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Anterior cingulate activity to salient stimuli is modulated by autonomic arousal in Posttraumatic Stress Disorder

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ABSTRACT

Reduced ventral anterior cingulate (vACC) activity to threat is thought to reflect an impairment in regulating arousal networks in posttraumatic stress disorder (PTSD). Concurrent functional magnetic resonance imaging (fMRI) and skin conductance response (SCR) recording were used to examine neural functioning when arousal networks are engaged. Eleven participants with PTSD and 11 age- and sex-matched non-traumatized controls performed an oddball task that required responding to salient, non-trauma-related auditory target tones embedded in lower frequency background tones. Averaged target-background analyses revealed significantly greater dorsal ACC, supramarginal gyrus, and hippocampal activity in PTSD relative to control participants.With-SCR target responses resulted in increased vACC activity in controls, and dorsal ACC activity in PTSD. PTSD participants had reduced vACC activity relative to controls to target tones when SCR responses were present. This reduction in vACC in PTSD relative to controls was not apparent in without-SCR responses. These findings suggest that a reduction in vACC in PTSD occurs specifically when arousal networks are engaged.

1. Introduction

A disturbance in the regulation of arousal is a core pathology implicated in posttraumatic stress disorder (PTSD: Frewen and Lanius, 2006). Although many neuroimaging studies examine limbic activity in response to threat in PTSD, no imaging studies have directly examined neural activity in relation to autonomic arousal.

Neuroimaging studies in PTSD have reported impairments in ventral and rostral anterior cingulate activity (ACC: Bremner et al., 1999; Shin et al., 2005; Williams et al., 2006a) and ventral medial prefrontal regions (Lanius et al., 2001) in response to threatening stimuli. Some neuroimaging studies in PTSD have reported concurrent increases in amygdala activity (Shin et al., 2005; Williams et al., 2006a). The ventral portion of the ACC is thought to regulate affective arousal and limbic networks (Devinsky et al., 1995; Bush et al., 2000), and ventro-medial prefrontal regions have been implicated in fear-extinction processes (Phelps et al., 2004). These findings have led to a neurobiological model of PTSD in which reductions in ventromedial PFC inhibitory activity are thought to lead to heightened amygdala reactivity to threat (Frewen and Lanius, 2006; Rauch et al., 2006.

Reductions in anterior cingulate activity in PTSD have not always been found. In a recent study, we examined fMRI responses to salient, non-threatening tones in a selective attention oddball paradigm and found *increased* dorsal and rostral ACC activity coupled with increased left amygdala reactivity in PTSD relative to control participants (Bryant et al., 2005). We concluded that the reductions in rostral ACC activity may be specific to stimuli that engage arousal networks (such as threatening stimuli).

The present study aims to test this hypothesis by examining neural activity associated with autonomic arousal in PTSD in response to salient stimuli in a cognitive task. The selective attention oddball task reliably engages the ACC (Bryant et al., 2005; Yoshiura et al., 1999) and will allow us to examine the impact of arousal, as indexed by the skin conductance response (SCR) without the potential confound of emotional stimuli. In a recent functional magnetic resonance imaging (fMRI) oddball study in healthy controls, we found that responses to with-SCR target tones were associated with greater activity in amygdala, ventromedial and lateral frontal regions, whereas responses to without-SCR targets were associated with activity in dorsolateral frontal cortex and supramarginal gyrus (Williams et al., 2007).

In the current study, we compare PTSD participants with age- and sex-matched healthy controls on their responses to targets that evoke autonomic arousal in an auditory oddball paradigm. If reductions in vACC activity in PTSD require the engagement of arousal networks, vACC activity should be reduced in PTSD relative to control participants

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in targets with SCR, and this effect should not be apparent for targets without SCR. Enhanced amygdala activity should be expected to occur in the PTSD group for targets with SCR relative to controls.

2. Methods

2.1. Participants

Eleven participants with PTSD (9 males, 2 females) and 11 age- and sex-matched non-traumatized controls were included in the study. PTSD participants were recruited from the Centre for Traumatic Stress Studies, Westmead Hospital.[1] Controls were derived from our previous fMRI-oddball study (Williams et al., 2007) and were selected to be age- and sex-matched with the PTSD participants. PTSD participants were a treatment-seeking sample, who were diagnosed by clinical psychologists using the Clinician Administered PTSD Scale (CAPS: Blake et al., 1990). Five were survivors of physical assault, and six had survived motor vehicle accidents. The average time post-trauma was 4.45 years (S.D. = 5.5). Comorbidity was examined using the Structured Clinical Interview for DSM-IV Axis 1 Disorders—Clinician Version (SCID-CV; First et al., 1997). Seven participants had comorbid depression, and one had comorbid panic disorder. Four participants were receiving antidepressant medication (citalopram, paroxetine and mirtazepine, in stable doses for at least 3 months before the study). Mood was assessed using the Depression, Anxiety and Stress Scales (DASS; Lovibond and Lovibond, 1995). Control participants had no history of psychiatric disorder and no history of trauma. Both PTSD and control participants were excluded if they had a history of head injury, neurological disorder, substance abuse, serious medical condition related to thyroid, heart or cancer, or severe visual or hand impediments. Relevant human ethics committees approved the study, and informed consent was obtained.

