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ORIGINAL PAPER

Neurocircuitry of disgust and anxiety in obsessive-compulsive disorder: A positron emission tomography study

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Abstract *Background:* Disgust and fear are basic emotions that have different elicitors and expressions, and that appear to be mediated by different neurocircuits. Although obsessive-compulsive disorder (OCD) is classified as an anxiety disorder, disgust may be involved in its pathogenesis. Functional magnetic resonance imaging (fMRI) studies of disgust-inducing visual stimuli in OCD have suggested disorder specific alterations in brain activation during these tasks. *Methods:* Subjects with OCD and healthy controls (HC) underwent positron emission tomography (PET) brain scanning after injection of $H_2{}^{15}O$. During PET, subjects either watched slides designed to evoke feelings of disgust (OCD $= 5$, HC $= 11$), expected the delivery of an electrical shock (OCD $= 11$, HC $= 13$), or rested (OCD $= 11$, HC $= 14$). After the anticipatory anxiety and resting tasks, anxiety ratings, heart rate, and electrodermal measures were obtained. Statistical parametric mapping (SPM) was used to analyze regional cerebral blood flow (rCBF) data. *Results:* Comparison of OCD subjects with controls on differences in rCBF across the disgust-inducing and resting tasks showed that OCD was characterized by greater rCBF in the left insula. In OCD the disgust-inducing task increased right lateral orbitofrontal cortex rCBF compared to resting, whereas in controls there was no difference in rCBF between these tasks. Anxiety ratings, heart rate, and electrodermal activity increased during anticipatory anxiety in both groups, and comparison of rCBF in OCD subjects with controls in anticipatory anxiety versus resting state also found no significant differences. *Conclusions:* OCD may be characterized by a disruption in disgust processing, such that there is a decrease in appropriate disgust (such as that evoked by

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observing disgust in others) and an increase in inappropriate disgust (such as that evoked by contamination stimuli). The insula may play a particularly important role in mediating such putative disruptions. The sample studied here was small, and further work is required to determine whether disgust-induced activation patterns in OCD are more apparent in specific subtypes of this disorder, whether they are specific to OCD, and whether they are normalized by treatment.

Introduction

Fear and disgust are basic emotions that have clear relevance to the anxiety disorders in general, and to obsessive-compulsive disorder in particular (Phillips *et al*., 1998; McKay, 2002). Animal studies have demonstrated that the amygdala plays a key role in mediating fear and anxiety (Davis, 1997; Le Doux, 1998), and this structure and its associated neurocircuitry have been implicated in a range of functional imaging studies of the anxiety disorders (Gorman *et al*., 2000; Davis and Whalen, 2001). In contrast, disgust appears mediated primarily by insula and striatum (Phillips *et al*., 1998; Sprengelmeyer *et al*., 1998; Adolphs *et al*., 2003), structures that have been implicated in functional imaging studies of obsessive-compulsive disorder in particular (Rauch *et al*., 1998; Kim *et al*., 2001).

The possibility that disgust plays a role in the pathogenesis of OCD is supported by a number of other findings (Stein *et al*., 2001). First, there is a strong relationship between the emotion of disgust and obsessive-compulsive symptoms (Muris *et al*., 1999; Mancini *et al*., 2001; Olatunji *et al*., 2004; Thorpe *et al*., 2003; Tsao and McKay, 2004). Second, a seminal series of studies of disorders with striatal dysfunction found that in both Huntington's disorder and OCD, there was impaired recognition of disgust, but not of other basic emotions (Sprengelmeyer *et al*., 1996, 1997). Third, functional magnetic resonance (fMRI) research on OCD has found that while the pattern of brain activation during a threat-inducing task was similar in OCD and controls, during a disgust-inducing task there was greater activation of the right insula in OCD (Shapira *et al*., 2003).

