner. Patients then received eight sessions of CBT that comprised education, imaginal and *in vivo* exposure, and cognitive therapy. Treatment response was assessed 6 months after therapy completion.

Results. Seven patients were treatment responders (defined as a reduction of 50% of pretreatment scores) and seven were non-responders. Poor improvement after treatment was associated with greater bilateral amygdala and ventral anterior cingulate activation in response to masked fearful faces.

Conclusions. Excessive fear responses in response to fear-eliciting stimuli may be a key factor in limiting responses to CBT for PTSD. This excessive amygdala response to fear may reflect difficulty in managing anxiety reactions elicited during CBT, and this factor may limit optimal response to therapy.

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Key words: Cognitive behaviour therapy, fMRI, post-traumatic stress disorder, treatment prediction.

Introduction

Cognitive behaviour therapy (CBT) is the treatment of choice for post-traumatic stress disorder (PTSD). Across a broad range of acute and chronic populations, CBT has been shown to perform better than other psychological or psychopharmacological interventions (Foa & Meadows, 1997; Harvey *et al*. 2003). Despite this relative success of CBT, half of patients still suffer PTSD after treatment (Bradley *et al*. 2005). Most CBT interventions for PTSD involve repeated exposure to trauma reminders and/or memories, as well as cognitive restructuring techniques that aim to teach more realistic appraisals of the trauma and oneself. Accordingly, successful response to CBT involves management of anxiety elicited by trauma memories and related cognitions (Foa & Meadows, 1997). Consistent with this proposal, there is evidence that limited response to CBT is predicted by pretreatment PTSD severity (Blanchard *et al*. 2003).

There is increasing recognition that fundamental mechanisms of psychotherapy need to be understood by determining the biological mechanisms underpinning psychotherapy (Linden, 2006). Understanding the biological differences between patients who do and do not respond to treatment will both elucidate the biological mechanisms of available treatments and advance our capacity to match treatments to different patients (Etkin *et al*. 2005). The majority of studies that have used neuroimaging techniques to predict treatment response have focused on major depression or obsessive-compulsive disorder, and the majority of these have studied prediction of pharmacotherapy (for reviews, see Etkin *et al*. 2005; Evans *et al*. 2006). These studies have measured neural activity during rest or during symptom provocation tasks. The latter approach can be a more sensitive measure because it allows assessment of neural responses to stimuli that

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Table 1. *Clinical details for PTSD participants* ($n=14$)

Group	Age (years)	Gender	Trauma	Duration (years)	Co-morbidity	Antidepressants	Medications
NR	30	F	Assault	0.5	Nil	Nil	Nil
NR	55	M	MVA	1	MDD	Citalopram	Nil
NR	35	F	Assault	15	MDD, panic	Paroxetine	Nil
NR	26	M	Assault	8	MDD	Nil	Nil
NR	53	F	MVA	0.5	MDD	Nil	Nil
NR	27	F	Hold-up	2	Nil	Nil	Nil
NR	65	M	MVA	3	MDD	Mirtazepine	Nil
TR	39	M	Police	17	MDD	Paroxetine	Nil
TR	38	M	MVA	1	Nil	Nil	Nil
TR	45	F	MVA	2	Nil	Nil	Nil
TR	33	F	Assault	11	Nil	Nil	Nil
TR	44	F	Assault	1	MDD	Citalopram	Nil
TR	52	F	Hold-up	1	MDD	Nil	Nil
TR	49	M	Police	17	MDD	Paroxetine	Nil

PTSD, Post-traumatic stress disorder; NR, treatment non-responder; TR, treatment responder; F, female; M, male; MVA, motor vehicle accident; MDD, major depressive disorder.

are important in the maintenance of the disorder, and therefore may be more attuned to detecting neural activity that predicts treatment response (Evans *et al*. 2006). To date, there are no reports of neural predictors of treatment response for PTSD.

Current biological models of PTSD are based on fear-conditioning models and posit that a traumatic event (unconditioned stimulus) leads to a strong fear reaction (unconditioned response) that becomes conditioned to many stimuli associated with the traumatic event. Accordingly, when people are exposed to reminders of the trauma (conditioned stimuli), they experience a strong fear reaction (conditioned response) (Charney *et al*. 1993). Consistent with animal models of extinction learning (Davis & Myers, 2002), biological models posit that recovery from PTSD involves successful learning that the previously conditioned stimuli are no longer threatening (Bryant, 2006).

