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Differential activity of subgenual cingulate and brainstem in panic disorder and PTSD

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ABSTRACT

Most functional neuroimaging studies of panic disorder (PD) have focused on the resting state, and have explored PD in relation to healthy controls rather than in relation to other anxiety disorders. Here, PD patients, posttraumatic stress disorder (PTSD) patients, and healthy control subjects were studied with functional magnetic resonance imaging utilizing an instructed fear conditioning paradigm incorporating both Threat and Safe conditions. Relative to PTSD and control subjects, PD patients demonstrated significantly less activation to the Threat condition and increased activity to the Safe condition in the subgenual cingulate, ventral striatum and extended amygdala, as well as in midbrain periaquaeductal grey, suggesting abnormal reactivity in this key region for fear expression. PTSD subjects failed to show the temporal pattern of activity decrease found in control subjects.

Panic disorder (PD) and posttraumatic stress disorder (PTSD) are anxiety disorders with evolving neurocircuitry models. Biological studies of anxiety disorders have focused on comparisons between patient groups and healthy controls, with only one neuroimaging study to date directly comparing PD and PTSD (Lucey et al., 1997). This resting state (single photon emission computed tomography, SPECT) study found significant cerebral blood flow (CBF) differences in obsessive compulsive disorder (OCD) and PTSD compared with PD and controls in bilateral superior frontal cortices and right caudate nuclei. However, to develop disorder-specific behavioral and pharmacological treatment approaches, knowledge of the differences in the underlying dysfunctional neurocircuitries in these disorders is required. Neurobehavioral and neurocircuitry models of PTSD suggest amygdalar hyperactivity and ventromedial prefrontal hypoactivity to external threat (Milad, Rauch, Pitman, & Quirk, 2006) whereas panic disorder appears to be marked by internally generated threat (Lissek et al., 2009) driven by dysfunctional ventromedial prefrontal (ACC), amygdalar and brainstem regions (Graeff & Del-Ben, 2008). Core components of panic disorder include autonomic signs like increased respiration, heart rate, and blood pressure which are modulated by key regions in the basal forebrain and the brainstem. The medial frontal cortical network (including Brodmann area 25) provides a major output to the hypothalamus and brain stem and contributes to this visceromotor system (Price, 1999). The ventral striatum, known for its central role in reward processing is implicated in coding emotional intensity and self-relatedness of a variety of stimuli, independent of their valence (Phan et al., 2004). The bed nucleus of the stria terminalis/extended amygdala may regulate fear perception and mediate anxiety (Davis & Shi, 1999).

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Table 1
Subject characteristics.

Primary diagnosis	Age	Gender	Secondary diagnosis
None	24	Male	None
None	28	Male	None
None	42	Female	None
None	33	Male	None
None	34	Male	None
None	31	Female	None
None	40	Female	None
None	49	Female	None
Panic disorder	35	Male	Generalized anxiety disorder (GAD), past Major depressive disorder (MDD)
Panic disorder	39	Male	Social phobia, agoraphobia
Panic disorder	50	Female	GAD, MDD
Panic disorder	24	Male	None
Panic disorder	34	Female	Past PTSD
Panic disorder	49	Female	GAD, specific phobia, personality disorders (avoidant, obsessive compulsive, and paranoid)
Panic disorder	28	Male	None
Panic disorder	36	Female	None
PTSD	45	Male	Mild MDD, GAD (subthreshold)
PTSD	37	Female	Social phobia, specific phobia, OCD, dysthymia
PTSD	36	Female	None
PTSD	38	Male	None
PTSD	41	Male	Binge eating disorder
PTSD	47	Female	Past EtOH dependence, past substance induced mania
PTSD	50	Female	Past MDD, past EtOH and substance dependence
PTSD	39	Male	GAD, MDD