In this study, we using positron emission tomography (PET) after injection of $H_2{}^{15}O$ to study regional cerebral blood flow (rCBF) in OCD subjects and healthy controls during a disgust-inducing task, an anticipatory anxiety task, and a control resting task. Previous fMRI work on disgust in OCD patients has focused on visual stimuli to induce disgust. The task used here was suited for the relatively longer scan acquisition time needed in PET. In line with the fMRI findings, we hypothesized that structures involved in the processing of disgust would be differentially activated in OCD compared to controls across the disgust-inducing and resting tasks, whereas the two groups would not differ across the anticipatory anxiety and resting tasks.

Methods

Subjects

11 adults with OCD and 14 healthy volunteers, matched for age, gender, and handedness, were studied (Table 1). OCD subjects were recruited from the community through media advertisements, physicians' referrals, and national OCD support groups, while healthy controls were recruited by media advertisements. The protocol was approved by the Institutional Review Board of the National Institutes of Health, and all subjects gave informed written

Table 1 Demographic and clinical details of participants

	OCD patients ($n = 11$)	Healthy controls ($n = 14$)	p
Age	33.09 (8.6)	33.21 (8.4)	NS
Gender (male/female)	M4/F7	M5/F9	NS
Spielberger trait anxiety	60.0 (12.9)	30.6 (12.0)	$p < 0.001$
Y-BOCS	25.7 (5.6)	—	
Ham-D	13.7 (2.4)	—	
NIMH Global	6.1 (1.5)	—	
NIMH OCD	8.3 (0.9)	—	
NIMH Depression	5.0 (1.3)	—	
NIMH Anxiety	4.5 (1.1)	—	

Note. Data are provided as means with standard deviations in parentheses. Y-BOCS: Yale-Brown Obsessive-Compulsive Scale. Ham-D: Hamilton Depression Rating Scale. NIMH: National Institutes of Mental Health. NS: non-significant.

consent after the purpose, procedure, and potential risks of the study had been presented and discussed.

OCD subjects met DSM-III-R criteria for OCD. OCD subjects were excluded if they had a comorbid mood or anxiety disorder on structured diagnostic interview (Spitzer *et al*., 1987), if they had a lifetime history of neurological disorder including Tourette's disorder, major general medical disorder, mental retardation, or psychotic disorder. Controls were excluded if they had current or past substance abuse or other axis I disorder on structured diagnostic interview, compulsive personality disorder, neurological disorder, or major general medical disorder.

OCD subjects were off all psychiatric medications for 4 weeks, and all subjects abstained from all other prescription and nonprescription drugs for at least 2 days (or 4 weeks if the medication was likely to have CNS side effects), and from alcohol, caffeine and smoking for 24 h prior to the scan. OCD subjects and controls had normal laboratory profiles (including CBC, blood chemistry, VDRL, thyroid function tests, prothrombin time, and partial thromboplastin time), and normal results of physical, audiological, visual, and neurological examination (including chest X ray and electrocardiogram).

Both OCD patients and healthy controls completed the Spielberger State-Trait Anxiety Inventory (STAI) (Table 1). OCD patients were also assessed with the Yale-Brown Obsessive-Compulsive Scale, the Hamilton Depression Rating Scale, and the National Institutes of Mental Health (NIMH) Severity Scales for global symptoms, OCD, depression, and anxiety (Table 1).

Procedure

Patients and controls were scanned using $H_2[15]O$ and a multislice PET scanner (Scanditronix PC2048-15B, Scanditronix, Uppsala, Sweden), which acquires 15 contiguous, cross-sectional images simultaneously, each 6.5 mm thick. Within-plane resolution is 6.5 mm (full width at half-maximum (FWHM)). Head movement was minimized by using a thermoplastic mask that was molded to each subject's head and attached to the scanner bed. Each scan was obtained while the subject performed one of the tasks described below.

Subjects began each task 1 min before the intravenous injection of a 10 mL bolus of 40 mCi of $H_2{}^{15}O$. Scanning commenced when the brain radioactive count rate reached a

threshold value and continued for 4 min thereafter. Arterial blood radioactivity was sampled continuously with an automatic blood sampling device from the time of injection to the end of scanning. A transmission scan was used to correct images for attenuation. rCBF values, in units of ml/100 mg tissue/min, were calculated for each pixel using the sampled blood activity curve and the rapid least squares method (Carson *et al*., 1987).

