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Altered olfactory processing and increased insula activity in patients with obsessive-compulsive disorder: An fMRI study

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ABSTRACT

Obsessive-compulsive disorder (OCD) patients show increased insula activation to disgust-inducing images compared to healthy controls (HC). We explored whether this disgust reactivity was also present in the olfactory domain by conducting the first fMRI study of olfaction in OCD. Neural activation in response to pleasant and unpleasant odors (vs. unscented air) was investigated in 15 OCD and 15 HC participants using fMRI. OCD participants (vs. HC) had increased left anterior insula activation to *unpleasant* odors (vs. unscented air), which positively correlated with their disgust sensitivity and ratings of the unpleasantness and intensity of those odors. OCD participants (vs. HC) showed increased activation of caudate nucleus and left anterior and posterior insula to *pleasant* odors (vs. unscented air), which positively correlated with their OCD symptom severity, trait anxiety, frequency of feeling disgust, and odor intensity ratings. OCD participants had increased anterior insula activation to both pleasant and unpleasant odors, which correlated with their OCD symptoms, anxiety, disgust sensitivity, and frequency of feeling disgust. OCD patients might have a negative cognitive bias and experience all stimuli, regardless of valence, as being more unpleasant than healthy people. These findings further elucidate the neural underpinnings of OCD and may contribute to more effective treatments.

1. Introduction

Obsessive-compulsive disorder (OCD) is characterized by the persistent intrusion of intense, unwanted thoughts or images (obsessions), and repetitive, ritualistic behaviors or mental acts (compulsions) that are carried out in an attempt to neutralize anxiety (American Psychiatric Association, 2000). Although the etiology of OCD is unknown, structural functional neuroimaging studies (Rauch, 1998), clinical response to neurosurgery (Husted and Shapira, 2004), and neurophysiological and neuroimmunological data (Stein et al., 2000) suggest dysfunction in cortico-striatal-thalamic-cortical (CSTC) neurocircuitry, in particular abnormalities of the orbitofrontal cortex (OFC) and basal ganglia in OCD (Rauch and Jenike, 1993; McGuire et al., 1994; Lucey et al., 1995; Robinson et al., 1995; Rauch et al., 1997).

1.1. OCD and disgust

Several lines of evidence suggest that the emotion of disgust plays an important role in the pathogenesis and maintenance of OCD (Stein et al., 2001; Schienle et al., 2005; Husted et al., 2006). First, there is a strong relationship between the emotion of disgust/disgust sensitivity and obsessive-compulsive symptoms in both clinical and non-clinical populations (Muris et al., 1999; Mancini et al., 2001; Woody and Tolin, 2002; Schienle et al., 2003; Thorpe et al., 2003; Olatunji et al., 2004a, 2004b; Tsao and McKay, 2004; Olatunji and Sawchuk, 2005). Second, OCD patients have shown deficits in identification of facial representations of disgust, in comparison with other anxiety disorders (Sprengelmeyer et al., 1997). And third, OCD patients, especially those with contamination fears and washing compulsions, report experiencing intense disgust feelings during symptom provocation, (Phillips et al., 2000; Sieg and Scholz, 2001) and contamination concerns are the most common obsessions associated with OCD, (Rasmussen and Tsuang, 1986) presenting in up to 50% of people with OCD (Rachman and Hodgson, 1980; Rasmussen and Eisen, 1992).

Feelings of disgust may arise from sensory experiences (e.g., taste, smell) and from more abstract concerns (e.g., related to aspects of the body or to moral judgments) (Rozin et al., 1999). In accordance, OCD

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concerns may be concrete (e.g., about germs, bodily secretion, and illness) or more abstract (related to religious, ethical, and moral issues). OCD patients with contamination concerns often describe threat-relevant objects as “disgusting” rather than “frightening” (Sieg and Scholz, 2001; Tolin et al., 2004), and, after exposure to a disgusting object, cleaning rituals are seen (Rozin and Fallon, 1987). In addition, disgust in OCD patients seems to be more resistant to extinction than fear (Smits et al., 2002).