Several studies have explored systemic pathophysiologic differences between PD and PTSD. PTSD and PD patients may have distinct profiles with respect to cortisol levels and hypothalamic-pituitary-adrenal (HPA) responsivity (Marshall et al., 2002); carbon dioxide sensitivity (Talesnik, Berzak, Ben-Zion, Kaplan, & Benjamin, 2007); polysomnography (Sheikh, Woodward, & Leskin, 2003); heart rate variability (Cohen et al., 2000), genetic contributions (Skre, Onstad, Torgersen, Lygren, & Kringlen, 1993); and acquisition of conditioned fear-potentiated startle to learned safety and danger cues (Lissek et al., 2009). A study utilizing eyeblink electromyography, heart rate, and skin conductance responses (SCR) before and during treatment with alprazolam in PD and PTSD found a decrease in response probability and a decrease in the SCR in PD, but not in PTSD (Shalev, Bloch, Peri, & Bonne, 1998). Since both diseases share key symptoms (e.g. panic attacks) and both are thought to be elicited by abnormal fear conditioning/fear learning (Gorman, Kent, Sullivan, & Coplan, 2000; Phelps & LeDoux, 2005) direct experimental comparison can help to differentiate the neurobiological underpinnings of both diseases and give direction to specific therapeutic targets.

In this study, we used functional magnetic resonance imaging (fMRI) to compare neural responses in PD patients relative to PTSD patients and healthy comparison subjects during an instructed fear paradigm consisting of a Threat and a Safe condition (Butler et al., 2007; Phelps et al., 2001). In this task, the association of a previously neutral stimulus with a possible aversive event is learned by means of a verbal instruction given before the start of the scan. Symbolically acquired fear results in physiological fear responses and functional neuroimaging data comparable to the responses to a conditioned stimulus and its extinction in classical fear condition-