2.2. Experimental task

The experimental task and imaging/autonomic data acquisition procedures are identical to those reported in our previous fMRI oddball studies (Bryant et al., 2005; Williams et al., 2007). Participants were placed in a 1.5 T scanner and performed a standard auditory oddball task in which auditory tones were presented binaurally through headphones. Twenty target tones (1000 Hz; 15%) were presented in a pseudo-random sequence of 105 background tones (500 Hz; 85%). All stimuli were presented at 75 dB, 50 ms duration and 5 ms rise and fall time. The minimal intertarget interval was 10.72 s to ensure recovery of task-related signal change to baseline (Yoshiura et al., 1999). Subjects were instructed to make button-presses with the left and right hand simultaneously to target tones as quickly and accurately as possible, and to ignore background tones. Accuracy ratings of 100% were required in practice trials.

2.3. SCR acquisition and analysis

SCR data were acquired with an MRI-compatible system from digits II and III of the non-dominant hand with Ag–Ag chloride electrodes and 0.05 M sodium chloride gel. The presence of a valid SCR was determined by an increase in SCR amplitude of >0.05 μS, 1–3 s post-stimulus (Barry, 1990). Analysis software based on a sigmoid-exponential model enabled quantification of peak amplitude and latency of SCR (Lim et al., 1997; Williams et al., 2007).

2.4. fMRI acquisition and analysis

A Siemens Magnetom Vision Plus system with standard quadrature head coil was used to acquire 125 T*2-weighted volumes (one per stimulus) depicting changes in blood oxygen level-dependent (BOLD) signal. A gradient echo echoplanar sequence was used to acquire 15 axial non-contiguous slices of 6 mm thickness (0.6 mm interslice gap) parallel to the intercomissural line: TR 3.5 s, TE: 80 ms, matrix 128 × 128; FOV 24 cm × 24 cm; flip angle 90°. Preprocessing and statistical analysis were performed with Statistical Parametric Mapping Software (SPM2: Wellcome Department of Neurology). To control for movement artefact, images were realigned to the first in time series, normalized into standardized Montreal Neurological Institute (MNI) space and smoothed with an 8-mm Gaussian kernel. An HRF-convolved event-related model was created to correspond to target and background stimuli. Individual contrast files were created for each subject to examine target-background contrasts.

To test our a priori hypotheses, search region of Interest (ROI) analyses were undertaken using WFU_Pickatlas for anterior cingulate, amygdala, hippocampus, lateral frontal regions and supramarginal gyrus, defined by AAL masks (Tzourio-Mazoyer et al., 2002; Williams et al., 2007). Boundaries used to define the vACC were identical to those used in our previous study (Bryant et al., 2005). We compared voxel by voxel activations within each region of interest (ROI) elicited by target compared with background tones. To examine the effect of autonomic arousal, individual contrast files were established for targets which an SCR (with SCR) and targets that did not (without SCR). Related samples *t*-tests were used to compare "with-SCR" (relative to an implicit background baseline) and "without-SCR" stimuli (relative to an implicit background baseline) within each group. Between-group contrasts employed independent samples *t*-tests within each condition. Significant activations were determined using an alpha level of $p<0.01$ (uncorrected) and an extent threshold of at least 5 voxels. To examine activation in non-hypothesized regions, secondary whole-brain analyses were performed using an alpha level of $p<0.001$ and an extent threshold of at least 5 contiguous voxels. Finally, to control for depression and medication status in our PTSD sample, we conducted control analyses (averaged target-background, and sub-averaged analyses) after removing depressed participants on antidepressant medications.

3. Results

3.1. Demographic data

One-way analyses of variance revealed no significant differences in age [$F_{(1,20)} = .014$, $P>0.05$] or education [$F_{(1,20)} = 0.19$, $P<0.05$: controls, mean = 11, PTSD, mean = 11.2) between the groups. There were significantly greater DASS depression scores in the PTSD group (mean = 11.5 (S.D. = 5.4) than in the control group (mean = 3.5, S.D. = 1.8) [$F(1,20) = 11.2$, $P<0.01$].

3.2. Reaction time data

There were no significant differences in reaction time between the PTSD and control groups [$F_{(1,20)} = 3.71$, $P>.05$].

