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ORIGINAL ARTICLE

Prefrontal dysfunction during emotion regulation in generalized anxiety and panic disorders

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Background. The mechanisms that contribute to emotion dysregulation in anxiety disorders are not well understood. Two common disorders, generalized anxiety disorder (GAD) and panic disorder (PD), were examined to test the hypothesis that both disorders are characterized by hypo-activation in prefrontal cortex (PFC) during emotion regulation. A competing hypothesis that GAD in particular is characterized by PFC *hyper*-activation during emotion regulation (reflecting overactive top-down control) was also evaluated.

Method. Twenty-two medication-free healthy control (HC), 23 GAD, and 18 PD participants underwent functional magnetic resonance imaging (fMRI) during a task that required them to reappraise (i.e. reduce) or maintain emotional responses to negative images.

Results. GAD participants reported the least reappraisal use in daily life, and reappraisal use was inversely associated with anxiety severity and functional impairment in these participants. During fMRI, HCs demonstrated greater activation during both reappraisal and maintenance than either GAD or PD participants (who did not differ) in brain areas important for emotion regulation (e.g. dorsolateral and dorsomedial PFC). Furthermore, across all anxious participants, activation during reappraisal in dorsolateral and dorsomedial PFC was inversely associated with anxiety severity and functional impairment.

Conclusions. Emotion dysregulation in GAD and PD may be the consequence of PFC hypo-activation during emotion regulation, consistent with insufficient top-down control. The relationship between PFC hypo-activation and functional impairment suggests that the failure to engage PFC during emotion regulation may be part of the critical transition from dispositionally high anxiety to an anxiety disorder.

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Key words: Anxiety, emotion regulation, fMRI, generalized anxiety disorder, panic disorder, prefrontal cortex.

Introduction

Anxiety disorders are common (12-month prevalence: 18%; Kessler *et al*. 2005), and cause reduced quality of life (Mendlowicz & Stein, 2000; Lochner *et al*. 2003; Barrera & Norton, 2009) and loss of productivity (DuPont *et al*. 1996). Many investigations have sought to understand how pathological anxiety is maintained. Conceptual models have highlighted the role of anxious arousal and negative affectivity as predisposing factors (Clark & Watson, 1991), and avoidance as a key maintaining factor (Reddy *et al*. 2006; Aupperle & Paulus, 2010). In addition, the role of emotion regulation is increasingly receiving attention (Mennin, 2006; Campbell-Sills & Barlow, 2007; Amstadter, 2008; Aldao *et al*. 2010; Cisler *et al*. 2010).

Emotion regulation has been defined as 'cognitive and behavioral processes that influence the occurrence, intensity, duration, and expression of emotion' (Campbell-Sills & Barlow, 2007). One of the most studied forms of emotion regulation is reappraisal, or 'changing how we think about a situation in order to decrease its emotional impact' (Gross, 2002). Reappraisal is associated with positive affect, interpersonal functioning, and well-being (Gross & John, 2003). Individuals with anxiety disorders are thought to have poorer emotion regulation skills, including reappraisal (Campbell-Sills & Barlow, 2007; Amstadter, 2008; Cisler *et al*. 2010); however, the evidence supporting this hypothesis is mixed (Decker *et al*. 2008; Aldao *et al*. 2010; Werner & Gross, 2010).

The neural substrates of reappraisal have been studied in both healthy adults and individuals with

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anxiety disorders. Studies of healthy adults have consistently found activation in dorsomedial, dorsolateral, and ventrolateral prefrontal cortex (PFC) during reappraisal (Ochsner & Gross, 2005; Lieberman, 2007). However, whether and how these substrates differ in individuals with anxiety disorders remains unclear. Studies of social anxiety disorder and posttraumatic stress disorder (PTSD) found less PFC activation in patients than healthy controls during reappraisal (Goldin *et al*. 2009*a*, *b*; New *et al*. 2009). However, a study of young adults with high trait anxiety found the opposite: greater PFC activation during reappraisal in those with higher anxiety (Campbell-Sills *et al*. 2011).

In the current study, our aim was to examine the common and distinct neural bases of emotion regulation in healthy and clinically anxious participants, while also comparing two common anxiety disorders, generalized anxiety disorder (GAD) and panic disorder (PD). Emotion dysregulation has been hypothesized to play a key role in GAD: patients with GAD may not be as skilled at adaptively regulating negative emotions and may instead suppress emotions (Mennin *et al*. 2002, 2005). Although to our knowledge the neural bases of reappraisal in GAD have not been examined, other neuroimaging studies of GAD have suggested a tendency to over-engage prefrontal top-down control (Mathew *et al*. 2004; Etkin *et al*. 2009).

The role of emotion dysregulation in PD has been even less well-studied than in GAD. One study found that reliance on suppression as an emotion regulation strategy maintains anxiety and avoidance in patients with PD (Levitt *et al*. 2004). Furthermore, inflexible emotion regulation may moderate the relationship between anxiety sensitivity and PD (Cisler *et al*. 2010). Biological models have pointed to insufficient top-down control as a factor in the generation of panic (Kent & Rauch, 2003). However, to our knowledge, there have been no neuroimaging studies of reappraisal in PD.