Studies support the role of disgust in OCD (Mancini et al., 2001; Thorpe et al., 2003; Olatunji et al., 2004a, 2007; Tsao and McKay, 2004; Olatunji and Sawchuk, 2005; Cisler et al., 2009) and the notion that disgust is distinct from other negative affective states (e.g., anxiety and depression) (Mancini et al., 2001; Woody and Tolin, 2002; Olatunji et al., 2004b; Tolin et al., 2006). The distinction between fear/anxiety (i.e., sympathetic activation) and disgust (i.e., parasympathetic activation) is not just semantic or phenomenological, these emotions are characterized by different neural processes (Olatunji and Sawchuk, 2005). Functional imaging in healthy people and patient-based studies have shown that, while the human amygdala plays a significant role in fear recognition (Calder, 2003; Phelps and LeDoux, 2005; LeDoux, 2007), the insular cortex and putamen appear to underlie disgust recognition (Calder et al., 2007; Mataix-Cols et al., 2008; Olatunji et al., 2010).

Functional imaging, clinical, and lesion studies have shown that the insular cortex and striatum (caudate nucleus and putamen), which are involved in disgust processing (measured by perception of and response to facial expressions of disgust and disgust-inducing stimuli), are also implicated in OCD (Calder et al., 2000, 2001, 2007; Stein et al., 2000; Husted et al., 2006; Mataix-Cols et al., 2008; Olatunji et al., 2010). Insula cortex and striatum are activated in response to both disgusting and OCD symptom related stimuli in patients with OCD (Stein et al., 2001; Berle and Phillips, 2006). More specifically, studies have found greater activation of insula (right [Shapira et al., 2003], left [Stein et al., 2006], and bilaterally [Schienle et al., 2005; Berlin et al., 2015]) in response to disgust-inducing images in OCD patients compared to controls. Since the neural circuits involved in disgust processing appear to be important in the etiology of OCD (Husted et al., 2006; Berlin et al., 2015), we focused on disgust processing in OCD in the current study.

1.2. Olfaction, OCD, and disgust

In addition to being involved in disgust processing and OCD, the anterior insula is also involved in olfaction (Rouby, 2005). Structural imaging and lesion studies have shown that regions involved in primary and secondary olfactory processing, including the insular and anterior cingulate cortices, amygdala, and OFC, overlap with brain areas where abnormalities have been found in patients with OCD (Cicerone and Tanenbaum, 1997; Tallis, 1997; Yousem et al., 1997; Levy et al., 1998; Purcell et al., 1998; Sobel et al., 1998; Varney and Bushnell, 1998; Szeszko et al., 1999; Pujol et al., 2004; Valente et al., 2005; Wiesmann et al., 2006; Rotge et al., 2009, 2010; Segalas et al., 2011, 2014).

There is evidence of olfactory deficits in people with neurodegenerative (e.g. Alzheimer's Disease) and psychological disorders (e.g. schizophrenia, mood and eating disorders, and OCD) (Segalas et al., 2014). But to date, few studies have investigated olfactory identification in OCD patients. Two studies found deficits in olfactory identification (using the University of Pennsylvania Smell Identification Test [UPSIT; Doty, 1995]) in OCD patients compared to healthy controls (HC) (Goldberg et al., 1991; Barnett et al., 1999). But, Goldberg et al. (1991) only included five OCD participants, and the magnitude of the impairment in Barnett et al. (1999) was small and did not equate to anosmia. Using the Sniffin' Sticks test (SST), a measure of odor detection, discrimination, and identification, Segalas et al. (2011, 2014) found that OCD patients had olfactory deficits in all three domains. In addition Segalas et al. (2014) found that OCD patients' odor identification errors and odor detection thresholds were associated with volumetric changes in their left medial orbital gyrus and left anterior cingulate cortex respectively, brain areas typically implicated in the neurobiology of OCD. Nevertheless, several other studies have found no difference in olfactory discrimination or detection between OCD patients and HC (Locatelli et al., 1996; Barnett et al., 1999; Hermesh et al., 1999; Fenger et al., 2005). Methodological differences between these studies may explain these discrepancies, or olfactory function may be variable within OCD populations.

We hypothesize that OCD patients will have abnormalities in their sensitivity to odors, in particular their emotional responses to them, while maintaining normal odor discrimination and identification. More specifically, we predict that OCD patients may be more sensitive than healthy participants (i.e., increased subjective negative emotions and neural activity in brain regions related to disgust processing, e.g. the insula cortex) to unpleasant olfactory stimuli, which may lead to, or exacerbate, their obsessions and compulsions. Indeed, data from an animal study suggests that increased cortical-limbic responsiveness to olfactory stimuli with affective properties can trigger compulsive behaviors (McGrath et al., 1999).

Some evidence indicates that OCD patients are less sensitive to the positive valence of pleasant odors. For example, in an electroencephalogram study in OCD patients during olfactory stimulation with a pleasant odor (sweet orange), Locatelli et al. (1996) found that control participants showed a power increase in the slower beta frequencies in the temporal lobe in response to the pleasantly scented air (vs. unscented air), while OCD patients showed no modification or a slight decrease. Therefore, we hypothesize that OCD patients will experience positive odors as less positive then control participants and that this may correlate with increased insula activation.