3.3. SCR data

There were no significant differences between the groups in number of SCRs [$F_{(1,20)} = 0.03$, $P>0.05$], average SCR amplitude [$F_{(1,20)} = 3.9$, $P>0.05$), or rise time of SCR responses [$F_{(1,20)} = 0.32$, $P>0.05$). The PTSD group had slower SCR decay times than the controls [$F_{(1,20)} = 4.45$, $P<0.05$). The average number of targets with SCRs in the control group was 112/220 (51%), and 115/220 (52%) for PTSD participants.

3.4. Averaged analysis (target-background)

In response to targets, PTSD participants revealed larger activity than controls in right rostral ACC (16 40 18; voxels = 57; $t = 2.67$, $P<0.01$), bilateral hippocampus (26 −12 −22; −34 −22 −10; voxels = 217,155; $t = 2.36$, $P<0.01$), and right supramarginal gyrus (64 −20 38, voxels = 79, $t = 2.97$, $P<0.01$). There were no greater activations in controls. There were no greater activations in controls in non-hypothesized regions in whole-brain analyses, but the PTSD group displayed greater activity in right superior frontal cortex (22 18 40, $t = 5.09$, $P<0.001$, voxels = 91), right fusiform gyrus (30 −30 −22, $t = 4.04$, $P<0.001$, voxels = 9), left thalamus (−2 −18 2, $t = 4.01$, $P<0.001$, voxels = 12), right middle frontal gyrus (36 20 38, $t = 3.98$, $P<0.001$, voxels = 10), right parahippocampal gyrus (28 −12 −24, $t = 3.79$, $P<0.01$, voxels = 8), right supplementary motor area (10 −20 54, $t = 3.95$, $P<0.001$, voxels = 11), and left middle cingulate (−8 8 42, $t = 3.87$, $P<0.001$, voxels = 6) than controls.

These effects were largely replicated in a subsequent control analysis that removed depressed participants on antidepressant medications. In contrast to the main averaged analysis, this secondary analysis also found increased right dorsal lateral frontal cortex (44 22 14, $t = 3.62$, $P<0.01$, voxels = 267) in controls and failed to find greater hippocampal activity in PTSD.

3.5. Analysis 'with SCR'–'without SCR'

In controls, 'with-SCR' targets (minus 'without-SCR' targets) engaged the right vACC network (4 34 −8; voxels = 35, $t = 2.86$, $P<0.01$), left supramarginal gyrus (−62 −32 42, $t = 3.1$, $P<0.01$, voxels = 37) and left inferior lateral frontal cortex (−52 10 4, $t = 4.83$, $P<0.01$, voxels = 25). In contrast, in PTSD participants, 'with-SCR' targets engaged the dorsal ACC network (8 24 18; voxels = 138, $t = 3.51$, $P<0.01$), right supramarginal gyrus (50, −24, 24; voxels 124, $z = 2.69$, $P<0.01$) and bilateral dorsolateral frontal regions (−44 30 42, $t = 3.06$, $P<0.01$, voxels = 198; 36 12 28, $t = 2.95$, $P<0.01$, voxels = 170).

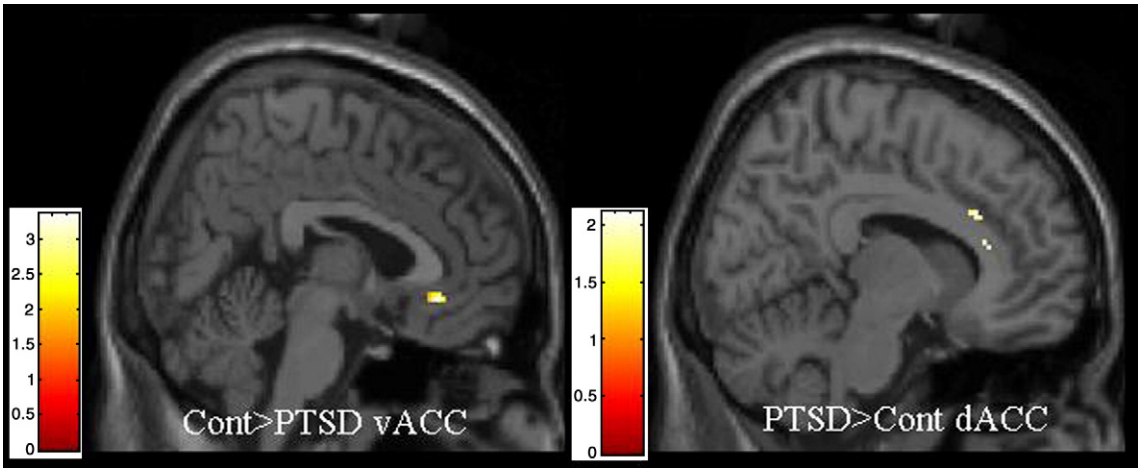

Fig. 1. Reduced BOLD activity in right ventral anterior cingulate cortex (4 34 −8, $t=2.86$, $P<0.01$) in PTSD ($n=11$) compared to controls ($n=11$) in response to 'with-SCR' targets, and increased BOLD activity in bilateral dorsal anterior cingulate cortex (30 6 32, $t=3.26$, $P<0.01$; −36 34 26, $t=3.2$, $P<0.01$) in PTSD to 'with-SCR' targets.

