ORIGINAL ARTICLE

Disorder-Specific Neuroanatomical Correlates of Attentional Bias in Obsessive-compulsive Disorder, Panic Disorder, and Hypochondriasis

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Context: Attentional bias to disease-relevant emotional cues is considered to be pathogenetically relevant in anxiety disorders.

Objective: To investigate functional neural correlates and disease specificity of attentional bias across different anxiety disorders.

Design: A cognitive and emotional Stroop task, consisting of congruent and incongruent color words, obsessive-compulsive disorder (OCD)–related and panic-related negative words, and neutral words, was used in 3 patient groups and a control group during functional magnetic resonance imaging.

Setting: Academic outpatient department for anxiety disorders.

Patients and Participants: Medication-free patients with OCD (n=16), panic disorder (PD) (n=15), and hypochondriasis (n=13) and 19 controls.

Main Outcome Measure: Voxel-wise analyses of cerebral blood flow changes for contrasts of interest (incongruent vs congruent color words, OCD-related vs neutral words, and panic-related vs neutral words) within and between groups.

Results: During incongruent vs congruent color naming, all patient groups recruited additional posterior brain regions relative to controls, but performance was impaired only in OCD. In OCD, color naming OCD-related, but not PD-related, words correlated with increased activation of frontal-striatal and temporal regions, although performance was unimpaired. In contrast, in PD, increased frontal-striatal involvement was found during color naming both OCD-related and panic-related words. In PD, color naming panic-related words was slowed and correlated with increased activation of the right amygdala and hippocampus. Patients with hypochondriasis showed a similar activation pattern to patients with PD.

Conclusions: Our results support the hypothesis of increased distractibility for irrelevant information in patients with OCD, PD, and hypochondriasis associated with frontal-striatal and limbic involvement compared with controls. Although patients with OCD did not display an attentional bias in behavior relative to controls, there was a clear, specific neural response during color naming OCD-related words, involving mainly ventral brain regions. In contrast, generalized emotional interference effects were found in PD and hypochondriasis, involving ventral and widespread dorsal brain regions, reflecting not only unconscious emotional stimulus processing but also increased cognitive elaboration.

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DIFFICULTY INHIBITING IRrelevant information, for instance obsessive thoughts and impulses, is a key feature of obsessive-compulsive disorder (OCD).[1,2] Because most of their attentional resources are allocated to threat cues related to their concerns, patients with OCD are limited in their ability to selectively attend to relevant information while simultaneously ignoring irrelevant competing information.[1] Similar cognitive dysfunctions have been described for panic disorder (PD).[3] Attentional bias in anxiety disorders is presumably not simply a by-product of emotional state but may play a major role in symptom causation and maintenance.[4-6] The critical process of gating (ie, inhibiting irrelevant information) has been linked to frontal-striatal function.[7,8] Impaired frontal-striatal function is considered to be of etiological importance in the affective, behavioral, and cognitive characteristics of OCD.[9] In contrast, the brainstem and limbic regions, such as the amygdala and (para)hippocampal region, are mainly implicated in the symptoms of PD.[10-13]

Cognitive interference occurs when processing one stimulus impedes simul-

taneous processing of another stimulus, as in the Stroop color-word task.[14] This task requires the ability to actively inhibit a fast automatic response (word reading) in favor of a slower voluntary response (color naming), resulting in increased response latencies and error rates during the interference condition (eg, "red" printed in blue ink) compared with the facilitation (or baseline) condition (eg, "red" printed in red [or black] ink).

Frontal involvement in interference processes was first demonstrated in lesion studies, showing impaired Stroop performance in patients with lesions in the left[15] and right[16] lateral prefrontal cortex. More extensive investigation of the neural correlates of interference in healthy subjects was undertaken with the advent of positron emission tomography,[17-21] functional magnetic resonance imaging (fMRI),[22-31] and magnetoencephalography.[32] In many,* but not all,[18,21,26,29,32] studies, interference was associated with increased activation of the anterior cingulate cortex (ACC). Prefrontal involvement in interference was reported in dorsolateral (DLPFC),[19,22,23,26-29,31,32] anterior (aPFC),[18,20,29,32] and ventrolateral (VLPFC)[21,25,26,28,29] prefrontal cortex subregions. Recent imaging studies have shown that ACC is primarily involved in response-related processes, such as performance monitoring, response conflict, and error detection.[24,27,28,31,33,34] In contrast, various prefrontal regions seem to be primarily responsible for the implementation of top-down attentional control (ie, higher order regulation of hierarchically lower attentional processes) per se, although the relative contribution of specific prefrontal subregions is insufficiently clear.[24,27,28,31] Other regions associated with interference were (pre)motor,[17,22,25,32] temporal,[17,22,23,25,29,31] parietal,[18-20,22,23,28,29,32] extrastriate[17,19-21,23,26,31] and insular[19,20,25] cortices, thalamus,[19,20,23] and striatum.[17,19,23,25]

In patients with OCD, neuropsychological studies using the Stroop color-word task have provided mixed evidence for impaired selective attention compared with control subjects.[1,35-40] Some studies showed that patients with OCD performed slower than control subjects[1,35] and made significantly more errors and had slower reaction times during the interference condition of the Stroop task.[1,37] This interference effect in patients with OCD was augmented when situational anxiety was high.[1] Moreover, decreased Stroop performance in patients with OCD was found to be correlated with decreased resting state regional cerebral metabolism rates in lateral prefrontal cortex,[35] in agreement with the notion of prefrontal involvement in the development of OCD.