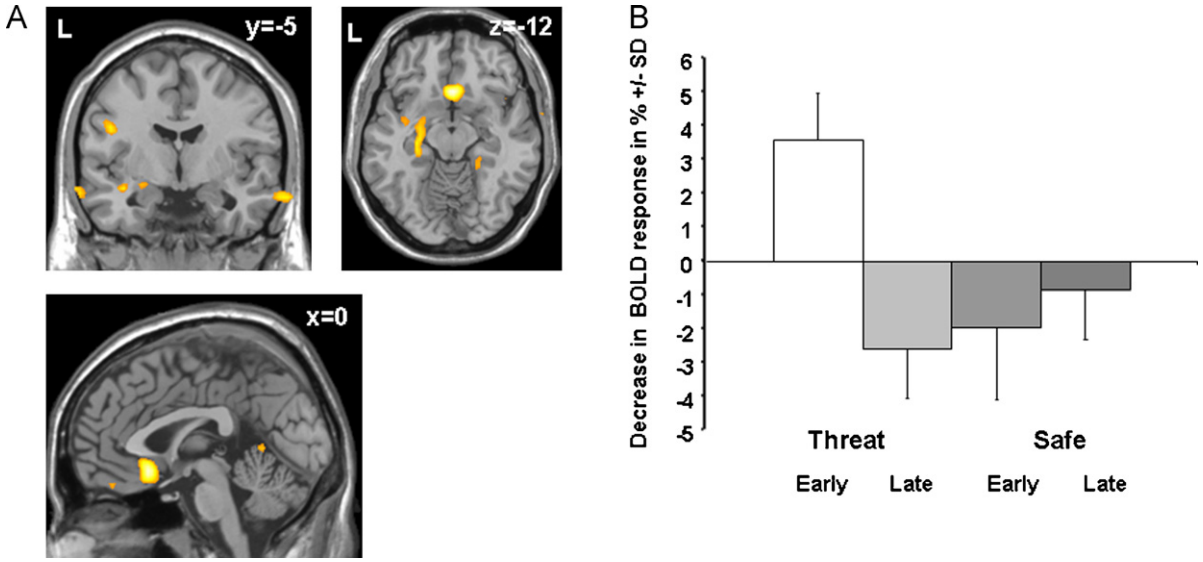

Fig. 1. (A) Coronal ($y = -5$), axial ($z = -12$), and sagittal ($x = 0$) sections showing increased amygdala activity and subgenual cingulate (Brodmann area 25) activity in early runs (parametric modeling of the Threat vs. Safe by Early vs. Late interaction) in Normal Control subjects ($p < 0.01$). (B) The bar plot shows the in BOLD response ± SD (%) at the point showing maximum activity for the Threat vs. Safe by Early vs. Late interaction in the amygdala (MNI [−21, 0, −12]). BOLD response is shown for Normal Controls, conditions [Threat, Safe], and study session [broken into Early and Late run] relative to a resting baseline.