There was significantly greater activity in vACC (4 34 −8, $t=2.86$, $P<0.01$, voxels = 35) and left inferior lateral frontal cortex (−52 12 2, $t=3.03$, $P<0.01$, voxels = 31) in controls than PTSD participants in response to 'with-SCR' targets. Fig. 1 presents these ACC findings.

In contrast, the PTSD group displayed greater activity in bilateral dorsolateral frontal cortex (30 6 32, $t=3.26$, $P<0.01$, voxels = 365; −36 34 26, $t=3.2$, $P<0.01$, voxels = 318) to 'with-SCR' targets than controls and greater activity in left supramarginal gyrus (−46 −38 28, $t=2.73$, $P<0.01$, voxels = 111).

These findings were replicated once removing depressed participants on antidepressant medication, with the addition that PTSD participants displayed greater activity in dorsal ACC than controls to targets 'with SCR' (8 32 10, $t=2.94$, $P<0.05$,voxels = 12).

4. Discussion

The present findings support the hypothesis that alterations in vACC activity in PTSD would be predominant when arousal networks were engaged in response to attended targets. We found activity in vACC in controls to targets with SCRs, but not in PTSD participants. Instead, the PTSD group revealed activity in the dorsal ACC in response to targets with SCR. Dorsal ACC activity has been related to elevated anxiety in a recent study (Simmons et al., 2008). The ventral portion of the ACC has been associated with regulating affective arousal networks (Bush et al., 2000). Whilst the current study did not employ affective stimuli, the majority of 'with-SCR' targets were relatively early in the stimulus sequence, and may reflect a response to novelty. Novel stimuli may be responded to as potential threats in PTSD participants relative to controls (Kimble et al., 2000; Williams, 2006b). Therefore, the findings suggest that deficits in vACC activity occur specifically when stimuli engage arousal networks.

The averaged target-background analysis revealed significant increases in dorsal ACC, hippocampus and supramarginal gyrus in the PTSD group relative to controls. This finding is largely consistent with our previous study (Bryant et al., 2005). Given the role of the dorsal ACC and the supramarginal gyrus in anxiety and attentional processing (Bush et al., 2000; Simmons et al., 2008; Yoshiura et al., 1999), and the hippocampus in context processing (Gray, 1987), this finding may reflect a generalized enhancement of stimulus processing in PTSD. The finding of reduced vACC activity in response to 'with-SCR' targets suggests that once arousal networks are engaged to novel, or potentially threatening stimuli, they may overwhelm affective vACC networks.

This conclusion is tempered by the failure to find significant amygdala activation in response to targets with SCRs. This contrasts with our previous findings of robust amygdala activity to targets 'with SCRs' in controls (Williams et al., 2007) and of greater amygdala activity in PTSD participants than controls in response to oddball targets (Bryant et al., 2005). Given the very small sample size of the present study, it is likely that this anomaly reflects a type 2 error. The current findings will need to be replicated with a larger sample size and it would be of particular interest to examine fMRI and concurrent SCR responses to affective stimuli in PTSD. Further, this study did not compare PTSD samples with trauma-exposed controls, and it is therefore unable to delineate the effect of trauma exposure from that of PTSD. Future studies should include trauma-exposed controls as a comparison group. Finally, this study did not investigate childhood traumas in the PTSD subjects, which may have considerable impact on arousal and affect regulation, and should be examined in future studies.

These limitations notwithstanding, the emphasis on arousal dysregulation in the present study complements prevailing models of PTSD that focus more narrowly on the extinction of conditioned fear and associated neurocircuitry (Frewen and Lanius, 2006; Rauch et al., 2006). Furthermore, our findings are consistent with evidence of impaired ACC function to anxious memories unrelated to the trauma (Lanius et al., 2003) and with evidence of no impairments in ACC function in a task employing non-emotional and non-arousing stimuli (Shin et al., 2007). Our findings suggest that once arousal networks are engaged in PTSD, they may overwhelm affective vACC networks.

In conclusion, the current findings suggest that diminished ventral ACC function in PTSD occurs specifically when arousal networks are engaged. This accords with hypotheses that diminished ventral ACC function in PTSD may be more evident in tasks involving emotional or threatening stimuli (Bryant et al., 2007; Shin et al., 2007). These findings highlight the need for neuroimaging studies in PTSD to account for variations in arousal, as this may be a significant source of variability in the PTSD neuroimaging literature.

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