We examined two competing hypotheses. First, based on the conceptualization that GAD involves an overactive top-down control system, one hypothesis posits that individuals with GAD exhibit PFC hyperactivation during reappraisal. This would be consistent with findings in non-treatment-seeking, high trait anxiety participants, including many with GAD symptoms (Campbell-Sills *et al*. 2011). A second hypothesis, based on the notion that emotion dysregulation and its neural bases are consistent across anxiety disorders, posits that both GAD and PD participants show *attenuated* prefrontal responding (reflecting inadequate top-down control) during reappraisal. This would be consistent with findings in other anxiety disorders.

Method and materials

Participants

This study was approved by the University of California San Diego Human Research Protections Program. After providing written informed consent, 139 participants underwent a semi-structured diagnostic interview (Sheehan *et al*. 1998). Of these, 24 healthy control (HC) adults were eligible who did not meet DSM-IV criteria (APA, 2000) for lifetime mood, anxiety, psychotic, or substance dependence disorders. In addition, 52 patients met DSM-IV criteria for clinically predominant PD ($n=24$; 20 with and four without agoraphobia), or clinically predominant GAD ($n=28$), and did not meet criteria for lifetime psychosis, past-year substance dependence, or past-month substance abuse. Due to the high rate of co-morbidity in anxiety disorders (Kessler *et al*. 2005), co-morbid mood and other anxiety disorders were allowed; however, individuals with co-occurring PD and GAD ($n=7$) were excluded. Two participants from each group were removed from the analysis due to poor functional magnetic resonance imaging (fMRI) data quality. The final dataset included 22 HC, 18 PD, and 23 GAD participants. In the GAD group, two participants had co-morbid major depression, two had obsessive-compulsive disorder, and eight had social anxiety disorder. In the PD group, two participants had co-morbid major depression, one had obsessive-compulsive disorder, and two had social anxiety disorder. All participants were free of psychotropic medications for 6 weeks prior to study enrollment (2 weeks for benzodiazepines).

All participants met safety and eligibility criteria for fMRI scanning: no neurological conditions, no implanted ferrous metal, and no history of loss of consciousness >5 min. Demographic characteristics of the 63 participants are presented in Table 1. There were group differences on age ($p<0.07$) and gender ($p<0.05$), therefore all group effects analyses were also run with age and gender as covariates.

Procedure

Eligible participants underwent a medical examination, including medical history, laboratory evaluation, EKG, and drug and pregnancy screen. Participants also completed questionnaires including the Overall Anxiety Severity and Impairment Scale (OASIS; Norman *et al*. 2006), the Penn State Worry Questionnaire (PSWQ; Meyer *et al*. 1990), the Anxiety Sensitivity Index (ASI; Reiss *et al*. 1986), and the Quick Inventory of Depressive Symptomology (QIDS; Rush *et al*. 2003). Fifty (78%) individuals participated in an optional adjunct study, and completed the Emotion

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Table 1. *Demographics and clinical features of participants*

	HC ($n=22$)	GAD ($n=23$)	PD ($n=18$)	ANX *v.* HC	GAD *v.* PD
Age in years (S.D.)	27 (9)	35 (11)	29 (7)	$t_{61}=2.0$†	$t_{39}=2.0$†
Gender (% female)	50%	74%	83%	$\chi^2=5.2$*	$\chi^2=0.5$
Education in years (S.D.)	15 (2)	16 (2)	14 (2)	$t_{61}=-0.6$	$t_{39}=1.9$†
Ethnicity (% Caucasian)	59%	74%	53%	$\chi^2=0.3$	$\chi^2=1.5$
Anxiety Severity (S.D.)	0.8 (1.2)	9.9 (3.2)	7.3 (3.4)	$t_{61}=10.2$*	$t_{39}=2.5$*
Worry (S.D.)	12.6 (1.1)	17.8 (2.7)	15.9 (3.7)	$t_{61}=6.1$*	$t_{39}=2.0$†
Anxiety sensitivity (S.D.)	7.5 (5.6)	28.1 (11.3)	35.3 (10.4)	$t_{61}=9.2$*	$t_{39}=-2.1$*
Depression (S.D.)	2.1 (1.2)	8.8 (4.4)	6.2 (4.1)	$t_{61}=5.8$*	$t_{39}=2.0$†
Reappraisal use (S.D.)	31.0 (6.1)	24.8 (8.0)	32.7 (5.2)	$t_{48}=-1.2$	$t_{27}=-3.1$*
Suppression use (S.D.)	12.0 (2.8)	15.3 (5.5)	15.3 (4.9)	$t_{48}=2.5$*	$t_{27}=0.02$
% with current MDD (past)	0% (0%)	9% (26%)	11% (22%)	$\chi^2=9.8$*	$\chi^2=0.1$

HC, Healthy controls; GAD, generalized anxiety disorder group; PD, panic disorder group; ANX, GAD and PD groups combined; S.D., standard deviation; MDD, major depressive disorder.

* $p<0.05$, † $p<0.07$.

Regulation Questionnaire (ERQ; Gross & John, 2003). All participants completed one fMRI scan before receiving 10 sessions of weekly individual cognitive behavioral therapy. Relationship of fMRI findings and therapy outcomes will be considered in a separate paper.