A potentially more powerful and specific way to investigate selective attention and response inhibition in anxiety disorders is based on an emotional analog of the Stroop task.[5] When patients with anxiety are presented with colored words relevant to their concerns, automatic semantic processing will delay voluntary color naming. This interference effect, however, is not restricted to patients; control subjects, after priming to an anxious state, also show interference during color naming of threat words.[41,42] Whalen et al,[43] using a counting version of the emotional Stroop task during fMRI in healthy subjects, reported significant activation in the affective (rostral) subdivision of the ACC during emotional interference in the absence of a behavioral interference effect. In contrast, the traditional Stroop task was correlated with increased activation of the dorsal ACC (cognitive subdivision of the cingulate cortex).[22] The authors suggested that rostral ACC activation reflected a regulatory response during successful suppression of task-irrelevant emotional information.

Neuropsychological studies using the emotional Stroop task in various anxiety disorders, such as generalized anxiety disorder,[44-46] PD,[47-53] OCD,[53-56] posttraumatic stress disorder (PTSD),[57-59] social phobia,[46,60-64] and spider phobia,[65,66] all (but 1[53]) showed robust interference effects in patients during color naming threat-related words. It is not yet clear, however, whether this effect is specific to disease-related threat words or extends to general threat domains (or even positive emotional material), although some anxiety disorders seem to be more specific in their attentional bias than others. Whereas patients with OCD[54-56,67] and social phobia[46,63,64] showed a predominantly disease-specific attentional bias, threat word interference in generalized anxiety disorder[46] and PD[49] was found to be more generalized.[51,52] A second issue of consideration in emotional interference is the explicit vs implicit nature of the attentional bias. Most studies using subliminal stimulus presentation support the assumption that interference is not dependent on conscious strategies.[5,52,68,69]

To summarize, evidence from imaging data in healthy subjects as well as from neuropsychological studies in subjects with an anxiety disorder appear to be in agreement with the hypothesis of frontal involvement in emotional Stroop interference. However, direct evidence for the underlying neuronal substrate in anxiety disorders is lacking, with a single exception.[70] Shin et al[70] found activation of the rostral ACC in Vietnam veterans without PTSD during trauma-related emotional interference, similar to the results of Whalen et al[43] in healthy volunteers, but not in veterans with PTSD. Shin et al suggested that the absence of rostral ACC activation in patients with PTSD reflected the inability of this region to inhibit amygdalar hyperresponsivity, although no amygdala activation was found during threat-related emotional processing in their patients with PTSD. They did not include additional experimental groups, so the specificity of their findings remains to be confirmed.

The aim of the present study was to investigate the neural substrate of both cognitive and emotional Stroop interference across anxiety disorders by addressing the following questions. First, is increased cognitive interference, as found in OCD, syndrome specific? Second, do patients with an anxiety disorder show an attentional bias only for stimuli relevant to their concerns? Third, is the neuronal substrate of emotional interference different across anxiety disorders? To answer these questions, fMRI data of patients with OCD, PD, and hypochondriasis were compared with data of healthy control subjects during performance of a Stroop task containing color-congruent color words, color-incongruent color words, OCD-related negative words, panic-related negative words, and neutral words. Although emotional Stroop interference at a behavioral level can be demonstrated using either supraliminal or sublimi-

*References 17-20, 22, 24, 25, 27, 28, 30, 31.

nal stimuli, we chose to present overt (supraliminal) stimuli based on observations that covert stimuli are not very effective in eliciting regional cerebral blood flow changes in the amygdalar region,[71,72] unless in an aversive conditioning paradigm.[73] In agreement with the results of previous studies, we hypothesized that patients with OCD would show increased interference effects for incongruent vs congruent color words. In addition, we expected significant interference effects in OCD for disease-specific threat words only compared with generalized interference effects (ie, for PD-related and OCD-related words) in PD. To investigate whether any increased responsiveness to PD-related and OCD-related words was specific to OCD and/or PD, we included a third experimental group of patients with hypochondriasis. In hypochondriasis, obsessions or compulsions are by definition restricted to illness concerns. However, compared with PD, in patients with hypochondriasis these worries typically do not spiral into panic.[74] We expected to find frontal-striatal as well as limbic (including amygdala) regions correlated with emotional interference in all patient groups compared with healthy controls.

METHODS

SUBJECTS

Eighteen patients with OCD (6 men and 12 women; mean ± SE age, 33.4 ± 2.4 years), 15 patients with PD (8 men and 7 women; mean ± SE age, 33.7 ± 2.5 years), 14 patients with hypochondriasis (12 men and 2 women; mean ± SE age, 40.6 ± 3.2 years), and 19 healthy control subjects (10 men and 9 women; mean ± SE age, 30.3 ± 1.9 years) performed the Stroop task while fMRI data were collected. Mean age ($P = .04$) and male-female ratio ($P = .04$) were both higher in the hypochondriasis group compared with other groups. All subjects were right-handed. Patients were recruited from the outpatient clinic for anxiety disorders of GGZ Buitenamstel/VU University Medical Center, Amsterdam, the Netherlands, and the Netherlands Anxiety, OCD, and Phobia Foundation, Driebergen. The medical ethical review board of the VU University Medical Center approved the study, and all participants provided written informed consent.

Exclusion criteria were the presence of major internal and/or neurological illness, other psychiatric disorders, and the use of psychotropic medication. Subjects had to have stopped taking medication for at least 4 weeks. One patient with OCD had comorbid hypochondriasis, 1 patient with hypochondriasis had comorbid PD, and 1 patient with OCD was found to have a vascular malformation near the ACC. These 3 patients were excluded from further analysis.

Diagnoses were established using the Structured Clinical Interview for *DSM-IV* Axis I Disorders.[75] To assess symptom characteristics and severity scores, the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS),[76] the Padua Inventory-revised,[77,78] the Y-BOCS for Hypochondriasis,[76] and the Whitley Index[79] were used. In addition, the Body Sensations Questionnaire[80] was administered to patients with PD.