Preclinical research has elucidated the neural underpinnings of fear conditioning (Davis, 1992; LeDoux, 1998). There is converging evidence from a variety of experimental techniques demonstrating a crucial role of the amygdala in the acquisition and expression of conditioned fear (Davis, 2000). Accordingly, biological models of PTSD have hypothesized amygdala-mediated fear conditioning to underlie the disorder (Charney *et al*. 1993). Specifically, it has been proposed that reduced medial prefrontal cortex (mPFC) activity leads to impaired inhibition over amygdala fear-processing networks, resulting in amygdala hyper-responsivity in PTSD (Bremner *et al*. 1999). Consistent with this model, there is strong evidence for reduced activation in the mPFC in PTSD patients during fear processing across a range of brain-imaging studies (e.g. Liberzon *et al*. 1999). In addition, there is also evidence for increased amygdala response to fear stimuli in PTSD (Liberzon *et al*. 1999; Rauch *et al*. 2000; Armony *et al*. 2005).

On the premise that CBT for PTSD involves successful management of fear responses elicited during therapy, we proposed that treatment response would be predicted by neural networks that promote fear regulation. We therefore hypothesized that poor response to CBT would be associated with greater activation in the amygdala and reduced mPFC recruitment during fear processing before treatment.

Method

Fourteen treatment-seeking participants (eight females, six males) of mean age 42.2 years were survivors of interpersonal violence ($n=9$) or motor vehicle accidents ($n=5$) that occurred an average of 4.4 years before treatment. All participants were right-handed. Table 1 presents a summary of clinical characteristics of the PTSD sample. Diagnoses of PTSD were made by clinical consensus by two clinical psychologists (independent of the study), according to DSM-IV criteria (APA, 1994) using the Clinician-Administered PTSD Scale (CAPS; Blake *et al*. 1990). Participants with a history of neurological disorder, psychosis, or current substance abuse were excluded. Nine participants had co-morbid major depressive disorder,

and one had co-morbid panic disorder diagnosed by the Structured Clinical Interview for DSM-IV (SCID; First *et al*. 1997). Six participants were medicated with antidepressant medication (three in the treatment responder group and three in the treatment non-responder group), which was not altered during the course of the study. The study also included a comparison group of 14 healthy participants who had had never experienced a criterion A stressor and with no current or lifetime psychiatric disorders. Informed written consent was obtained from participants according to the institutional review board.

Participants received eight once-weekly sessions of CBT. Therapy involved education, imaginal exposure, cognitive restructuring, and relapse prevention (see Bryant *et al*. 2003). Prior to treatment, participants viewed standardized grey-scale face stimuli (Gur *et al*. 2002) that consisted of four female and four male individuals depicting fear and neutral expressions. Participants viewed faces under a rapidly presented viewing condition in a backwards masking paradigm (Rauch *et al*. 2000). We used a rapid presentation paradigm because there is convergent evidence that it activates amygdala response in PTSD individuals (Rauch *et al*. 2000; Armony *et al*. 2005). Furthermore, recent commentaries have proposed that fear stimuli presented outside awareness engage neural networks that are particularly relevant to pathological anxiety states because preconscious fear processing underpins many anxiety disorders (Etkin *et al*. 2005). All faces were matched for overall luminosity and size, and were equally aligned on a black background template. Each sequence comprised 240 stimuli (120 fear and 120 neutral) in a pseudo-random sequence of 30 blocks (comprising eight fear or eight neutral stimuli each). Each face (fear or neutral) stimulus was presented for 16.7 ms, followed by a 163.3-ms neutral mask. These durations were based on parameters established in a psychophysics experiment, undertaken using an equivalent block design task, that demonstrated that participants could not detect the content of non-conscious presentations (Williams *et al*. 2004). This timing was sufficient to saturate the retina, but precluded conscious awareness of the presence of the stimulus. Our protocol was based on signal detection (Macmillan, 1986), and provides an exhaustive criterion for ensuring unconscious processing of fear. The inter-stimulus interval (ISI) was 1088 ms. The ISI was jittered by ± 200 ms to ensure that stimulus onset did not coincide with a constant slice position during image acquisition. Face stimuli were presented using a projector (Sanyo ProX, Multiverse Projector) and mirror system. Participants received standardized and synchronized visual and audio (through headphones) instructions and were asked to actively attend to the face stimuli, in preparation for a post-scanning briefing about these stimuli. Participants were instructed to focus on the first face even though it may be difficult to see.