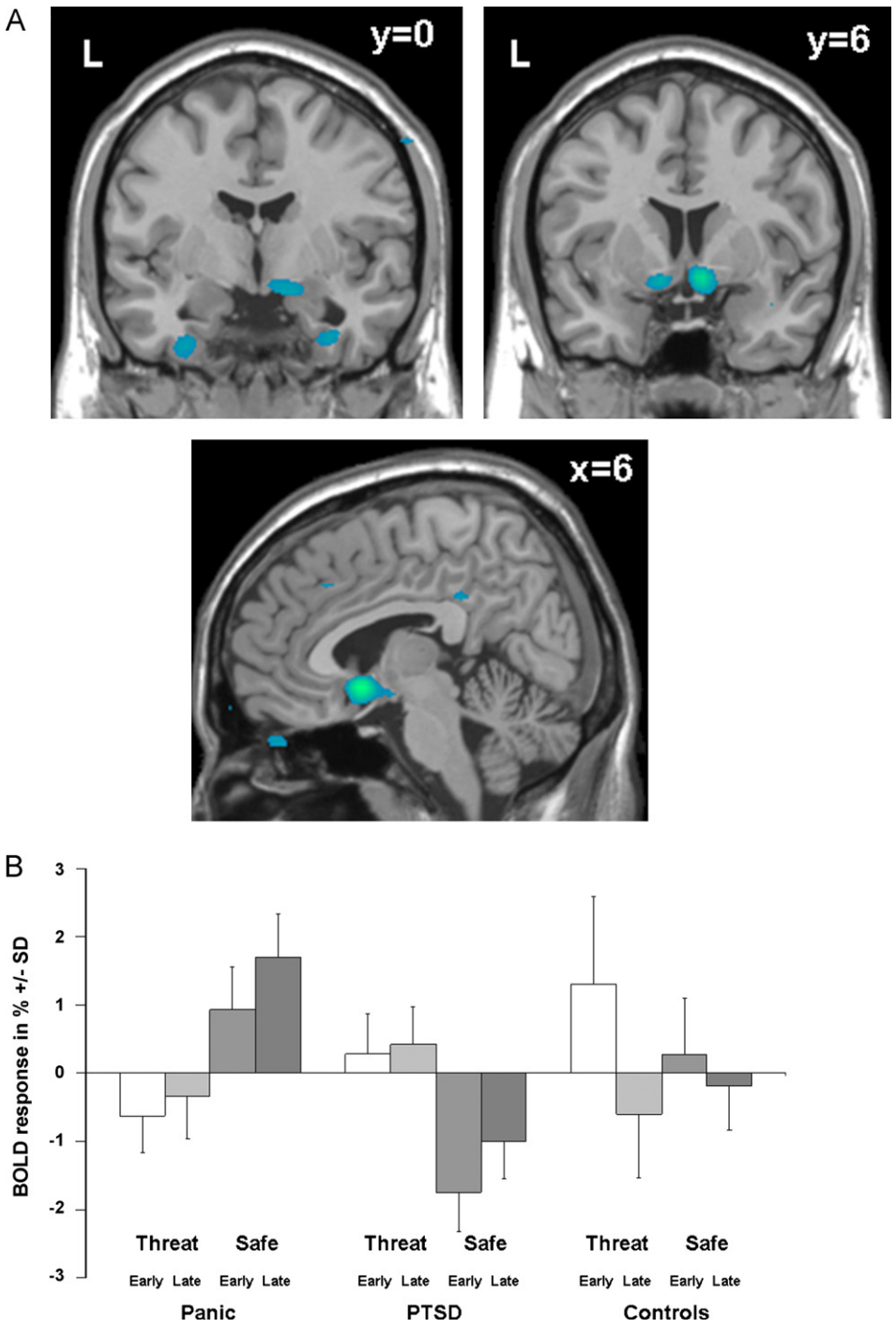

Fig. 2. (A) Coronal ($y = 0$ and $y = 6$), and sagittal ($x = 6$) sections showing decreased subgenual cingulate (Brodmann area 25), ventral striatum, and extended amygdala activity for the Threat vs. Safe condition in Panic vs. PTSD subjects ($p < 0.01$). (B) The bar plot shows BOLD response ± SD (%) at the point showing maximum activity for the Threat vs. Safe condition in Panic vs. PTSD subjects [6, 12, −9]. This point is located in the subgenual anterior cingulate cortex. BOLD response is shown for groups [Panic, PTSD, Normal Controls], conditions [Threat, Safe], and study session [broken into Early and Late run] relative to a resting baseline.

ing (Butler et al., 2007; Phelps et al., 2001). Based on Butler et al. we hypothesized that in healthy comparison subjects brain regions involved in fear processing, i.e. medial prefrontal, insula, ventral striatal, amygdalar and brainstem, would exhibit increased activity for Threat vs. Safe conditions and would habituate over time in a subset of those regions (Butler et al., 2007). For PTSD subjects, we hypothesized that these same regions would not exhibit habituation from early to late runs of the experimental paradigm. For PD subjects, we hypothesized that these same regions would exhibit abnormal reactivity to the (external) Threat and Safe conditions.

1. Method

1.1. Participants

Participants were 8 subjects meeting DSM-IV criteria for PD (mean age = 37 years, range = 24–50); 8 subjects meeting DSM-IV criteria for PTSD (mean age = 42 years, range = 37–50); and 8 healthy comparison subjects (mean age = 35 years, range = 24–49). PTSD and comparison subjects were a matched subset of larger groups. Each group consisted of 4 female and 4 male right-

Table 2
Interaction contrast PD vs. PTSD × Threat vs. Safe.

Brain region	MNI coordinates *x*, *y*, *z*	*Z*-value	*p*-value uncorr	*p*-value SVC corr
Relative increased activity				
Dorsal midbrain/mesial periaquaeductal grey	6, −24, −18	4.49	<0.0001	0.003