Tasks were presented in randomized order, with scans separated from each other by approximately 9 min to allow for radiation decay, testing, and preparation for the subsequent scan. Duplicate but not identical tasks had previously been given to all subjects to ensure their comprehension of and compliance with instructions during the PET scanning. For the disgust-inducing task, participants were shown a series of slides with written descriptions of scenes or objects that they had ranked as moderately disgusting (disgust score of 60–80, where 0: "none" and 100: "total gross-out").

During the anticipatory anxiety task, participants observed a countdown on a screen with the expectation of receiving a physical shock of greater activity as wait time increased. During the control task, the phrase "Please rest now" was displayed on a monitor. At the end of the anticipatory anxiety and resting tasks, the State Scale of the STAI and a 10 point analogue scale for anxiety was administered to assess subjects' experience of anxiety during these conditions (0 indicating "not at all," and 10 indicating "very much so"). In addition, two electrodermal activity measures were obtained (skin conductance response (SCR) magnitude and nonspecific response (NSR) frequency), and following the scans arterial blood samples were analysed for 3-methoxy-4-hyroxyphenylglycol (MHPG).

All of the subjects were scanned at rest, 13 of the controls and all of the OCD subjects were scanned during the anticipatory anxiety task, and 11 of the controls and 5 of the OCD subjects were scanned during the disgust-activation task. As not all subjects completed all experimental tasks, only controls and OCD subjects who underwent scanning during anticipatory anxiety, or during disgust-activation, were compared, and they remained matched for age, gender, and handedness. We had originally hoped to include a symptom provocation task in the OCD subjects, but too few of these scans were completed to allow for a meaningful analysis.

Data analysis

Task-related differences in rCBF were tested using Statististical Parametric Mapping (SPM) (Friston *et al*., 1991), which scales each three-dimensional image set to the dimensions of the Montreal Neurological Institute stereotaxic space, so allowing statistics to be calculated for each voxel sampled. Images during the experimental (disgust, threat) and control conditions were realigned to minimize variance due to head torsion, stereotaxically normalized against the mean image, and smoothed with a 12-mm FWHM Gaussian kernel to reduce noise due to anatomic heterogeneity across subjects. rCBF for each voxel was corrected for variations in global blood flow using proportional scaling.

Small volume gray matter templates were constructed to constrain the search volume for statistical analysis to particular regions of interest (ROI) (Matochik *et al*., 2003). This was done using MEDx 3.42 (Sensor Systems, Sterling, VA). The a priori regions or volumes were segmented on a T1-weighted MR image spatially normalized to the same stereotaxic space (i.e., MNI space) and with the same voxel dimensions as the PET images. A trace was manually drawn around the volume of interest on all slices where the structure was evident. The segmentation was done without strict anatomical boundaries so as to encompass the entire area around the structure of interest.

The series of 2-D graphics outlined the borders of a particular structure were derived into a 3-D contour and used as a small volume template. Bilateral small volume templates were made for the cingulate gyrus [infragenual area (Brodmann Area [BA]) 25, 32), perigenual (BA 24, 32, 33) and dorsal midcingulate regions (BA 24) regions], orbitofrontal cortex [medial region (BA 11), including the gyrus rectus and medial orbital gyrus; and the lateral orbital region (BA 11, 47), including lateral orbital gyrus], lateral prefrontal cortex [middle and inferior frontal gyrus (BA 9, 10, 44, 45, 46)], insula, caudate, lentiform nucleus, amygdala, and hippocampus.

Using the general linear model approach implemented in SPM2, relative differences in voxel count between the two groups were determined. Within the a priori search volumes, the voxel-wise threshold was set at $p < 0.001$ (two-tailed), and clusters of contiguous voxels (extent $\geq$20) that passed this threshold were considered significant at $p < 0.05$ corrected for multiple comparisons. The hypothesis was that a comparison of OCD versus controls would show that during the disgust-inducing task as compared with rest there would be increased activation in insula, striatum, and lateral orbitofrontal cortex in OCD subjects, but that during anticipatory anxiety as compared with rest there would be increased activation of amygdala and cingulate cortex in both groups.