Imaging was performed on a 1.5 T Siemens Vision Plus scanner using an echo echoplanar protocol. A total of 90 functional T2*-weighted volumes (three per stimulus block) were acquired, comprising 15 non-contiguous slices parallel to the intercommissural (AC–PC) line, with 6.6 mm thickness and TR = 3.3 s, TE = 40 ms, flip angle = 90°; FOV 24×24 cm², matrix size 128×128. Three initial 'dummy' volumes were acquired to ensure blood oxygen level-dependent (BOLD) saturation. Preprocessing (realignment and unwarping, spatial normalization into standardized MNI space, smoothing using an 8-mm full-width half-maximum (FWHM) isotropic Gaussian kernel) and statistical analysis of functional magnetic resonance imaging (fMRI) data were conducted using Statistical Parametric Mapping (SPM2, Wellcome Department of Neurology, London, UK).

To examine change in PTSD severity independent of initial severity, residual change was calculated from a regression of pretreatment total CAPS scores on post-treatment total CAPS scores (Siegle *et al*. 2006). Whole-brain voxelwise regressions of residual PTSD severity on mean fMRI signal for fear (or neutral) facial expression were used to detect neural activity associated with treatment recovery (Type 1 error: $p < 0.001$). To test *a priori* hypotheses, significant clusters in activated regions from whole-brain analysis (amygdala and anterior cingulate) were examined in correlation and planned contrast analyses. Group differences were examined in a series of independent sample *t* tests (treatment responder *versus* non-responder; controls *versus* treatment responder; controls *versus* treatment non-responder) using the same hypothesis-driven regions of interest (ROIs). ROIs were defined by the Automated Anatomical Labelling (AAL) masks (Tzourio-Mazoyer *et al*. 2002). Neural activity was examined for the contrast of fear *versus* neutral with an α-level of $p < 0.05$ (small volume corrected) and an extent threshold of > 5 contiguous voxels per cluster.

Results

The average pretreatment CAPS score was 75.5, and the post-treatment score was 38.6. Seven participants were treatment responders (defined as a reduction of 50% of pretreatment scores) and seven were non-responders. There was a significant difference between the groups in change in total CAPS scores from pre- to post-treatment [$F(1, 12) = 10.9$, $p < 0.01$], with treatment responders displaying greater PTSD