Task

Two processes were examined with the emotion regulation task: in each trial, individuals either maintained or reappraised their emotional responses to negative images. Each trial was 24 s long, with a scrambled image presented for the first 12 s and a negative image for the last 12 s (Supplementary Fig. S1). After the first 1–3 s (jittered) of scrambled image presentation the words 'Rate Emotion (1–4)' appeared for 3 s, cuing participants to provide a baseline rating of their emotional experience from 1 (not at all negative) to 4 (very negative). Next, 1–3 s later, participants received an instruction to either 'Keep Up Emotion' (Maintain) or 'Reduce Emotion' (Reappraise) to the negative image they were about to see. The instruction remained on the screen for 3 s, followed by continued presentation of the scrambled image (1–3 s). Participants then viewed the target negative image for 4–6 s, implementing the instruction they had just received. They then received the cue to rate their negative emotion (3 s), followed by continued presentation of the negative image (3–5 s). The period of interest was the 4–6 s when the participant was maintaining or reappraising their emotional reactions.

The images used in the task were 12 negatively valenced images for each condition, selected from the International Affective Picture System (Lang *et al*. 2008), with a pixel-wise scrambled version of each image presented as a baseline at the start of each trial. More information about the images and the task are given in Campbell-Sills *et al*. (2011), though there is no overlap in subjects between those reported here and in Campbell-Sills *et al*. (2011).

Prior to fMRI scanning, participants were trained on the task. For the Maintain condition participants were instructed to 'maintain your emotional reaction until the picture disappears'. For the Reappraise condition, participants were asked to 'change the way that you think about the picture in order to decrease your negative emotions'. Suggested reappraisal strategies included generating a positive interpretation or taking a more detached perspective. Participants practiced out loud on sample images, to confirm understanding.

Image acquisition

One 9-min 40-s BOLD fMRI run was acquired, using a Signa EXCITE 3.0-T GE scanner (T2*-weighted echo planar imaging, TR = 2000 ms, TE = 32 ms, FOV = 240 × 240 mm^3, 64 × 64 matrix, thirty 2.6-mm axial slices with a 1.4-mm gap, 290 scans). For anatomical reference, a high-resolution T1-weighted image (SPGR, TI = 450, TR = 8 ms, TE = 3 ms, FOV = 250 × 250 mm^3, flip angle = 12°, 172 sagittally acquired slices with 1-mm thickness) was obtained during the same session.

Image processing

All structural and functional image processing was done with the Analysis of Functional NeuroImages

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(AFNI) software package (Cox, 1996). The AFNI function *3dToutcount* was used to identify the number of voxels classified as outliers at each time point: any time point with >2 S.D. outlier voxels than the subject's mean were excluded from analysis. Voxel time-series were interpolated to correct for non-simultaneous slice acquisition and corrected for three-dimensional motion. Anatomical and echo planar volumes were co-registered using an algorithm that minimizes the amount of image translation and rotation (Saad *et al*. 2009).

Individual participant time-series data were analyzed with AFNI's *3dDeconvolve* program. The orthogonal regressors of interest were those indicating the Maintain, Reappraise, and Baseline conditions (see Supplementary Fig. S1). Additional regressors of non-interest modeled the emotion rating periods and post-rating viewing period at the end of each trial, as well as linear and quadratic trends in the time-series and motion regressors based on the time-series alignments in the roll, pitch, and yaw directions. Regressors were convolved with a modified gamma variate function to account for the hemodynamic response (Boynton *et al*. 1996) using the AFNI program *waver*. Following deconvolution, data were converted to percent signal change, by dividing the coefficient by the zero-order regressor within each voxel. Data were normalized to Talairach coordinates (Talairach & Tournoux, 1988) and subjected to a 4-mm Gaussian blur for spatial smoothing.

To protect for multiple comparisons, Monte Carlo simulations ($n=10\,000$) using AFNI's *3dClustSim* program demonstrated that minimum cluster volumes of 640 μl for a per-voxel threshold of $p<0.01$ (one-sided) for whole-brain analysis with 4-mm spatial smoothing would result in a cluster-wise $p<0.05$. Therefore, only clusters of $\geqslant 640$ μl are reported.

Statistical analysis

Analyses of self-report and behavioral data were performed with PASW Statistics (version 18.0.0, USA). Single subject analysis of functional images was performed using the AFNI software package (Cox, 1996), and group-level statistical analyses were completed using the R statistical package (http://cran.r-project.org). Group analysis was conducted at each voxel using the R library *fmri* to read in and write out full AFNI data files for voxel-wise analysis. Specifically, using the R library *nlme*, a linear mixed-effects model was computed with group (HC, PD, GAD) as a fixed factor and condition (Reappraise, Maintain; each contrasted with Baseline) as a grouped factor within subjects. Subjects were modeled as random factors.

First, to determine whether there were condition-specific group differences, we examined the group × condition interaction. Next, because examining the main effect of group by combining both conditions would be difficult to interpret, we examined the main effect of group in each condition separately, and also identified regions of overlap that showed significant group effects in both conditions. These analyses were subjected to a volume-adjusted threshold such that each voxel met a statistical threshold ($p<0.01$, one-sided) and was part of a cluster of ≥ 640 μl, corresponding to a whole-brain adjusted $p<0.05$. All group effects were also examined with age and gender as covariates. Finally, planned contrasts between HCs and anxious participants, and between GAD and PD participants, were obtained from cluster averages to describe the characteristics of the group and interaction effects. Cohen's *d* was computed using pooled standard deviation.