Results

Self-rating scores of anxiety for the OCD group indicated that they were significantly more anxious than the controls during the resting scan condition, and that there was a significant increase in anxiety ratings in both groups during the anticipatory anxiety task (Table 2). Similarly, heart rate was significantly higher in OCD patients than in controls during the resting scan condition, and this again increased significantly in both groups during anticipatory anxiety. Also, NSR scores were significantly higher during anticipatory anxiety than at rest. Nevertheless, anxiety ratings, heart rate, and skin conductance increased

Table 2 Psychological and physiological measures during the anticipatory anxiety and resting tasks

Rating	Anticipatory anxiety OCD patients	Anticipatory anxiety healthy controls	Resting condition OCD patients	Resting condition healthy controls	ANOVA Task	ANOVA Diagnosis
State anxiety	37.6 (18.2)	13.9 (9.8)	29.5 (14.7)	6.3 (5.5)	$p < 0.00001$ (AA > R)	$p < 0.00001$ (OCD > NC)
Analog anxiety	6.7 (3.0)	2.8 (1.7)	4.8 (3.8)	0.5 (1.0)	$p < 0.00001$ (AA > R)	$p < 0.00001$ (OCD > NC)
Heart rate (/min)	79.9 (13.8)	74.9 (19.4)	72.2 (12.5)	67.7 (11.3)	$p < 0.002$ (AA > R)	$p < 0.0001$ (OCD > NC)
MHPG (ng/mL)	6.4 (8.4)	9.7 (7.8)	5.0 (4.1)	7.4 (2.4)	NS	NS
SCR	0.2 (0.2)	0.1 (0.1)	0.1 (0.1)	0.4 (0.9)	NS	NS
NSR	15.3 (13.3)	15.1 (16.7)	5.3 (5.0)	4.1 (6.0)	$p < 0.02$ (AA > R)	NS

Note. State Anxiety refers to the State Scale of the Spielberg Trait-State Inventory. The analog scale for anxiety was measured on a scale of 1–10. MHGP: 3-methoxy-4-hyroxyphenylglycol. SCR: skin conductance response magnitude. NSR: nonspecific response frequency. AA: Anticipatory anxiety. R: Resting. NS: non-significant.

to a similar extent in OCD patients and healthy controls during the anticipatory anxiety task (Table 2).

Activation patterns in the specified brain regions during the anticipatory anxiety task as compared to the rest condition, did not significantly differ between OCD subjects versus controls (Table 3). Comparison of these tasks in the OCD subjects and in the controls separately, showed that during anticipatory anxiety there was decreased activation in different regions of the cingulate in OCD subjects ($-2, 48, -7$; $p = 0.003$, and $-8, 7, 27$; $p = 0.006$), but areas of increased rCBF (8, 43, -2; $p = 0.016$) and decreased rCBF (-4, 46, -4; $p = 0.02$) in this region in controls.

Increased and decreased rCBF in the specified brain regions during the disgust-induced task as compared to the rest condition, were assessed in OCD subjects versus controls (Table 3). OCD subjects had a significantly greater increase in rCBF in left insula than did controls (maximally significant Talairach co-ordinates 42, -4, 0; $p = 0.003$—Fig. 1), and there were no differences in decreased rCBF. Comparison of rCBF during these tasks in the OCD group alone demonstrated areas of increased rCBF in right lateral orbitofrontal cortex (-48, 26, -15; $p = 0.001$) during disgust, while in the group of control subjects there were no significant changes.

Discussion

It should be emphasized that the data here are limited in view of the low overall sample size, the low number of subjects who completed all the imaging tasks, and the absence of a control task involving stimuli typically feared by patients with OCD. Nevertheless, these data are consistent with previous work indicating that the neural substrate of disgust and of fear is different, that there are some similarities in neuronal activation during anticipatory anxiety in OCD and normals, and that in OCD there are differential patterns of neuronal activation during disgust-inducing tasks.