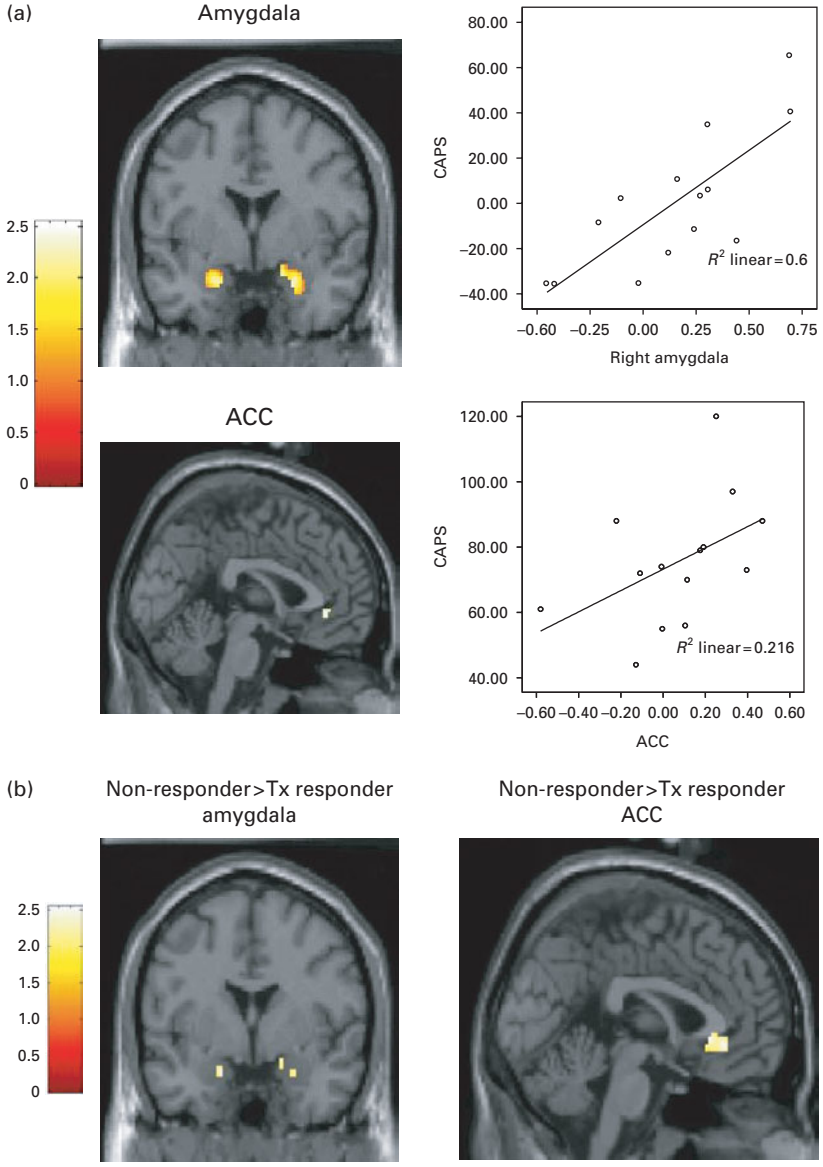

Fig. 1. (*a*) Positive correlations between the post-treatment Clinician-Administered Post-Traumatic Stress Disorder Scale (CAPS) score (controlling for pretreatment CAPS score) and amygdala and anterior cingulate cortex (ACC) activity to fearful faces prior to treatment. (*b*) Group differences in amygdala and ACC activity between treatment non-responders ($n=7$) and treatment responders ($n=7$).

symptom reduction than non-responders. Initial PTSD severity accounted for 19.3% of variance in post-treatment CAPS severity scores. The average pretreatment score on the Beck Depression Inventory (BDI; Beck *et al*. 1996) was 26.5 and the post-treatment score was 17.9. There were no significant differences between treatment responders and non-responders on change in total BDI score from pre- to post-treatment [$F(1,12)=1.36$, $p>0.05$].

To test *a priori* hypotheses, correlations were conducted between post-treatment PTSD severity and amygdala and anterior cingulate cortex (ACC). Significant positive correlations were found between post-treatment CAPS scores and bilateral amygdala (right: 24, 0, −22; $z=3.25$, $p=0.000$; voxels = 105; $r=0.75$, $p<0.01$; left: −18, −2, −22; $z=3.48$, $p=0.000$; voxels = 98; $r=0.8$, $p<0.01$) (Fig. 1*a*). There was a significant positive correlation between ventral ACC and post-treatment CAPS (0, 36, −4; $z=2.04$, $p=0.021$; voxels = 17; $r=0.55$, $p<0.05$).

Treatment non-responders had significantly greater bilateral amygdala prior to treatment than treatment responders (right: 26, 2, −10; $z=1.85$, $p<0.05$; voxels = 16; left: −18, −2, −20; $z=2.13$, $p<0.05$;

voxels = 23) and significantly greater activity in the right ventral anterior cingulate (0, 26, −2; $z = 2.23$, $p < 0.05$; voxels = 96) (Fig. 1*b*). Treatment responders had significantly greater bilateral dorsal ACC activity than treatment non-responders (left: −4, −2, 30; $z = 3.54$, $p = 0.000$; voxels = 95; right: 8, 6, 28; $z = 3.11$, $p = 0.010$; voxels = 29).

Overall, PTSD participants had markedly greater bilateral amygdala activity (right: 26, 2, −16; $z = 2.48$, $p = 0.007$; voxels = 107; left: −26, −2, −12; $z = 2.33$, $p = 0.01$; voxels = 35) and greater right rostral ACC activity (8, 32, 14; $z = 3.02$, $p = 0.001$; voxels = 687) than controls. Relative to controls, the treatment non-responders had significantly greater bilateral amygdala activity to fear (right: 26, 4, −18; $z = 3.23$, $p = 0.001$; voxels = 117; left: −16, −4, −18; $z = 2.42$, $p = 0.008$; voxels = 77). Treatment responders also displayed greater amygdala activity than controls, but this increase was of smaller magnitude than that of the non-responders (right: 32, −8, −12; $z = 2.14$, $p = 0.016$; voxels = 38; left: −26, −8, −12; $z = 2.20$, $p = 0.014$; voxels = 12). In terms of ACC, treatment non-responders had greater activity in right rostral (2, 40, 16; $z = 2.66$, $p = 0.004$; voxels = 316) and right ventral (2, 22, −8; $z = 2.43$, $p = 0.008$; voxels = 26) ACC and reduced activity than controls in dorsal ACC (−4, −2, 30; $z = 2.42$, $p = 0.008$; voxels = 31). Treatment responders had similar increases in bilateral (predominantly left) rostral and dorsal ACC (left: −2, 36, 30; $z = 3.64$, $p = 0.001$; voxels = 469) than controls.