The insula may be involved in modulating the influence of emotions on cognitive functions in general (Goldin et al., 2008), and has been shown to be involved in affective tasks independent of the specific emotion, and in monitoring “ongoing internal emotional states” (i.e., feelings) (Damasio et al., 2000; Schienle et al., 2002).

FMRI provides a direct method to examine differences in neural responses to target stimuli between OCD patients and HC. However, olfactory stimuli have never been used to trigger neural responses in an fMRI task with OCD patients. The literature thus far is sparse and more research is needed to better characterize the degree to which disgust and olfaction play a role in OCD and what implications this association has for the development of novel treatments for OCD. We have therefore conducted the first study to examine olfaction in OCD using fMRI. We investigated the function of the olfactory system in response to pleasant and unpleasant odors in OCD patients compared to matched HC using a uniquely designed olfactometer together with fMRI. Based on the literature described above, we hypothesized that there would be a strong relationship between insula activation and disgust sensitivity in patients with OCD.

2. Methods

2.1. Participants

Thirty participants between the ages of 18 and 50 (inclusive) were recruited for this study via Mount Sinai clinician referrals, private practice clinician referrals (obtained by calling and emailing therapists requesting that they refer patients or post our flyer in their office), and advertisements on Craig's List, social media, and Mount Sinai's email newsletter. The study was carried out in accordance with the Declaration of Helsinki and written informed consent was obtained from all participants.

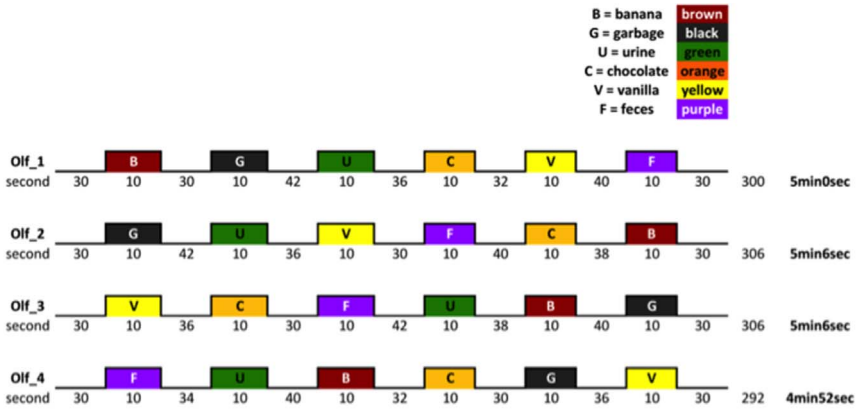

Fig. 1. fMRI stimulus presentation design. Note: OLF_1= block 1; OLF_2= block 2; OLF_3= block 3; OLF_4= block 4.

2.2. Screening

Participants were administered a short measure of intelligence (Wechsler Abbreviated Scale of Intelligence [WASI; Wechsler, 1999]), a neurological history (assessing lifetime incidence of head injury, seizures, migraines, loss of consciousness, birth trauma, encephalitis, and other neurological conditions), and structured clinical interviews for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) Axis I (SCID-I) and Axis II (SCID-II) disorders (First et al., 1997). In addition, a qualified clinical psychologist ascertained the diagnosis of OCD and administered the Yale-Brown Obsessive Compulsive Scale (Y-BOCS; Goodman et al., 1989) to measure symptom severity in OCD patients and exclude healthy control participants with undiagnosed OCD. Participants in the OCD group were all outpatients and were required to meet diagnostic criteria for OCD with minimal comorbid diagnoses as per the exclusion criteria listed below, while a current diagnosis of any disorder on the SCID-I or SCID-II precluded participation as a healthy control.

Participants were excluded if they had a history of or current neurological illness, including a history of seizures or head trauma/injury with a loss of consciousness of > 30 min; an IQ < /=80 as assessed with the WASI; current or lifetime DSM-IV-TR diagnosis of bipolar disorder or other psychotic disorder/psychosis; history of DSM-IV-TR personality disorder considered by the investigator to interfere with assessment; current or recent (within six months) DSM-IV-TR diagnosis of substance/alcohol abuse or dependence (with the exception of nicotine/caffeine dependence); positive urine drug screen; significant suicidal or violent behavior in the judgment of the investigator; serious suicide risk; clinically significant unstable medical disorder; flu or cold with reduced olfactory sensitivity; positive pregnancy urine test or self-reported pregnancy; metal implant or claustrophobia. Participants were also administered the UPSIT (Doty et al., 1984; Doty, 1995) and were excluded if they exhibited anosmia. The cut-off score for anosmia on the UPSIT varied for each participant since the norms are age and gender dependent. Smoking was not an exclusion criterion, but only one participant, an OCD patient, reported smoking (7 cigarettes per day).