The main effect of task (Reappraise *versus* Maintain) across all participants was then examined; however, using the statistical and volume thresholds described above yielded clusters so large they were difficult to interpret and report. Therefore a per-voxel threshold of $p<0.001$ with a minimum cluster size of 256 μl was used. Monte Carlo simulations ($n=10\,000$) using AFNI's *3dClustSim* program demonstrated that this statistical and volume combination also yields a whole-brain cluster-wise $p<0.05$.

Results

Self-report measures

Table 1 summarizes the self-report questionnaires. One-way ANOVA analyses revealed a significant main effect of group on overall anxiety severity and impairment, worry, anxiety sensitivity, and depression ($p<0.001$). Follow-up *t* tests comparing patients and controls showed higher scores in patients on all measures ($p<0.001$). Follow-up *t* tests comparing GAD and PD revealed differences in anxiety sensitivity (PD higher, $p<0.05$) and overall anxiety severity and impairment (GAD higher, $p<0.05$) only.

The groups also differed on emotion regulation use in daily life (reappraisal $p<0.005$, suppression $p=0.05$). Follow-up *t* tests showed greater use of suppression in patients ($p<0.05$) with no difference between GAD and PD. Patients and controls did not differ on reappraisal use, but GAD reported less reappraisal use than PD ($p<0.005$). Reappraisal use was inversely associated with overall anxiety severity and impairment in GAD ($r=-0.61$, $p<0.05$) but not PD ($r=0.14$, N.S.). When controlling for age, gender, and depression severity, all self-report differences

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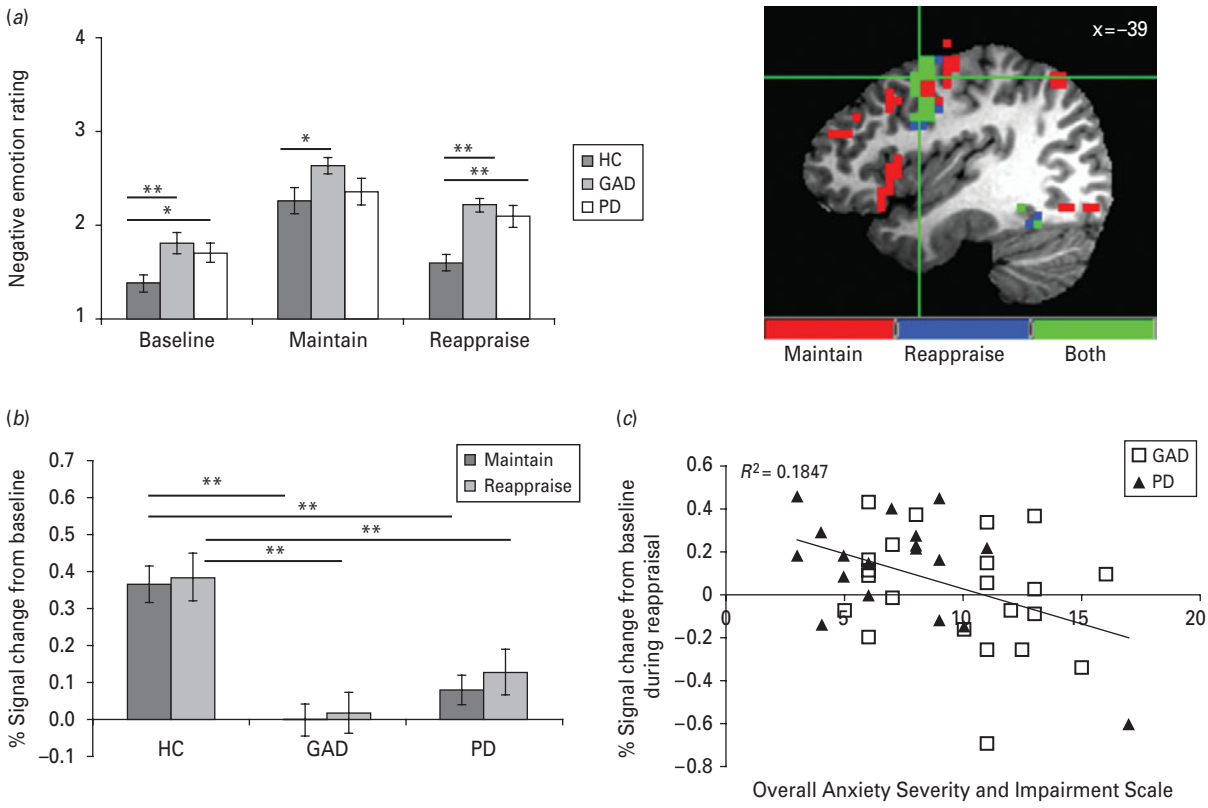

Fig. 1. (*a*) Negative emotion ratings during the task. HC, Healthy control; GAD, generalized anxiety disorder; PD, panic disorder. Asterisks indicate significant group differences within a condition (* $p<0.05$, ** $p<0.005$). (*b*, *c*) Attenuated left dorsolateral prefrontal cortex (PFC) activation during reappraisal GAD and PD is correlated with anxiety severity. Activation extracted from the region showing group differences in activation in both the Reappraise and Maintain conditions. (*b*) Left dorsolateral PFC activation during reappraisal and maintenance (* $p<0.05$, ** $p<0.005$). (*c*) Left dorsolateral PFC activation during reappraisal associated with anxiety severity and impairment in patients with anxiety disorders.

remained significant ($p<0.05$) except group differences in suppression use ($p=0.08$).