Right caudate	9, 12, 3	3.72	<0.0001	0.045
Relative decreased activity				
Subgenual cingulated, ventral striatum, and extended amygdala	6, 12, −9	−4.43	<0.0001	0.05

handed subjects. Among the patients, there were current secondary diagnoses of generalized anxiety disorder, social phobia, specific phobia, major depressive disorder, dysthymia, and personality disorders (Table 1). Otherwise, all participants were free of other psychiatric diagnoses, substance abuse, and significant neurological or medical disorders. No subjects were on psychiatric medication, except one PD subject (sertraline, bupropion). Written informed consent was obtained from the participants in accordance with an IRB-approved protocol.

1.2. Experimental paradigm

Prior to scanning, subjects determined the level of electrodermal stimulation to be received during the scan via a standardized dial-up procedure to a level of intensity experienced as "uncomfortable but not painful" to standardize subjective stimulus aversiveness across subjects. The scanning session consisted of a "Threat" condition, about which participants were told "an electrodermal stimulation can occur at any time", and a "Safe" condition during which participants were told they would receive no stimulations. Threat and Safe were signified by the presentation of easily distinguishable colored squares via an MR-compatible screen. Presentation of stimuli was controlled by the Integrated Functional Imaging System (Invivo, Orlando, FL) using E-prime software (Psychology Software Tools, Pittsburgh, PA). Pairing of colors with conditions was counterbalanced across participants. Each color appeared for a period of 12 s followed by a 18 s rest period. There were five pseudo-randomly ordered blocks of each color per scanning run, and two scanning runs (first run = early run; second run = late run) per study session. Participants did not receive any electrodermal stimulation during scanning.