TASK PARADIGM

The Stroop paradigm used in the present study consisted of 6 conditions: congruent color words (eg, "red" printed in red), incongruent color words (eg, "red" printed in blue), OCD-related negative words (eg, dirty, mess, uncertain), panic-related negative words (eg, heart attack, crowd, faint), and 2 baseline conditions with neutral words (eg, percent, month, oval). The OCD-related words were selected based on studies of Lavy et al[55,66]; panic-related words were derived from earlier research of attentional bias in PD.[48]

Stimuli were presented in a block design, consisting of 18 randomized blocks (3 blocks of each condition), each containing 16 words. Each word was presented during 2 seconds, followed by a 200-millisecond blank screen. Subjects were asked to respond as fast as possible by pressing the button corresponding to the color of the ink (yellow, green, red, blue), regardless of the meaning of the word. After performing the task, subjects were asked to rate subjective distress using a 100-point analog scale.

fMRI DATA ACQUISITION

Imaging was performed on a 1.5-T Sonata magnetic resonance system (Siemens, Erlangen, Germany) with a standard circularly polarized head coil. Stimuli were projected on a screen at the end of the scanner table, which was seen through a mirror mounted above the subject's head. Two magnet-compatible 4-key response boxes were used to record the subject's performance and response times (RTs). To reduce motion artifacts, the subject's head was immobilized using foam pads.

For fMRI, an axial echo planar sequence (repetition time = 1.99 seconds, echo time = 45 milliseconds, matrix = 64 × 64, field of view = 192 × 192 mm, flip angle = 90°) was used (28 sections, 3 × 3-mm in-plane resolution, 3.6-mm between-plane resolution), which was selected based on its sensitivity to signal changes in the (orbital) prefrontal cortex. In total, 296 echoplanar imaging volumes per subject were scanned, 48 echoplanar imaging volumes in each condition. In addition, a coronal T1-weighted magnetic resonance image was acquired (matrix = 256 × 160, voxel size = 1 × 1 × 1.5 mm, 160 sections).

IMAGING DATA ANALYSIS

Imaging data were analyzed using SPM99 (Wellcome Department of Cognitive Neurology, London, England). After discarding the first 6 volumes, time series were corrected for differences in section acquisition times and realigned. Spatial normalization into approximate Talairach and Tournoux space was performed using a standard SPM echoplanar imaging template. Data were resectioned to 2 × 2 × 2-mm voxels and spatially smoothed using a 6-mm gaussian kernel. Subsequently, data were bandpass filtered and analyzed in the context of the general linear model, using boxcar regressors convolved with the canonical hemodynamic response to model responses during each condition.

For each subject, weighted contrasts were computed for cognitive color-word interference (incongruent vs congruent color words), for OCD-related emotional interference (OCD-related negative words vs neutral words), and for panic-related emotional interference (panic-related negative words vs neutral words). These contrast images containing parameter estimates for main effects were entered into a second-level (random effects) analysis, using 1-way analyses of variance (ANOVAs) for each contrast. Main effects and group × task interaction effects are reported at a $P < .05$ significance level corrected for multiple comparisons using the False Discovery Rate method.[81]

RESULTS

CLINICAL CHARACTERISTICS

Patients with OCD had significantly higher scores on the Y-BOCS (mean ± SE, 23.4 ± 1.7) and Padua Inventory–revised (mean ± SE, 63.2 ± 5.6) than subjects from the other

Table 1. Response Times Averaged Within Each Condition for Each Subject*

	Controls	Subjects With PD	Subjects With OCD	Subjects With Hypochondriasis
Congruent color words	831 ± 31	891 ± 33	834 ± 32	873 ± 34
Incongruent color words	985 ± 25	1027 ± 28	1062 ± 45	1073 ± 34
OCD-related words	874 ± 25	949 ± 27	943 ± 43	953 ± 36
Panic-related words	898 ± 20	1057 ± 29	986 ± 46	1022 ± 34
Neutral 1	870 ± 25	967 ± 27	934 ± 39	984 ± 39
Neutral 2	867 ± 28	902 ± 26	940 ± 41	912 ± 33

Abbreviations: OCD, obsessive-compulsive disorder; PD, panic disorder.
*Values are expressed as mean ± SE in milliseconds.

Table 2. Performance Scores Expressed as Percentage of the Total Number of Responses Within Each Condition for Each Patient*

	Controls	Patients With PD	Patients With OCD	Patients With Hypochondriasis
Congruent color words	83 ± 4.6	87 ± 2.5	85 ± 5.4	79 ± 7.5
Incongruent color words	84 ± 4.5	82 ± 5.2	74 ± 7.4	75 ± 7.3
OCD-related words	86 ± 4.9	93 ± 2.5	89 ± 5.3	86 ± 8.2
Panic-related words	87 ± 4.9	90 ± 3.2	87 ± 6.2	82 ± 8.0
Neutral 1	84 ± 4.6	88 ± 3.2	85 ± 5.2	80 ± 7.9
Neutral 2	87 ± 4.9	90 ± 3.8	88 ± 6.4	83 ± 7.9

Abbreviations: OCD, obsessive-compulsive disorder; PD, panic disorder.
*Values are expressed as mean ± SE in percentages.

groups (ANOVA, $F_{3,53}=144$; $P<.001$ and $F_{3,52}=22$; $P<.001$, respectively). Patients with hypochondriasis scored significantly higher on the Y-BOCS for Hypochondriasis (mean±SE, 25.9±3.6) and the Whitley Index (mean±SE, 24.4±2.4) than subjects from the other groups (ANOVA, $F_{3,55}=60$; $P<.001$ and $F_{3,55}=34$; $P<.001$, respectively). Mean±SE Body Sensations Questionnaire scores in patients with PD were 38.1±3.3, in agreement with previous findings.[82]