Behavioral task effects

Fig. 1*a* illustrates the results of a 3 (group: HC, PD, GAD) × 3 (condition: Baseline, Maintain, Reappraise) repeated-measures ANOVA on the negative emotion ratings collected during the task. Emotion ratings differed by condition, with most negative emotion during the Maintain condition, and least during Baseline ($F_{2,110}=94.0$, $p<0.001$). Paired t tests confirmed that emotion ratings significantly differed across all conditions in each of the three groups ($p<0.05$). Ratings also differed by group, with HCs reporting less intense emotions than either PD or GAD subjects ($F_{2,55}=7.3$, $p<0.005$). There was also a group × condition interaction ($F_{4,110}=2.4$, $p=0.05$): HCs reported significantly less negative emotion than GAD or PD subjects during Baseline and Reappraisal, and less negative emotion than GAD subjects during the Maintain condition ($p<0.05$). Emotion ratings in the GAD and PD groups did not differ from each other in any condition ($p>0.09$).

In order to control for differences in negative emotion at baseline, differential emotion ratings (i.e. Reappraise minus Baseline and Maintain minus Baseline) were also examined. No group differences were found for either condition ($p>0.1$). All behavioral results were unchanged when controlling for age and gender.

fMRI task effects

Across all participants, greater activation to Maintain than Reappraise was observed in many brain areas, including medial supplemental motor area, bilateral inferior parietal lobule, posterior cingulate, bilateral posterior insula, and bilateral middle temporal gyrus. Greater activation to Reappraise than Maintain was observed across all participants in bilateral middle occipital gyrus, right fusiform gyrus, and right precuneus (Supplementary Table S1).

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Table 2. *Regions demonstrating a significant differential effect of condition* (*Reappraise* versus *Maintain*) *across groups*

Region	BA	Peak				Volume (μl)
		x	y	z	*F* statistic	
Parietal lobe						
Left postcentral gyrus/ inferior parietal lobule	3, 40	−42	−29	48	7.53	2944

BA, Brodmann area.

fMRI group×task interaction effects

Voxel-wise whole-brain analysis of group (HC, GAD, PD) × task (Reappraise, Maintain) interactions revealed a cluster in the left post-central gyrus extending to the inferior parietal lobule. The interaction was due to significantly greater activation in HCs than either GAD or PD subjects in the Maintain condition, but no group differences during the Reappraise condition (Table 2).

fMRI group effects – maintenance

During the Maintain condition, significant group differences were observed in several prefrontal regions: dorsomedial PFC, bilateral dorsolateral and ventrolateral PFC, and dorsal anterior cingulate. These were all characterized by significantly greater activation in HCs than anxious participants ($d = 1.05$–1.77), with only right ventrolateral PFC and dorsal anterior cingulate demonstrating significant differences between the two anxiety groups (PD > GAD, $d = 0.90$ and 0.64, respectively). Of these prefrontal regions, all but right ventrolateral PFC and dorsal anterior cingulate continued to show significant group effects when controlling for age and gender.

HCs also demonstrated significantly greater activation than anxiety patients in other regions, including left anterior insula, bilateral caudate and thalamus, left superior parietal lobule, left fusiform gyrus, bilateral middle and superior temporal gyrus, posterior cingulate, and left middle occipital gyrus ($d = 0.61$–1.45). GAD and PD subjects differed in right middle and superior temporal gyrus and left superior parietal lobule (PD > GAD, $d = 1.01$–1.14), as well as left middle occipital gyrus (GAD > PD, $d = 0.83$). All regions except posterior cingulate continued to show significant group effects when controlling for age and gender (Table 3*a*, Figs 1 and 2).

fMRI group effects – reappraisal

During Reappraisal, HCs demonstrated significantly greater activation than anxiety patients in several regions, including dorsomedial and bilateral dorsolateral PFC, left fusiform gyrus and right middle occipital gyrus ($d = 0.82$–1.37). GAD and PD subjects differed in right middle occipital gyrus only (PD > GAD, $d = 0.77$). Dorsomedial PFC, left dorsolateral PFC, and left fusiform gyrus had at least four voxels of overlap with regions that also showed significant group effects during the Maintain condition. When controlling for age and gender, only bilateral dorsolateral PFC continued to show significant group effects (Table 3*b*, Figs 1 and 2).

Brain-behavior relationships

Relationships between self-report measures and average brain activation were examined for the two prefrontal regions (dorsomedial and left dorsolateral PFC) that differed between anxious and control participants during both reappraisal and maintenance. Because activation in these regions did not differ between GAD and PD, correlations were conducted on the combined group of anxious participants.

Among anxious participants, those with greater anxiety severity and associated impairment showed relatively less activation in PFC during both reappraisal and maintenance. Specifically, individuals reporting greater anxiety severity and functional impairment had less activation in left dorsolateral PFC during reappraisal ($r = -0.43$, $p = 0.005$) and in dorsomedial PFC during both reappraisal ($r = -0.38$, $p < 0.05$) and maintenance ($r = -0.33$, $p < 0.05$) (Figs 1 and 2). The relationships between activation during reappraisal and anxiety severity remained significant when controlling for age and gender, and marginally significant ($p < 0.07$) when controlling for depression severity (in dorsolateral PFC; dorsomedial PFC, N.S.).