1.3. Image acquisition

Gradient echo echo-planar functional images (TR = 1200; TE = 30; flip angle = 70°; FOV = 240 mm; fifteen 5 mm slices; 1 mm interslice gap; matrix = 64 × 64) sensitive to blood oxygen level-dependent (BOLD) signal were obtained with a GE-Sigma 3T MRI scanner. Images were acquired using a modified z-shimming algorithm to minimize susceptibility artifact at the base of the brain (Gu et al., 2002). An identically sliced reference T1 weighted anatomical image was acquired to aid re-orientation and co-registration. A high-resolution T1 weighted anatomical image was acquired using a spoiled gradient recalled acquisition sequence (TR/TE = 30/8 ms, flip angle = 45, FOV = 240 mm, 100 1.5 mm axial slices; matrix = 256 × 256).

1.4. Image processing and data analysis

Modified SPM software (Wellcome Department of Imaging Neuroscience) was used for processing the data, which included manual AC-PC re-orientation of all anatomical and EPI images; realignment of EPI images to correct for slight head movement between scans and for differential spin excitation history based on intracranial voxels; extraction of physiological fluctuations such as cardiac and respiratory cycles from the EPI image sequence (Frank, Buxton, & Wong, 2001); co-registration of functional EPI images to the corresponding high-resolution anatomical image based on the rigid body transformation parameters of the reference anatomical image to the latter for each individual subject; stereotactic normalization to a standardized coordinate space (Montreal MRI Atlas version of Talairach space) based on the high-resolution anatomical image; spatial smoothing with an isotropic Gaussian kernel (FWHM = 7.5 mm).

Using customized fmristat software (Worsley et al., 2002), a two-stage voxel-wise linear mixed-effects model was utilized to examine the key Group/Condition contrasts of interest. First, a whole-brain voxel-wise multiple linear regression model was employed at the individual subject level which comprised the regressor of interest, the covariates of no interest (the first-order temporal derivative of the regressor of interest, global and physiological fluctuations, realignment parameters, scanning period means, and baseline drift up to the third order polynomials) and an AR(1) model of the residual time series to accommodate temporal correlation in consecutive scans. Second, at the group level, a mixed-effects model was used, which accounts for intra- and inter-subject variability, and allows for population-based inferences to be drawn. Age and gender were used as covariates of no interest in an analysis of covariance setting.

A voxel-wise inference at the group level was then drawn according to Gaussian random field theory. Initial uncorrected threshold was $p < 0.001$; comparisons were considered significant at $p < 0.05$ in either whole brain correction or in small volume correction in *a priori* regions of interest (amygdala, basal ganglia and vmPFC) selected based on previous results (Butler et al., 2007; Phelps, Delgado, Nearing, & LeDoux, 2004; Phelps et al., 2001). BOLD activity t-maps are shown at voxel-wise *p*-values less than 0.01 for the purpose of presentation only.

2. Results

During debriefing all subjects indicated that they had expected to receive an electrodermal stimulation during the presentation of the Threat stimulus and that this expectation was associated with the feeling of fear which decreased with repeated presentations over time.

In healthy control subjects significant activation was exhibited in the contrast of Threat versus Safety in bilateral anterior insula, bilateral basal ganglia and thalamus, bilateral dorsal anterior cingulate and bilateral dorsolateral prefrontal cortex (Butler et al., 2007). In the contrast of Safe versus Threat, increased activation was found in bilateral primary motor cortex, bilateral hippocampi/parahippocampi, bilateral posterior cingulate/precuneus and angular gyri as well as in bilateral medial and lateral orbitofrontal cortex from a larger sample (Butler et al., 2007). Previous studies have shown an attenuation of amygdalar activity and relative decrease followed by an increase of vmPFC/sgACC activity over time (Butler et al., 2007; Phelps et al., 2004, 2001). Parametric modelling of trials over time revealed an initial decrease of amygdalar activation (Fig. 1A; cp. Butler et al., 2007) which was mainly driven by the Threat condition (Fig. 1B) and accompanied by a co-variation in sgACC activity (Fig. 1A).