TASK PERFORMANCE

Behavioral data for 1 patient with hypochondriasis were lost because of technical problems. Mean RTs and performance rates for each group are listed in **Table 1** and **Table 2**. Across groups, RTs showed a significant increase for incongruent vs congruent color words (ANOVA, $F_{1,61}=129.8$; $P<.001$) and panic words vs neutral words (ANOVA, $F_{1,61}=34.7$; $P<.001$) but not for OCD words vs neutral words (ANOVA, $F_{1,61}=0.7$; $P=.40$). Between-group comparisons revealed that the increase for panic words vs neutral words was greater in patients with PD and hypochondriasis compared with both patients with OCD (ANOVA, $F_{1,30}=6.5$; $P=.02$ and $F_{1,27}=4.8$; $P=.04$, respectively) and controls (ANOVA, $F_{1,33}=9.1$; $P=.007$ and $F_{1,30}=10.4$; $P=.003$, respectively). The RTs for color naming neutral words were also longer in patients with PD (ANOVA, $F_{1,33}=6.9$; $P=.02$) and hypochondriasis (ANOVA, $F_{1,30}=6.7$; $P=.02$) compared with controls. The increase in RTs for incongruent vs congruent color words in subjects with OCD was greater than in patients with PD (ANOVA, $F_{1,30}=4.2$; $P=.049$) and marginally greater than in control subjects (ANOVA, $F_{1,34}=3.4$; $P=.08$). Correlation analyses showed significant associations between subjective distress scores and increased RTs for color naming panic-related words in patients with PD (Pearson $r=0.56$; $P=.047$) and for color naming OCD words in patients with OCD ($r=0.63$; $P=.01$).

Analysis of performance scores across all groups (Table 2) showed a significant increase in error rates during incongruent vs congruent color naming (ANOVA, $F_{1,61}=5.6$; $P=.02$) but not during color naming panic words vs neutral words (ANOVA, $F_{1,61}=0.3$; $P=.57$). The increase in error rates was greater in subjects with OCD compared with controls (ANOVA, $F_{1,34}=4.1$; $P=.05$), whereas compared with controls, performance was unimpaired in patients with PD and hypochondriasis. Paradoxically, error rates decreased across groups during color naming OCD words vs neutral words (ANOVA, $F_{1,61}=36.1$; $P<.001$). Paired comparisons showed that this decrease was greater in patients with hypochondriasis (ANOVA, $F_{1,30}=5.8$; $P=.02$) and marginally greater in patients with PD (ANOVA, $F_{1,33}=2.9$; $P=.10$) compared with controls. Correlation analyses showed a significant negative association between subjective distress scores and performance during color naming panic words in the hypochondriasis group ($r=-0.72$; $P=.008$).

IMAGING DATA

Incongruent vs Congruent Color Words

Across all groups, regions showing increased blood oxygenation level dependent (BOLD) signal during color

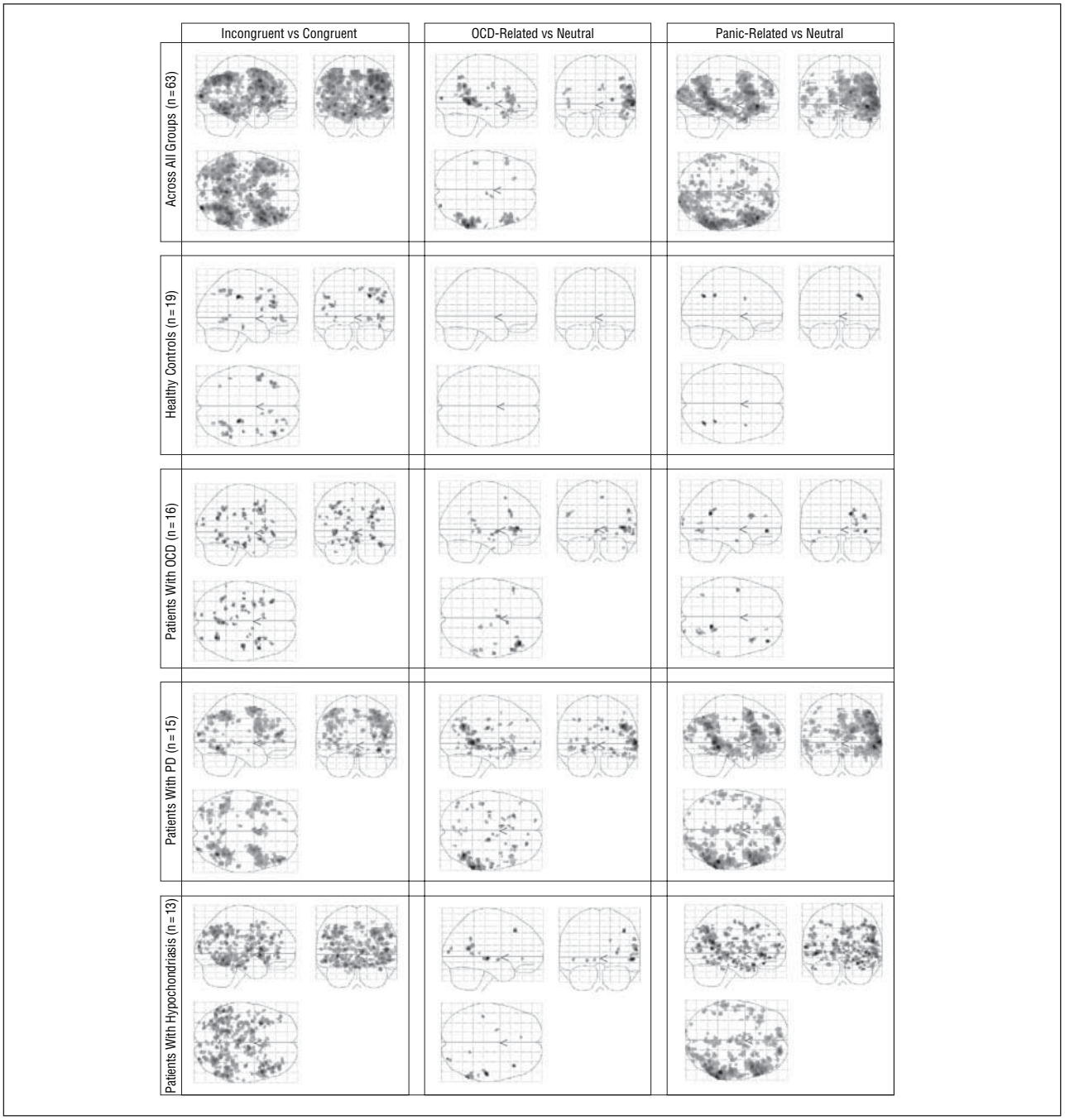

Figure 1. "Glass brain" renderings showing main effects for the contrasts of interest (incongruent vs congruent color words, obsessive-compulsive disorder [OCD]–related vs neutral words, and panic-related vs neutral words). PD indicates panic disorder.