Fear and disgust likely evolved for different purposes, they have different elicitors, and are accompanied by different facial expressions (Darwin, 1965). Localization of fear and disgust in different neuronal substrates was further suggested by preliminary electrophysiological and autonomic nervous system studies (Davidson *et al*., 1990; Collet *et al*., 1997; Yartz and Hawk, 2002), and by evidence from patients with amygdala or insula lesions of dissociation in neural systems for these recognizing emotions (Calder *et al*., 2000; Stein *et al*., 2001; Adolphs *et al*., 2003). Although not all data is entirely consistent (Gorno-Tempini *et al*., 2001; Stark *et al*., 2003; Phan *et al*., 2002); a number of recent imaging studies have been able to confirm that different neuronal circuits are activated by disgust and fear-inducing tasks (Reiman, 1997; Phillips *et al*., 1997, 1998; Sprengelmeyer *et al*., 1998; Surguladze *et al*., 2003). This finding is seen not only in healthy controls, but also in OCD (Shapira *et al*., 2003).

The role of the insula, which is part of gustatory cortex, containing neurons that respond to pleasant and unpleasant tastes (Rolls, 1994), in disgust recognition is consistent with the hypothesis that this emotion evolved to lead to avoidance of potentially harmful decayed food (Rozin and Fallon, 1987). Ventral cortico-striatal thalamic circuits link medial temporal and orbitofrontal structures, so perhaps establishing associations to bad tastes and smells. While disgust is initially elicited by taste or order aversion in infants, during development there is an extension to cover other features of food and then to other stimuli, so that in adulthood disgust can be experienced after violation of body borders, after interpersonal contamination, and after moral violations of purity vs sanctity (Rozin *et al*., 1999). Such stimuli and specific

Table 3 Clusters of significance found with SMP comparisons

Comparison of task to resting condition	Region of interest	Cluster extent	Cluster-level significance (corrected)	Local max *x*	Local max *y*	Local max *z*	z	Voxel-level significance (family wise error rate)
Disgust activation (OCD vs Controls)	L insula	101	.003	42	−4	0	4.47	0.002
Disgust deactivation (OCD vs Controls)	—							
Disgust activation—OCD	R lateral orbitofrontal cortex	24	<0.001	−48	26	−15	4.31	0.015
Disgust deactivation—OCD	—							
Disgust activation—Controls	—							
Disgust deactivation—Controls	—							
Anxiety activation (OCD vs Controls)	—							
Anxiety deactivation (OCD vs Controls)	—							
Anxiety activation—OCD	—							
Anxiety deactivation—OCD	Cingulate	41, 34	0.003, 0.006	−2, −8	48, 7	−7, 27	4.91, 3.92	<0.001, 0.012
Anxiety activation—Controls	Cingulate	29	.016	8	43	−2	3.35	0.065
Anxiety deactivation—Controls	Cingulate	23	0.022	−14	46	−4	4.16	0.006

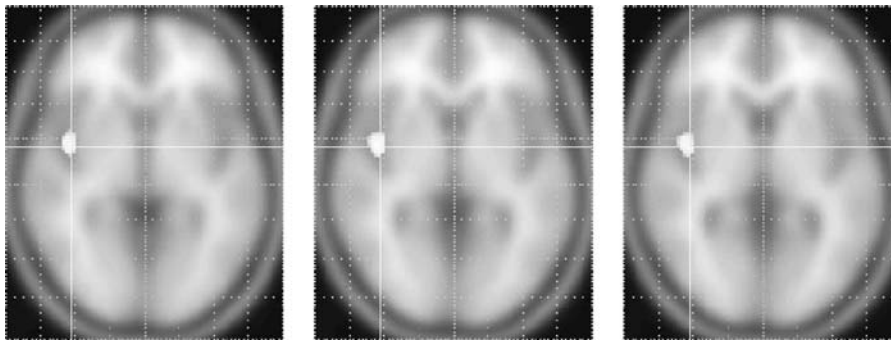

Fig. 1 rCBF in left insula is significantly higher ($p = 0.003$) in OCD subjects than in controls, when comparing the disgust-inducing versus the resting tasks. The Talariach co-ordinates of the local maximum are 42, −4, 0. The images are in neurological orientation

responses to them (eg washing, avoidance, magical thinking) are redolent of key features of OCD (Stein *et al*., 2001).