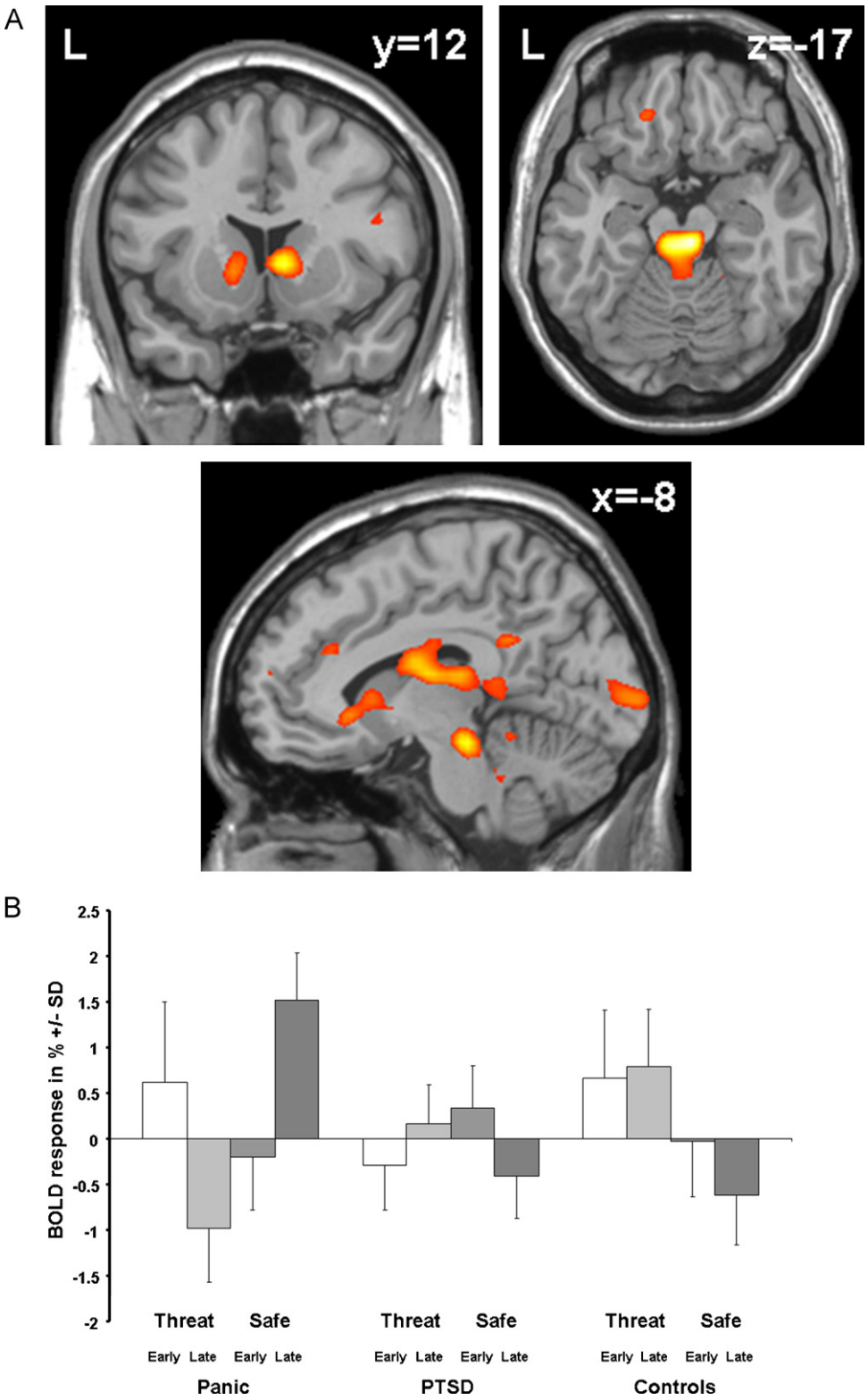

Fig. 3. (A) Coronal ($y = 12$), axial ($z = -17$), and sagittal ($x = -8$) sections showing increased dorsal midbrain/mesial periaquaeductal grey and (right) caudate for the Threat vs. Safe by Early vs. Late interaction in Panic vs. PTSD subjects ($p < 0.01$). (B) The bar plot shows BOLD response ± SD (%) at the point showing maximum activity for the Threat vs. Safe by Early vs. Late interaction in Panic vs. PTSD subjects MNI [6, −24, −18]. This point is located in the tegmental periaqueductal gray area. BOLD response is shown for groups [Panic, PTSD, Normal Controls], conditions [Threat, Safe], and study session [broken into Early and Late run] relative to a resting baseline.

The main comparison of interest, PD versus PTSD patients, found less activation in the Threat versus Safe contrast in regions including the subgenual cingulate (Brodmann area 25), ventral striatum, and extended amygdala, with contrast maximum in the subgenual cingulate ([6, 12, −9], $Z = -4.43$, voxel-wise $p < 0.0001$, $p < 0.05$ [corrected]; Fig. 2A, Table 2). These findings were due to an increase in activation to the Safe condition in PD patients, co-varying with an increased activity to the Threat condition in PTSD patients (Fig. 2B). When the study sessions were broken into Early (first run) and Late (second run) components, healthy control subjects activated this

region most strongly in the Early Threat condition while PTSD subjects activate this region equivalently in the Early and Late Threat conditions (Fig. 2B).

The direct contrast of Early (first half) and Late (second half) components of the Threat versus Safe comparison revealed increased activity in PD versus PTSD patients, most prominently in the dorsal midbrain/mesial periaquaeductal grey (MNI [6, −24, −18], $Z = 4.49$, voxel-wise $p < 0.0001$, $p < 0.003$ [corrected]; Fig. 3A; Table 2) and right caudate (MNI [9, 12, 3], $Z = 3.72$, voxel-wise $p < 0.0001$, $p < 0.045$ [corrected]; Fig. 3A; Table 2). Inspection of the BOLD responses in the dorsal midbrain/mesial periaquaeductal grey (MNI [6, −24, −18]; Fig. 3B) revealed a time-by-condition interaction in PD patients with a marked response to the late Safe condition.

3. Discussion

Using cognitively instructed fear, this study demonstrates significantly less activation to threat cues and increased activity to safety cues in the subgenual cingulate, ventral striatum, extended amygdala and midbrain periaquaeductal grey in PD patients, suggesting abnormal reactivity in these regions for fear expression. PTSD subjects, in comparison, failed to show the temporal pattern of activity decrease found in control subjects.

Considering the role of these regions in the regulation of visceromotor, autonomic, and emotional circuitry (Price, 1999), decreased activation of the subgenual cingulate, extended amygdala, and ventral striatum in the Threat versus Safe contrast in PD versus PTSD patients is notable. This same network appears to be activated in healthy control subjects under the most threatening condition (Early Threat), and in PTSD subjects fails to habituate over time under threat conditions, supporting models of failure of PTSD patients to habituate to threatening stimuli (Protopopescu et al., 2005).