Similarly, across anxious participants, those who worried more had less activation in dorsomedial PFC during negative emotion maintenance ($r = -0.34$, $p < 0.05$) (Fig. 2). This relationship remained significant when controlling for age, gender, and depression severity. There were no associations between PFC

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Table 3. *Regions demonstrating a significant group effect in* (*a*) *the Maintain* versus *Baseline contrast and* (*b*) *the Reappraise* versus *Baseline contrast*

Region	BA	Peak			*F* statistic	Volume (μl)	Effect
		x	y	z			
(*a*) Maintain *versus* Baseline contrast							
Frontal lobe							
Dorsomedial PFC	6, 8	−10	31	56	14.03	19712	HC > PD = GAD
Dorsal ACC†	32	10	15	36	8.12	640	HC > PD = GAD
Dorsal ACC†	32, 24	−6	31	20	8.90	1536	HC > PD > GAD
L dorsolateral PFC	6, 9, 8	−42	−1	52	15.89	11456	HC > PD = GAD
L dorsolateral PFC	9, 10	−30	19	28	12.16	5696	HC > PD = GAD
R dorsolateral PFC	6, 8	42	−5	60	10.93	4096	HC > PD = GAD
L ventrolateral PFC	45, 46	−42	19	20	8.19	1472	HC > PD = GAD
R ventrolateral PFC†	44, 45	62	11	12	7.60	1088	HC > PD = GAD
R ventrolateral PFC†	47, 45	42	39	−8	10.22	1024	HC > PD > GAD
Temporal lobe							
R middle and superior temporal gyrus	22, 21	62	−45	4	10.90	4736	HC = PD > GAD
R temporal pole	38	46	3	−16	7.16	704	HC > PD = GAD
L middle temporal gyrus	21	−54	−45	0	11.03	1088	HC > PD = GAD
L superior temporal gyrus	22	−50	−45	16	7.98	960	HC = PD > GAD
Parietal lobe							
Posterior cingulate†	23, 31	−6	−45	20	7.25	1344	HC > PD = GAD
L superior and inferior parietal lobule	7, 40	−50	−57	52	7.08	896	HC = PD > GAD
R supramarginal gyrus	40	38	−37	36	6.09	704	HC > PD > GAD
Occipital lobe							
L fusiform gyrus	19, 18	−30	−61	−12	9.25	1216	HC > PD = GAD
L middle occipital gyrus	37	−46	−61	−4	6.64	640	HC > GAD > PD
R cuneus	17	22	−85	0	7.63	1024	HC > PD > GAD
Subcortical							
Bilateral thalamus/caudate, L anterior insula	13	−30	23	0	11.85	20736	HC > PD = GAD
L cerebellum/L fusiform gyrus	37	−34	−41	−20	9.33	1344	HC > PD = GAD
L cerebellum		−26	−69	−28	8.55	2176	HC > PD > GAD
R cerebellum		34	−57	−24	10.61	1600	HC > PD = GAD
R cerebellum		18	−57	−28	9.24	640	HC > PD = GAD
(*b*) Reappraise *versus* Baseline contrast							
Frontal lobe							
L dorsolateral PFC/premotor cortex	6, 9, 8	−38	3	32	11.49	4544	HC > PD = GAD
R dorsolateral PFC†	9	58	15	28	6.17	960	HC > PD = GAD
R dorsolateral PFC	9	34	7	28	6.32	640	HC > PD = GAD
Dorsomedial PFC†	6	−10	27	56	5.23	640	HC > PD = GAD
Temporal lobe							
L fusiform gyrus/cerebellum†	37	−34	−49	−20	7.95	1216	HC > PD = GAD
Occipital lobe							
R middle occipital gyrus†	17	30	−85	12	9.08	2560	HC > PD > GAD
Subcortical							
L cerebellum†		−22	−73	−24	9.37	704	HC > PD > GAD

BA, Brodmann area; PFC, prefrontal cortex; ACC, anterior cingulate cortex; L, left; R, right; HC, healthy control; PD, panic disorder; GAD, generalized anxiety disorder.

† Region no longer significant when controlling for age and gender.