naming incongruent vs congruent color words (**Figure 1**) were present in right aPFC; bilateral DLPFC; VLPFC; dorsal ACC; motor, premotor, supplementary motor, insular, inferior parietal, superior and middle temporal, temporal-occipital and peristriate cortices; striatum; thalamus; hypothalamus; rostral brainstem and cerebellar cortex; and in left fusiform gyrus. Group × task interaction effects are shown in **Table 3**. Compared with control subjects, increased activation was found in patients with OCD in right precuneus, left parahippocampal gyrus, and left brainstem; in patients with PD in right fusiform gyrus; and in patients with hypochondriasis in bilateral inferior parietal cortex and precuneus, left insular cortex, and left rostral brainstem. No regions of significantly increased activation were found in control subjects compared with patients.

OCD-Related vs Neutral Words

Color naming OCD-related words compared with neutral words, across all groups (Figure 1), was correlated with increased BOLD signal in bilateral VLPFC, left orbitofrontal cortex (OFC), right middle temporal cortex, bilateral superior temporal cortex, right parietal-

Table 3. Brain Regions Showing Significant BOLD Signal Increase Correlating With Cognitive Interference, Group × Task Interactions*

	Healthy Controls>			Patients With OCD>			Patients With PD>			Subjects With Hypochondriasis>		
	Brain Regions	BA	*z* Value	Brain Regions	BA	*z* Value	Brain Regions	BA	*z* Value	Brain Regions	BA	*z* Value
Healthy controls				R precuneus	7	3.46	R fusiform gyrus	19	4.91	R/L inferior parietal cortex	39, 40	R 4.04, L 4.61
				L parahippocampal gyrus	36	3.45				R/L precuneus	7, 31	R 4.47, L 4.08
				L rostral brainstem		3.35				L rostral brainstem		4.57
Subjects with OCD	No significant regions						R fusiform gyrus	19	4.96	No significant regions		
Subjects with PD	No significant regions			No significant regions						No significant regions		
Subjects with hypochondriasis	No significant regions			No significant regions			No significant regions					

Abbreviations: BA, Brodmann area; BOLD, blood oxygenation level dependent; L, left; OCD, obsessive-compulsive disorder; PD, panic disorder; R, right.
*Significant at $P<.05$ corrected. Cognitive interference using incongruent vs congruent color words. Group × task interaction where column is greater than row.

occipital cortex, and right precuneus. Group × task interactions are presented in **Table 4**. Compared with control subjects, all patients showed widespread increased involvement of frontal-striatal regions. Whereas patients with OCD, compared with control subjects, showed significantly increased activation of bilateral amygdala and left hypothalamus during color naming OCD-related words, patients with PD and hypochondriasis did not (**Figure 2**). In patients with OCD, increased activation of the right amygdala was found compared with patients with PD, and of right VLPFC and temporal and supplementary motor cortex compared with patients with hypochondriasis.

Panic-Related vs Neutral Words

Across all groups, color naming panic-related words compared with neutral words (Figure 1) was correlated with increased BOLD signal in bilateral frontal-striatal regions, temporal-parietal cortices, fusiform gyrus and thalamus, right hippocampus, right amygdala, and left rostral brainstem. Group × task interactions are presented in **Table 5**. Compared with control subjects, patients with PD showed increased activation bilaterally in the aPFC, ACC, and inferior parietal cortex and right-sided in the DLPFC, VLPFC, OFC, thalamus, middle temporal cortex, amygdala (**Figure 3**A), and hippocampus (Figure 3B). Similar regions were identified when comparing PD with OCD; in addition, subjects with OCD vs control subjects did not yield significant interaction effects. In contrast, patients with hypochondriasis showed a similar activation pattern to patients with PD, although no activation was found in the amygdala and ACC.

EFFECT OF DISEASE SEVERITY

No specific brain regions were found when correlations were investigated between OCD interference–related BOLD responses and symptom severity in OCD as measured by the Y-BOCS and Padua Inventory–revised. Similarly, no correlation was found between panic interference–related activation patterns in patients with PD and Body Sensations Questionnaire scores. State anxiety was correlated with increased activation of right VLPFC ($z=4.67$) and left extrastriate cortex ($z=4.78$) in subjects with OCD during presentation of OCD-related vs neutral words. No such state anxiety effects were found in patients with PD or hypochondriasis.

COMMENT

In the present study, a cognitive and emotional Stroop task was used to investigate the neuroanatomical correlates of attentional bias across different anxiety disorders. The present results support the hypothesis of increased distractibility for irrelevant information in patients with OCD, PD, and hypochondriasis compared with healthy control subjects, associated with frontal-striatal and limbic involvement. Moreover, we found clear differences between patients with OCD on the one hand and patients with PD and hypochondriasis on the other. In particular, patients with OCD displayed increased cognitive interference compared with healthy control subjects, which was accompanied by activation of posterior brain regions. Although patients with OCD did not display an attentional bias in behavior during color naming OCD-related words relative to control subjects, there was a clear and specific neural response in mainly ventral and limbic brain regions. In contrast, patients with PD and hypochondriasis displayed no interference for incongruent vs congruent words but showed an attentional bias for both panic-related and OCD-related information, involving both ventral and dorsal brain regions.