Studies in rats and humans have shown that the medial prefrontal cortex plays a critical role in the retention and expression of extinction memory (Milad et al., 2006; Morgan, Romanski, & LeDoux, 1993), with subgenual cingulate cortex specifically mediating successful extinction learning and retention (Phelps et al., 2004). Deficits in fear extinction have been hypothesized to play a central role in PTSD (Milad et al., 2006), and such deficits have recently been demonstrated in psychophysiologic studies of PTSD (Blechert, Michael, Vriends, Margraf, & Wilhelm, 2007) as well as PD (Michael, Blechert, Vriends, Margraf, & Wilhelm, 2007). Our results complement these findings that PTSD and PD might, in part, be related to deficits in extinction learning subserved by the same neuroanatomical region (subgenual cingulate) but by different functional/neuronal mechanisms (cp. Fig. 2B). While Normal Control subjects show strong ventromedial prefrontal cortex activity in the Early Threat condition alone, PTSD subjects show weaker ventromedial prefrontal cortex activity which persists across the Early and Late Threat conditions.

The increased activation of the medial frontal cortical network and, in the late phase, the brainstem to the Safe condition in PD patients (a reversal of the activation pattern seen in PTSD patients and healthy controls) is particularly interesting and is intriguingly in-line with recent behavioral evidence for an impairment of discrimination learning in PD (Lissek et al., 2009) which might reflect elevated fear responding to learned safety cues. One possible explanation for this finding is that unlike PTSD, in which dysfunction is related to external threat, PD is largely concerned with internal viscero-somatic threat, possibly generated in the brainstem (Gorman et al., 2000; Protopopescu et al., 2006).

The ventromedial prefrontal cortex and brainstem findings in this study are especially interesting in light of a recent fMRI study demonstrating that threat imminence elicits a prefrontal-periaqueductal gray shift in humans (Mobbs et al., 2007). This study used electrodermal "shock" stimuli in concert with a virtual predator maze task, and showed that activity in the (mesial) periaquaeductal gray correlated with increased subjective sense of dread and decreased confidence of escape (Mobbs et al., 2007). Conversely, in the same study, decreased dread and increased confidence of escape was associated with increased activity in the ventromedial prefrontal cortex. In the current study, PD subjects in the Early Threat (strongest external threat) condition activated the brainstem but not the ventromedial prefrontal cortex (in line with the Mobbs findings on "imminent threat"). This contrasts with the healthy control subjects who activated ventromedial prefrontal cortex in addition to brainstem in the Early Threat condition. PD subjects in the Late Safe condition (perhaps the strongest internal visero-somatic threat condition as it is the farthest from task defined external threat) demonstrated their strongest brainstem and ventromedial prefrontal cortex activations, in contrast to healthy control and PTSD subjects, who had their lowest activations in these regions in this Late Safe condition.

One limitation of this study is that a subset of PD and PTSD subjects had a range of psychiatric comorbidities, typical in most PD and PTSD diagnosed individuals, and reflecting an overlap of clinical and likely biological features. However, no systematic disparity in comorbid diagnoses was present between groups, making it unlikely that comorbid diagnoses explain any systematic variance or the central findings of the present study. Furthermore, condition- and group-specific activity in the hypothesized regions was exhibited despite those comorbidities in a mixed-effects model that is considered statistically more stringent and capable of addressing inter- and intrasubject variability and generalizable to the larger population. The same line of arguments holds true for another issue to consider, namely the current medication of one PD subject. Yet another limitation is the small number of participants in each group mainly limited by the number of recruitable PD subjects. To mitigate this limitation, subjects were matched across groups as closely as possible and, as above, a mixed-effects model was used to address inter- and intrasubject variability and to improve generalizability to the general population. Nevertheless, it will be important in the future to conduct studies with additional patients and larger sample sizes, to extend and test the replicability of these findings, and to further address medication and comorbidity issues.

4. Conclusion

These findings contribute to the growing literature examining the potentially unique neurocircuitry subserving distinct anxiety disorders. Key findings in the present study may suggest a heightened sensitivity to internally generated, viscerosomatic threat in PD versus heightened sensitivity to external threat in PTSD, as well as to impaired discrimination learning in PD versus impaired extinction learning in PTSD on the behavioral level. Neuroimaging studies contributing to the characterization of more specific pathophysiological mechanisms underlying PD and PTSD may identify diagnostically and therapeutically relevant biomarkers.

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