2.3. Clinical measures

Participants completed a battery of questionnaires measuring OCD symptoms, disgust sensitivity, and emotion. They were administered the Disgust Scale – Revised (DS-R; Haidt et al., 1994), Hamilton Measure of Depression (HAM-D; Hamilton, 1960), State-Trait Anxiety Inventory (STAI; Spielberger, 1983), Padua Inventory of Obsessive Compulsive Disorder Symptoms (PI; Burns et al., 1996), Positive and Negative Affect Scale (PANAS; Watson et al., 1988) and the Disgust Subscale of the Subjective Emotion Questionnaire (SEQ Disgust; Berlin et al., 2005), which measures how often participants experience disgust on a Likert scale from 1 (almost always) to 4 (rarely/never).

2.4. FMRI olfaction task

Odors were delivered to a nasal mask (SleepNet Phantom Nasal Mask) at 1.5 l/minute and were extracted by vacuum pump to avoid mingling of odors in the nasal mask. Participants were exposed to pleasant “P” (banana, vanilla, chocolate) and unpleasant “U” (garbage, feces, urine) odors during fMRI via our custom-engineered, MRI-compatible olfactometer. All stimuli were supplied by Caravansons, LTD and were previously used in a study by Heining et al. (2003). Unscented/fresh air served as the “rest” stimulus, which is standard procedure in olfaction studies (Popp et al., 2004). The fMRI task consisted of 4 five-minute blocks. Each block consisted of 10 s ON (odors) and 30–42 s OFF (fresh air) intervals to prevent habituation and carry-over effects (Wang et al., 2005; Boyle et al., 2007). Two different odors of the same category (U or P) were alternated in each ON phase to prevent habituation. See Fig. 1 for the fMRI stimulus presentation design, which includes the order of odor presentation and length of time each odor was presented for in each of the 4 blocks.

2.5. Odor evaluation

After the scan, participants were presented with all six odors individually, while sitting up, for 8 s each in a randomized order (interspersed with unscented air to prevent habituation to the odors, for 30 s to one minute depending on how long it took them to complete the evaluation scales) and asked to rate each odor on intensity and magnitude with the following scales:

Labeled Magnitude Scale (LMS; Green et al., 1996): a semantically-labeled scale of intensity for a sensation that ranges from 0 (no sensation at all) to 100 (strongest sensation imaginable).

Labeled Hedonic Scale (LHS; Lim et al., 2009): measures hedonic magnitude; it rates the overall pleasantness of stimuli on a scale from −100 (most unpleasant imaginable) to 100 (most pleasant imaginable), with 0 being neutral.

2.6. Statistical Analysis

2.6.1. Questionnaire and descriptive analysis

Clinical scale measures and ratings of the valence and intensity of odors were compared between the groups using Mann-Whitney-*U*-Tests (two-tailed, alpha level 0.05). Within the OCD group, Spearman´s correlations examined the relationship between brain activation in regions showing group differences and clinical scales/ratings, namely the Y-BOCS total, PI total, DS-R total, STAI state and trait anxiety,

HAM-D total, SEQ disgust subscale, PANAS total negative affect score, and valence and intensity ratings.

2.6.2. Neuroimaging analysis

2.6.2.1. Neuroimaging data acquisition and preprocessing. Following sagittal localization and shimming, a high resolution, T-2 weighted anatomical volume of the whole brain was acquired using a Phillips Achieva 3 T system with a turbo spin-echo (TSE) pulse sequence (40 axial slices, repetition time [TR] =3000 ms, echo time [TE] =80 ms, flip angle =90°, field of view [FOV] =21.0 cm, matrix =512×512, voxel size =0.41×0.41×3.0 mm). Also, a high-resolution structural MP-RAGE (Magnetization Prepared Rapid Gradient Echo) scan was acquired with the following parameters: 172 Slices, thickness =1.0 mm, matrix size =220×210, FOV =22 cm, TR =7.5 ms, TE =3.4 ms and 8° flip angle.