In agreement with previous studies using the traditional Stroop color-word task, the present results showed the recruitment of prefrontal-striatal regions during cognitive interference. Prefrontal involvement implies the activation of various hierarchic subregions known to subserve different executive subprocesses necessary to perform the task.[83] While activation of VLPFC may reflect lexical processing (word generation)[84] and working

Table 4. Brain Regions Showing Significant BOLD Signal Increase Correlating With OCD-Related Emotional Interference, Group × Task Interactions*

	Healthy Controls>			Patients With OCD>			Patients With PD>			Subjects With Hypochondriasis>		
	Brain Regions	BA	*z* Value	Brain Regions	BA	*z* Value	Brain Regions	BA	*z* Value	Brain Regions	BA	*z* Value
Healthy controls				R VLPFC	45	3.86	L anterior PFC	10	4.18	R DLPFC	8	3.91
				L motor cortex	4	4.29	R medial PFC	8	3.67	R posterior ACC	31	3.78
				R SMA	6	4.01	R/L DLPFC	8, 9	R 3.91, L 3.98	L rostral ACC	24	3.91
				R/L dorsal ACC	24	R 3.68, L 4.09	L OFC	47	5.03	L pallidum		3.77
				L putamen		3.74	L (pre)motor cortex	4, 6	4.93	R/L superior temporal cortex	22	R 3.56, L 3.63
				R/L amygdala		R 3.63, L 3.80	L dorsal ACC/posterior cingulate	24, 31	3.94	R/L middle temporal cortex	21	R 4.20, L 3.58
				L hypothalamus		3.80	R/L putamen		R 4.19, L 3.75			
				R/L superior temporal cortex	22	R 4.21, L 3.90	R superior temporal cortex	22	4.10			
							R middle temporal cortex	21	4.12			
							R/L parietal-occipital cortex	39, 19	R 4.28, L 3.83			
							R/L cuneus	18, 19	R 4.67,L 4.11			
Subjects with OCD	No significant regions						No significant regions			No significant regions		
Subjects with PD	No significant regions			R amygdala		3.79				No significant regions		
Subjects with hypochondriasis	No significant regions			R VLPFC	45	4.39	L putamen		3.82			
				R middle temporal cortex	21	3.86	R middle temporal cortex	21	4.08			
				R SMA	6	3.84	L parietal-occipital cortex	19, 39	4.22			

Abbreviations: ACC, anterior cingulate cortex; BA, Brodmann area; BOLD, blood oxygenation level dependent; DLPFC, dorsolateral prefrontal cortex; L, left; OCD, obsessive-compulsive disorder; OFC, orbitofrontal cortex; PD, panic disorder; PFC, prefrontal cortex; R, right; SMA, supplementary motor area; VLPFC, ventrolateral prefrontal cortex.

*Significant at $P<.05$ corrected. Obsessive-compulsive disorder emotional interference using OCD-related vs neutral words. Group × task interaction where column is greater than row.

memory (maintenance of information),[85] activation of DLPFC and aPFC is associated with manipulation processes and complex executive control, respectively.[85] In addition to these prefrontal top-down control processes, ACC is presumably involved in performance monitoring, response conflict, and error detection.[24,27,28,31,33,34] Patients with PD and hypochondriasis performed similarly during incongruent vs congruent color naming compared with control subjects, but performance in patients with OCD was impaired. This finding is in agreement with Hartston and Swerdlow,[37] who reported increased color-word interference in patients with OCD compared with control subjects, but not with Moritz et al.[38] Increased regional brain activity associated with cognitive interference in patients compared with controls was observed in posterior regions only. This may reflect increased effort (ie, enhanced visual processing [fusiform and parahippocampal gyrus], heightened arousal [insular cortex and brainstem], and attention [precuneus and parietal cortex]). Compensation by recruitment of posterior regions has been found in patients with OCD before.[86] Moreover, altered frontal-striatal functioning in OCD is not restricted to attentional bias but has recently also been demonstrated during executive tasks.[87]

Interestingly, our behavioral data showed improved performance for color naming OCD-related words compared with neutral words. This effect was found in all groups but particularly in patients with PD and hypochondriasis. It is inconsistent with the results of most, but not all,[53] previous studies reporting increased RTs and error rates due to emotional interference.[5] Possibly, the use of supraliminal stimuli in a block design may have enabled subjects to devise strategies to facilitate task performance. Alternatively, patients with an anxiety disorder may engage in more extensive processing of threat stimuli compared with healthy controls.[88]

Across all groups, color naming OCD-related vs neutral words was correlated with activation of VLPFC, OFC, and posterior (temporal and parieto-occipital) regions. As expected, all 3 patient groups showed increased involvement of these regions. Although this increased prefrontal-striatal recruitment during OCD-related emotional interference was not restricted to patients with OCD but also present in patients with PD and hypochondriasis, important differences were also found between the patient groups. First, in patients with OCD, VLPFC was activated whereas patients with PD and hypochondriasis mainly showed DLPFC, aPFC, and medial prefrontal activation. Second, in patients with OCD, bilateral amygdala activation was found during color naming OCD-related words while no amygdala involvement was found in the other patient groups, as shown in Figure 2. The role of the amygdala in the evaluation of the behavioral significance of external stimuli and affective responses[89,90] has been addressed in a number of studies using fear paradigms in healthy controls.[73,91-95] Most previous imaging studies in OCD have observed amygdala involvement only in small samples and/or at lower statistical thresholds[96,97] or not at all,[98-101] which may have been owing to various methodological issues.[102] Strong reciprocal connections exist between the amygdala and widespread regions of frontal, insular, temporal, and occipital cortices.[103] Although at present our understanding of the neuronal circuits underlying human emotion perception is limited, 2 interacting systems have been hypothesized to subserve the different subprocesses of emotional appraisal and behavior.[90] First, a ventral system, including the amygdala, insula, ventral striatum, and ventral prefrontal regions (rostral ACC, VLPFC, OFC), is mainly important for the identification of the emotional significance of a stimulus and the generation of an autonomic, unconscious emotional response. Second, a dorsal system, consisting of the parahippocampal gyrus and dorsal regions of the frontal cortex (dorsal ACC, aPFC, DLPFC, and medial PFC), is engaged in additional regulation of the initial emotional response by combining cognitive and emotional input. The present results in patients with OCD are likely to reflect automatic processing of disease-specific emotional cues by the ventral system. Additional cognitive regulation seems to be reflected in the role of dorsal ACC. Involvement of dorsal ACC is consistent with the results of Shin et al.[70] They found dorsal ACC activation during emotional interference in their Vietnam veterans with PTSD while rostral ACC activity was found in the non-PTSD group. Although patients with OCD were capable of normal task performance, our behavioral data also showed that RTs as well as disease-specific neuronal responses in subjects with OCD were correlated with subjective distress ratings. This suggests that cognitive function in OCD is vulnerable to high levels of state anxiety.