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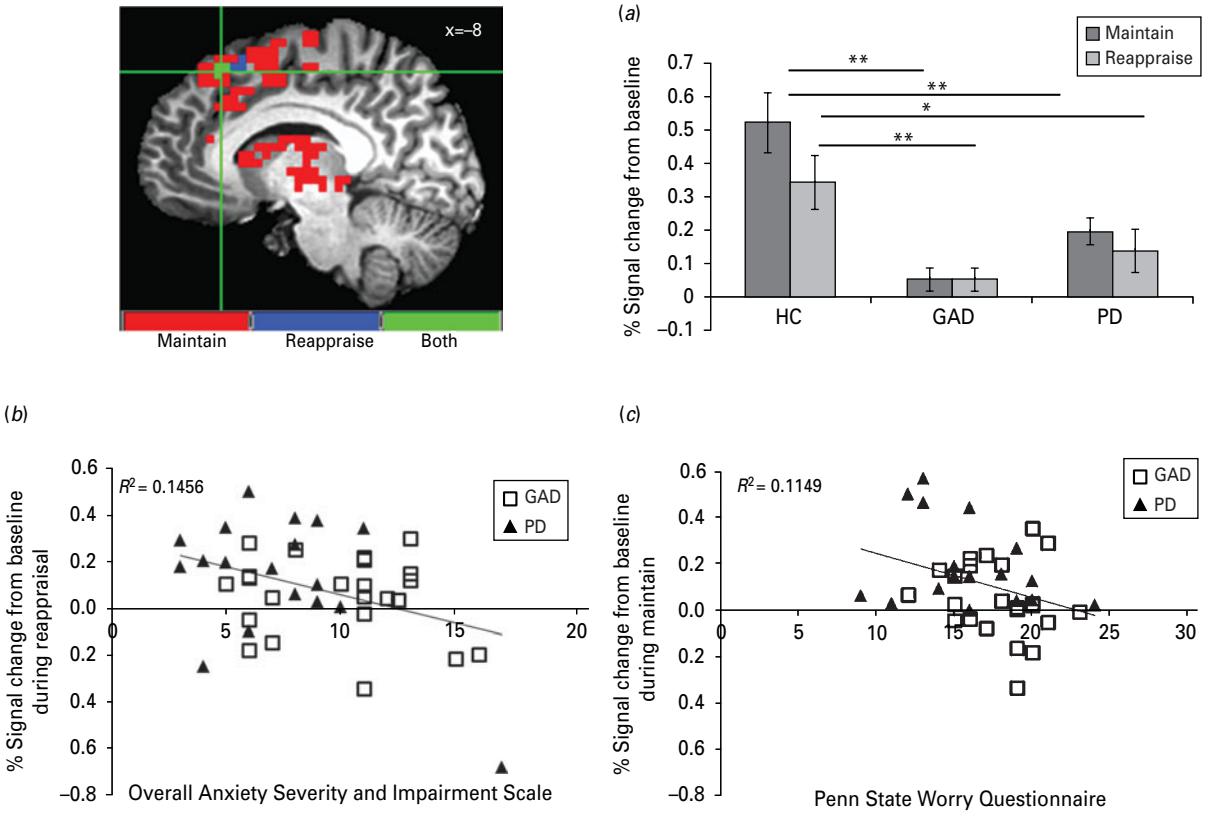

Fig. 2. Attenuated dorsomedial prefrontal cortex (PFC) activation in generalized anxiety disorder (GAD) and panic disorder (PD) is correlated with anxiety severity during reappraisal and correlated with worry severity during maintenance. Activation extracted from the region showing activation in both the Reappraise and Maintain conditions. (*a*) Dorsomedial PFC activation during each condition (* $p < 0.05$; ** $p < 0.005$). (*b*) Dorsomedial PFC activation during reappraisal associated with anxiety severity and impairment in patients with anxiety disorders. (*c*) Dorsomedial PFC activation during maintenance associated with worry severity in patients with anxiety disorders.

activation and worry severity during reappraisal, or between anxiety sensitivity, regular reappraisal use, or negative emotion ratings and PFC activation during either condition.

Discussion

This study examined two alternative hypotheses regarding the relationship of PFC activation and emotion regulation in PD and GAD. First, based on the conceptualization that GAD involves an overactive top-down control system, we hypothesized that GAD would exhibit *hyper*-activation in PFC during regulation. Second, based on the emotion regulation deficits common across anxiety disorders, a competing hypothesis was that both GAD and PD involve inadequate top-down control and therefore would show *attenuated* prefrontal responding during emotion regulation. The main neuroimaging finding showed that HCs activated dorsomedial and bilateral dorsolateral PFC more during reappraisal than those with GAD or PD. Therefore, the results of this study are consistent with the second hypothesis and support potential cross-disorder impairment in regulation of negative emotions.

Behaviorally, the groups did not differ in self-reported negative emotion during regulation when adjusting for baseline negative emotion ratings. This is consistent with previous reports that anxious individuals can successfully regulate emotions when explicitly trained and cued to do so (Goldin *et al.* 2009*b*; Campbell-Sills *et al.* 2011; Aldao & Mennin, 2012). Furthermore, the lack of difference in emotion ratings aids in interpretation of the fMRI results, as they cannot be readily explained by differential changes in internal emotional experience.

Unlike previous investigations (Campbell-Sills *et al.* 2011), no task effect or group × task interactions were found in PFC: group differences in prefrontal activation were present in both conditions. Both reappraisal and maintenance are active processes, and both involve conscious attempts to alter ongoing emotional experience. The use of such an active comparison condition may have contributed to the lack of

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differential effect in PFC, leading to the hypothesis that PFC recruitment may be broadly impaired in GAD and PD. For example, hypo-activations in PFC during a task requiring attentional control have been associated with trait anxiety (Bishop, 2009) consistent with concentration difficulties common in anxiety disorders (APA, 2000). Therefore, a decreased ability to recruit PFC may cut across multiple contexts relevant for anxiety disorders.

One region that did show a group × task interaction was the left inferior parietal lobule, where HCs but not anxious individuals showed greater activation during maintenance than reappraisal. The inferior parietal lobule together with the dorsolateral PFC is part of the central executive network, which is critical for top-down control during decision making, goal implementation, and other executive functions (Menon, 2011). The attenuated activation of this system during emotion regulation is consistent with the hypothesis that anxious participants exert insufficient goal-directed top-down control over brain systems that process emotional information.