Although each of the specific anxiety disorders may be characterized by the involvement of specific neuronal circuits, there are also circuits that cut across these conditions, and that may be particularly relevant in mediating phenomena such as fear and anticipatory anxiety. Ventral regions including the amygdala and inferior frontal cortex play an important role in identifying threat and responding with fear, and are activated in different anxiety disorders (Gorman *et al*., 2000; Davis and Whalen, 2001). More dorsal brain regions including the anterior cingulate may be particularly important in monitoring and regulating affective state (Reiman, 1997; Phillips *et al*., 2003). Previous findings examining anticipatory anxiety or threatening stimuli have demonstrated changes in the cingulate, with increased activation in some studies (Chua *et al*., 1999; Shapira *et al*., 2003), and deactivation in other work (Simpson *et al*., 2001).

We did not observe rCBF changes in these regions when comparing anticipatory anxiety and resting task data across OCD patients and healthy controls. This is consistent with the observation that similar increases in anxiety ratings, heart rate, and electrodermal activity were seen in both OCD patients and normal controls across these conditions. Nevertheless, the relatively small sample and low resolution provided by our scans may have resulted in false negative results. Certainly, significant differences in anxiety ratings and electrodermal activity were noted between OCD patients and healthy controls when analysed at either rest or during anticipatory anxiety. It should be emphasized that even if disgust is central in OCD, complex interactions with different emotions, including anxiety, may well be relevant to the phenomenology and pathogenesis of this disorder (Rachman, 1994; Power and Dalgleish, 1997). Conversely, disgust may also play an important role in other anxiety disorders (McKay, 2002; Wright *et al*., 2003).

Previous fMRI work has demonstrated that disgust-induced insula activation is greater in OCD patients with predominant contamination symptoms (Shapira *et al*., 2003). Pictures related to contamination also activate the insula in OCD patients with washing compulsions, but activate frontal-striatal circuits in OCD patients with checking compulsions (Phillips *et al*., 2000). Indeed, disgust may be particularly relevant to OCD with contamination concerns (Muris *et al*., 1999; Tsao and McKay, 2004; Thorpe *et al*., 2003; Olatunji *et al*., 2004; Mancini *et al*., 2001). Our data are consistent with the hypothesis that disgust-induced activation of the insula differs in OCD and controls, but our sample of OCD subjects

was too small to analyze on the basis of different symptom subtypes or individual differences in susceptibility to disgust. Future work is needed to fully characterize differences in disgust-induced brain activation in such subgroups. The literature is also inconsistent as to whether OCD is characterized by volumetric abnormalities in the insula (Kim *et al*., 2001, 2003).

It is noteworthy that OCD is on the one hand characterized by a specific dysfunction in the recognition of facial expressions of disgust (Sprengelmeyer *et al*., 1996, 1997), and on the other hand by increased insula activation on disgust-inducing tasks. A recent fMRI study found that the insula was activated both by an inhaled odorant that produced a strong feeling of disgust, and by observation of video clips showing the emotional facial expression of disgust (Wicker *et al*., 2003). The authors concluded that just as observing hand actions activates motor representations of action, so observing an emotion actives the neural representation of that emotion. It may be hypothesized that in OCD there is a disruption in disgust, such that is a decrease in appropriate disgust processes (as when observing disgust in others) and an increase in inappropriate disgust processes (such as those evoked by contamination stimuli). Further work is required to clarify the specificity of such disruptions to OCD, and to determine whether they are normalized during treatment.

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