In contrast to OCD-related words, color naming of panic-related words was not associated with differences in error rate, either across groups or between groups. However, RTs were significantly longer in patients with PD and hypochondriasis compared with patients with OCD and healthy controls. Our imaging data parallel these behavioral results. Compared with control subjects and patients with OCD, patients with PD showed increased activation of prefrontal areas (mainly right sided), right rostral ACC, amygdala, hippocampus, rostral brainstem, and thalamus. When comparing patients with hypochondriasis with patients with OCD and controls, a similar pattern was observed but without the involvement of the amygdala and rostral brainstem as was found in PD. However, contrasting subjects with PD and hypochondriasis did not yield significant interaction effects. Structural[104,105] as well as functional (resting state[106,107] and challenge[108]) neuroimaging studies in PD have repeatedly demonstrated the role of the amygdala and hippocampal region in the symptoms of PD. In addition, pharmacological challenge studies in PD have indicated a brainstem origin of panic attacks.[10] So far, only 2 fMRI studies were performed in PD. In these studies, patients with PD showed increased activation of prefrontal, anterior cingulate, and (para)hippocampal cortices in response to threat-related words[88] or imagery exposure.[109]

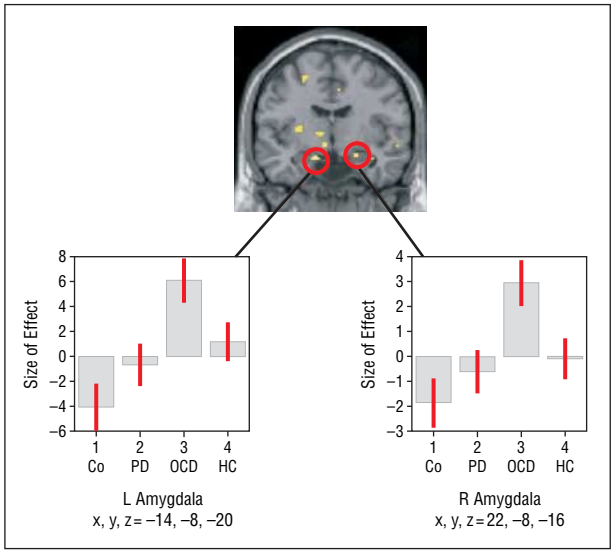

Figure 2. Increased blood oxygenation level dependent signal in left (L) and right (R) amygdala during obsessive-compulsive disorder (OCD)–related emotional interference in patients with OCD compared with control subjects (Co) and plot of size of effect in this region in group × task interaction. HC indicates hypochondriasis; PD, panic disorder.

The widespread dorsal prefrontal involvement in PD and, to a lesser extent, hypochondriasis again suggests (cognitive) modulation of emotional responses. However, in contrast to subjects with OCD during color naming OCD-related words, this seems to intervene with task demands. Whether this is due to stimulus characteristics (eg, greater salience of panic words relative to OCD words) or reflects differences in the processing of emotional material between OCD and PD and/or hypochondriasis is not yet clear. A post hoc comparison between neuronal activation patterns during color naming disease-specific words in OCD and PD showed increased recruitment of the dorsal system in patients with PD compared with patients with OCD (data not shown). This might reflect increased cognitive modulation elicited by the initial emotional response in PD and intervening with performance.

Concerning the issue of disease specificity, our data indicate a clear distinction between OCD on the one hand and PD and hypochondriasis on the other hand but not between PD and hypochondriasis. First, during incongru-

Table 5. Brain Regions Showing Significant BOLD Signal Increase Correlating With Panic-Related Emotional Interference, Group × Task Interactions*