In a previous study using this task (Campbell-Sills *et al*. 2011) PFC activation was greater in anxious participants during reappraisal, whereas here dorsolateral and dorsomedial PFC activation was greatest in HCs during both reappraisal and maintenance. However, the previous study used a non-clinical (i.e. non-treatment-seeking) sample. Studies of treatment-seeking adults with social anxiety disorder have found less PFC activation during reappraisal in anxious compared to healthy individuals (Goldin *et al*. 2009*a*, *b*), in line with the present results. This suggests that heightened PFC activation in anxious, non-clinical adults could be a compensatory mechanism in individuals with dispositionally high anxiety. This notion is consistent with previous investigations suggesting that dorsolateral PFC activation may serve a compensatory mechanism in less severe patients with GAD (Etkin *et al*. 2009) or major depression (Etkin & Schatzberg, 2011).

In contrast, anxiety associated with clinically significant impairment (i.e. disordered anxiety) could be associated with an inability to sufficiently engage PFC in the service of emotion regulation. We have previously suggested that inadequate top-down control in anxiety disorders could be the consequence of amplified bottom-up signals that make identifying salience more difficult (Paulus & Stein, 2010). In other words, chronic over-responsiveness of limbic circuitry in anxiety disorders (Etkin & Wager, 2007) may fatigue the top-down system, rendering it unable to effectively exert control when needed. Such emotion regulation deficits could perpetuate patients' belief that negative emotions are aversive and uncontrollable, continuing the cycle of amplified limbic inputs and fatigued top-down control and maintaining pathological anxiety. The inverse correlation between functional impairment and prefrontal activation supports the hypothesis that PFC hypo-activation could be a component of the transition from dispositionally high anxiety to disordered anxiety.

Although differences in neural activation between anxious and healthy participants were pronounced, there were few differences between GAD and PD. This supports the notion that decreased PFC engagement during emotion regulation is a common feature of the two disorders. However, activation in dorsomedial PFC during maintenance was inversely associated with worry severity. Worry, often conceptualized as an internal avoidance strategy, is a hallmark feature of GAD (Borkovec & Inz, 1990). Individuals with more severe worry may be less comfortable with affective arousal and more likely to avoid emotional stimuli, thereby showing diminished PFC activation during maintenance of negative emotions. On self-report measures, patients with GAD reported the least use of reappraisal in their daily lives. Furthermore, reappraisal use was associated with less anxiety severity and functional impairment in GAD, but not PD. These results support the theory (Mennin *et al*. 2002) that emotion dysregulation is especially important in understanding GAD.

In conclusion, patients with GAD and PD demonstrated less PFC activation than healthy controls during cognitive modulation of emotion, and those with the least PFC activation reported the greatest anxiety severity and impairment. When considered in conjunction with similar results in social anxiety disorder and PTSD (Goldin *et al*. 2009*a*, *b*; New *et al*. 2009), these results suggest a potential common neural basis of emotion dysregulation in anxiety disorders. Furthermore, these results highlight that emotion dysregulation may be related to functional impairment and treatment-seeking rather than a specific type of anxiety symptoms. However, given that patients with GAD reported least regular use of reappraisal, as well as the inverse association between worry and prefrontal activation, emotion dysregulation may be especially important in the etiology and maintenance of GAD (Mennin *et al*. 2002).

This study has several limitations. One limitation is the lack of a passive viewing condition, which may have contributed to the lack of task effect in PFC. Although a previous study using the same task (Campbell-Sills *et al*. 2011) did find such an effect, it was not replicated in this sample. The results should therefore be interpreted with caution. The absence of a passive viewing condition may also have contributed to the lack of group × task interaction in PFC. Without

such an interaction, the alternative hypothesis that top-down control is broadly impaired in GAD and PD cannot be ruled out. Future studies should utilize a variety of comparison conditions to more clearly differentiate the processes that are impaired in anxiety disorders.

Another limitation is that patients with GAD and PD differed on overall anxiety severity and impairment (greater in GAD) and habitual use of reappraisal (less frequent in GAD). In addition, the measure of habitual emotion regulation was only available for some participants, decreasing the power to detect effects related to this variable. However, there were few differences in neural activation between GAD and PD. Therefore it is unlikely that group differences on anxiety severity or emotion regulation use account for the results. As is common in anxiety disorders (Kessler *et al*. 2005), 10% of patients in this sample had co-morbid major depression, and an additional 24% reported past depressive episodes. However, associations between neural activation and anxiety changed only marginally when controlling for depressive symptoms, suggesting that depression severity cannot explain the findings.

The present study included only individuals with GAD or PD, but the results support the hypothesis that emotion dysregulation may be consistent across anxiety diagnoses. Future work should examine the neural bases of emotion regulation in other disorders. For example, emotion dysregulation in PTSD has been frequently noted (Roemer *et al*. 2001; Eftekhari *et al*. 2009; New *et al*. 2009; Bonn-Miller *et al*. 2011), suggesting that a better understanding of the neural bases of reappraisal in PTSD could be especially fruitful.

Last, successful emotion regulation can be accomplished in many ways, though here we only examined reappraisal and maintenance. Future work should examine subtypes of reappraisal (e.g. detachment, focusing on positive aspects) along with other emotion regulation strategies to understand how strategy selection impacts regulation success. A better grasp of the processes employed is important in moving past simply examining differences in activation location and intensity, and towards a more nuanced and mechanistic understanding.

Supplementary material

For supplementary material accompanying this paper visit http://dx.doi.org/10.1017/S0033291712002383.

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