Discussion

Poor response to CBT was associated with increased bilateral amygdala recruitment during fear processing before treatment. These networks have been linked to fear processing in both healthy controls (Liddell *et al*. 2005; Phan *et al*. 2006) and PTSD patients (Liberzon *et al*. 1999; Rauch *et al*. 2000; Armony *et al*. 2005). Although CBT requires activation of fear networks for CBT to be efficacious, there also needs to be adequate management of the anxiety elicited in therapy (Foa & Meadows, 1997). If amygdala-based fear processing is excessive, it may be more difficult to regulate the anxiety elicited during CBT. This interpretation is consistent with reports that poor response to treatment is associated with higher levels of pretreatment PTSD severity (Blanchard *et al*. 2003). This finding also accords with animal studies that show that rats display impaired extinction learning when extinction is preceded by arousing fear (Maren & Chang, 2006). This convergent evidence suggests that response to CBT is less beneficial when there is excessive anxiety prior to the therapy commencing. The current evidence provides the first evidence for the amygdala-based networks implicated in this apparent obstacle to treatment response.

Contrary to our hypothesis, we found that poor treatment response was associated with increased right ventral ACC recruitment. This finding may have occurred because of the nature of the rapid presentations of the fear stimuli. Rapid presentations of fear stimuli that use the backwards masking paradigm are thought to predominantly engage subcortical networks (Rauch *et al*. 2000), and may elicit 'bottom-up' activation through the brainstem and amygdala extending through to the ventral ACC, which may reflect automatic and rapid orienting to threat (Liddell *et al*. 2005). In this sense, the current paradigm may not be directly comparable with previous PTSD studies that report consciously processed fear stimuli that engage ventromedial PFC (vmPFC) regulatory networks (Lanius *et al*. 2001; Shin *et al*. 2005; Williams *et al*. 2006).

It is worth noting that recent commentators have suggested that the primary pathology in PTSD may be hyper-responsivity of the amygdala rather than deficient mPFC (Milad *et al*. 2006). Functional connectivity evidence suggests that there may be 'bottom-up' activation of the amygdala over the mPFC (Gilboa *et al*. 2004). This proposal is supported by evidence in PTSD patients (Rauch *et al*. 2000) and healthy controls (Liddell *et al*. 2005) of excessive amygdala response to fear stimuli that are presented in paradigms involving backward masking so that they potentially bypass top-down regulation by the mPFC. Relevant to this finding is evidence from animal research that the amygdala can influence mPFC (Garcia *et al*. 1999). Accordingly, our finding that pretreatment amygdala hyper-responsivity to fear predicting poor treatment response is consistent with evidence of the role of the amygdala in fear reactions.

It is interesting to contrast the current finding with previous studies that have investigated the neural networks associated with treatment response to CBT in different conditions. A study of obsessive-compulsive disorder that used positron emission tomography (PET) found that pretreatment activation in the left orbitofrontal cortex predicted treatment response for both behaviour therapy and fluoxetine (Brody *et al*. 1998). A study of CBT for social phobia found that social anxiety reduction was associated with reduced activation of amygdala and hippocampal regions during public speaking assessed before and after treatment (Furmark *et al*. 2002). These findings point to the distinct patterns of neural activity associated with treatment response for different disorders, and highlight the need for disorder-specific research to identify neural predictors of successful response.

In terms of depression, our finding contrasts with a recent study that found that *decreased* amygdala response to emotional stimuli predicted poor treatment response to CBT for depressed patients (Siegle *et al*. 2006). Depression (characterized by dampened arousal) and PTSD (characterized by elevated arousal) may require opposite levels of amygdala recruitment for successful treatment response. There is considerable evidence that rostral ACC activity prior to antidepressant treatment is predictive of good treatment response (Mayberg *et al*. 1997; Davidson *et al*. 2003; Saxena *et al*. 2003; Chen *et al*. 2007). It has been suggested that rostral ACC may integrate affective and cognitive processes, and this network's role in cognitive control over emotional responses may result in this region being predictive of treatment response to antidepressants (Etkin *et al*. 2005). Comparison between these studies and the present result are difficult, however, because we used subliminal presentations of fearful faces, which may engage different networks than stimuli used in depression studies.

We recognize that we did not include a comparison condition that received an alternate treatment to CBT. This form of comparison condition is required in future research to determine the specific predictive capacity of neural responses for CBT. Future research also needs to determine the neural networks that predict successful response to CBT and pharmacotherapy for PTSD. We also note the small sample size, which limits the statistical power of the study. These limitations notwithstanding, this study represents the first demonstration of neural processes predicting treatment response in PTSD and points to the need for further research to identify neural mechanisms that may promote better response to treatment. Future treatment studies should study the mechanisms by which amygdala activation predicts poor treatment response by indexing how amygdala activation is associated with avoidance, poor emotion regulation, or other strategies that may impede treatment response. Understanding the neural processes associated with successful response to CBT may point to specific mechanisms that can be modified to enhance treatment response.

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Declaration of Interest

None.

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