	Healthy Controls>			Patients With OCD>			Patients With PD>			Subjects With Hypochondriasis>		
	Brain Regions	BA	*Z* Value	Brain Regions	BA	*Z* Value	Brain Regions	BA	*Z* Value	Brain Regions	BA	*Z* Value
Healthy controls				No significant regions			R/L anterior PFC/R medial PFC	10	R 4.21, L 4.19	R medial PFC	10	3.38
							L medial PFC	8	4.01	R DLPFC	8	3.67
							R DLPFC	9, 46	3.64	L VLPFC	47	3.64
							R VLPFC	45, 47	3.73	R OFC	11	3.94
							R OFC	11	3.97	L SMA	6	4.38
							L SMA	6	3.96	L caudate nucleus		3.62
							R dorsal ACC	24	3.70	L thalamus		3.84
							L rostral ACC	24	3.52	L middle temporal cortex	21	4.05
							R thalamus		3.91	L superior temporal cortex	22	3.96
							R middle temporal cortex	21, 37	4.65	R hippocampus		3.89
							R amygdala		3.23			
							R hippocampus		3.57			
							R/L inferior parietal cortex	39	R 4.28, L 3.70			
Subjects with OCD	No significant regions						L anterior PFC	10	4.46	R medial PFC		4.11
							R/L DLPFC	9, 46	R 3.99, L 3.67	R/L DLPFC	9	R 3.71, L 3.93
							R VLPFC	44, 45	4.49	L VLPFC	47	4.50
							R OFC	11, 47	4.76	R/L (pre)motor cortex	4, 6	R 4.41, L 4.46
							L medial PFC	8	4.30	L rostral ACC	32	3.82
							R/L (pre)motor cortex	6	R 4.62, L 4.81	L posterior cingulate cortex	31	4.29
							R rostral ACC	24	3.57	R/L thalamus		R 4.37, L 4.17
							R/L thalamus		R 3.62, 3.71	L hypothalamus		4.09
							R rostral brainstem		4.16	R/L middle temporal cortex	21	R 4.17, L 3.77
							R/L middle temporal cortex	21, 37	R 5.39, L 4.31	L superior temporal cortex	22	3.76
							R hippocampus		3.24	R hippocampus		3.73
							R amygdala		3.21	R parahippocampal gyrus		4.20
							R/L parietal-occipital cortex	19, 39	R 5.09, L 4.42	L parietal-occipital cortex	39	3.92
							L precuneus	7	4.03	R/L cuneus	19	R 3.96, L 4.41
										R/L cerebellum		R 4.38, L 3.61
Subjects with PD	No significant regions			No significant regions						No significant regions		
Subjects with hypochondriasis	No significant regions			No significant regions			No significant regions					

Abbreviations: ACC, anterior cingulate cortex; BA, Brodmann area; BOLD, blood oxygenation level dependent; DLPFC, dorsolateral prefrontal cortex; L, left; OCD, obsessive-compulsive disorder; OFC, orbitofrontal cortex; PD, panic disorder; SMA, supplementary motor area; PFC, prefrontal cortex; R, right; VLPFC, ventrolateral prefrontal cortex.

*Significant at $P<.05$ corrected. Panic-related emotional interference using panic-related vs neutral words. Group × task interaction where column is greater than row.

ent vs congruent color naming, all patient groups recruited additional posterior brain areas relative to controls, but only in OCD was performance significantly impaired. Second, in OCD we observed increased recruitment of the ACC and limbic regions only during color naming of OCD-related vs neutral words whereas in patients with PD and hypochondriasis, widespread activity in prefrontal, striatal, and temporal regions was found during color naming of both OCD-related and panic-related words. This is consistent with the hypothesis of a more generalized attentional bias to threat cues in PD. However, both in OCD and PD, amygdala activation was found to be disease specific. Moreover, in OCD, state anxiety was correlated with longer RTs only during the disease-specific in-

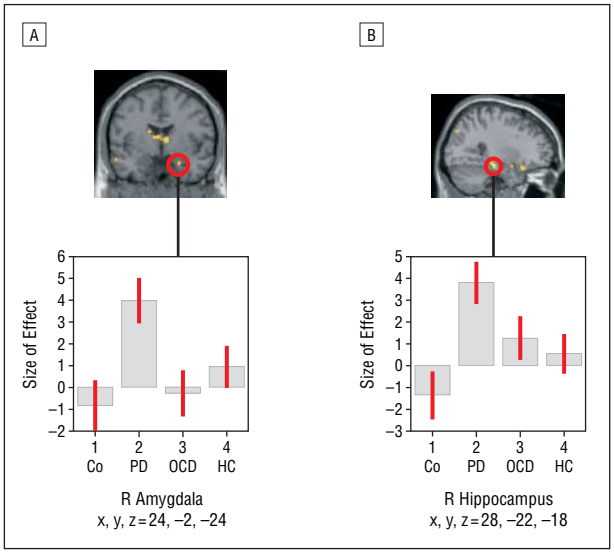

Figure 3. Increased blood oxygenation level dependent signal during panic-related emotional interference in patients with panic disorder (PD) compared with control subjects (Co) in right (R) amygdala (A) and R hippocampus (B) and plot of size of effect in these regions in group × task interaction. HC indicates hypochondriasis; OCD, obsessive-compulsive disorder.

terference condition. Based on similarities between hypochondriasis and OCD, inclusion of hypochondriasis in the spectrum of obsessive-compulsive disorders has been suggested.[110,111] However, other distinctive features provide support for the association between hypochondriasis and PD.[74] While hypochondriasis and PD co-occur and overlap phenomenologically,[112] this overlap is by no means complete.[113] The results from the present study apparently support the association between PD and hypochondriasis. We did, however, not include an extra category of disease-specific words for hypochondriasis, unrelated to panic and OCD.

To our knowledge, this study is the first to elucidate the neuronal correlates of color-word interference and attentional bias in 3 distinct, but related, disorders (ie, OCD, PD, and hypochondriasis). Strengths of the study are the inclusion of medication-free subjects, a large sample size permitting random effects analysis, and the comparison across different patient groups. A limitation of the present study is that the patients with hypochondriasis were significantly older than the other participants, although a post hoc analysis of covariance with age as a nuisance variable showed that the interaction effects, described in the present article, persisted after regressing out age. Second, we did not specifically investigate diagnostic subgroups (eg, patients with OCD with prominent washing or checking symptoms, or patients with PD with agoraphobia or lactate sensitivity). A third issue that needs to be further investigated is the possible role of strategic differences in task performance by comparing overt (supraliminal presented) vs covert (subliminal presented) stimuli. For example, decreased involvement of dorsal brain regions in OCD compared with PD, as observed in the present study, may reflect predominantly unconscious emotional stimulus processing in OCD.[90] Alternatively, it can be argued that condition effects in OCD may have been obscured by ongoing top-down control processes regardless of stimulus type, reflecting the difference between tonic and phasic symptoms in OCD and PD. Finally, future research is warranted to explore whether the behavioral and neuropsychological abnormalities observed in the present study are trait or state dependent (for example, whether these resolve after successful treatment).

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