Functional data were acquired using a gradient echoplanar (GE-EPI) sequence (34 coronal slices with 2 mm thickness, no skip, TR = 4000 ms, TE =18 ms, Flip angle =90°, FOV =21 cm, matrix =84×87). Anterior-to-posterior coronal acquisition was employed to reduce susceptibility artifacts in orbitofrontal cortex; due to the increased acquisition time for slices acquired in this orientation, BOLD signal was measured in a slab encompassing the anterior half of brain (up to ~y=25 in MNI space). Four separate runs of 80 volumes were acquired.

2.6.2.2. Data preprocessing and analysis. Preprocessing of functional data was performed using Statistical Parametric Mapping software v. 8 (SPM8; The Wellcome Dept. of Imaging Neuroscience, University College London) and included (in order): slice-time correction, realignment of functional images, coregistration of functional images to anatomical image, normalization to MNI152 template (an average of 152 T1 images from the Montreal Neurological Institute), and spatial smoothing of functional images with a 6 mm Gaussian kernel.

Analysis of neuroimaging data used the general linear model (GLM) as implemented in SPM8. At the first (subject) level, 7 regressors specified onset times for pleasant odor blocks (3 regressors: banana, vanilla, chocolate), unpleasant odor blocks (3 regressors: garbage, feces, urine), and the rest block. Regressors were modeled as epochs with durations set to block length (10 s for the odor blocks and between 30 and 42 s for rest blocks) and convolved with the canonical hemodynamic response function (HRF). Contrasts compared pleasant and unpleasant odors with rest and each other. Group-level comparisons between OCD patients and HC used two-sample *t*-tests, with a threshold of $p < 0.05$, corrected for multiple comparisons using family-wise error (FWE) at the cluster level. However, because of strong *a priori* predictions about the relationship between insula activation and disgust sensitivity, we also conducted a targeted region-of-interest (ROI) analysis in the insula that searched for activations surpassing a threshold of $p < 0.01$ (uncorrected) within a bilateral anatomical mask of the structure created using Wake Forest University's pickatlas tool (Maldjian et al., 2003).

3. Results

3.1. Demographics

Thirty participants (N =30) were recruited for this study. The OCD group consisted of 15 outpatients (n =15; 8 males [n =8], 7 females [n =7]) who were clinically diagnosed with OCD presenting with mixed subtypes, most of whom exhibited contamination obsessions (n =11) and/or contamination compulsions (n =8), and ranged in age from 22 to 50 years old (M =34.07, SD =9.38). OCD severity was categorized as mild (n =5), moderate (n =9), and severe (n =1) based on Y-BOCS scores.

Obsessive symptoms were categorized according to the Y-BOCS symptom checklist as: aggressive (n =12), contamination (n =11), sexual (n =7), hoarding (n =3), religious (n=5), symmetry/exactness (n =9), somatic (n =4), or miscellaneous (n =11). Compulsions were categorized as: cleaning/washing (n =8), checking (n =8), repeating rituals (n=9), counting (n =4), ordering/arranging (n =7), hoarding (n =2), or miscellaneous (n =13).

Current comorbid psychological disorders in the OCD group were as follows: Two OCD participants met criteria for one comorbid Axis-I diagnosis (dysthymic disorder, and minor depressive disorder, respectively). Two were diagnosed with two comorbid Axis-I disorders (major depressive disorder in partial remission and social phobia in partial remission; and major depressive disorder in partial remission and mild panic disorder with agoraphobia, respectively). And two met criteria for an Axis-II diagnosis (personality disorder not otherwise specified, and depressive personality disorder, respectively).

Fourteen patients with OCD were currently taking psychotropic medication. The majority of these patients (n =10) were taking a selective serotonin reuptake inhibitor (SSRI) as a monotherapy (n =5) or in combination with augmentation agents (n =5) e.g., buspirone, aripiprazole, trazodone. Five participants were on fluvoxamine, two were on fluoxetine, two were on sertraline, and one was on citalopram. One participant was taking clomipramine as a monotherapy and another venlafaxine monotherapy. One participant was prescribed parnate, trazadone, diazepam, and risperidone in combination. Ten OCD patients were undergoing psychological treatment intended to improve their OCD symptoms. However, despite their current pharmacological and psychological treatment, the OCD group still had significant levels of symptomatology/pathology (see Table 1). Patients on medication and in therapy represent an ecologically valid group of

Table 1
Clinical measures, odor valence and intensity, and smell identification results.

Variable	OCD			HC (N=15)			P-value
	N	Mean	SD	*N*	Mean	SD	
YBOCS	15	17.73	4.86	15	0.00	0.00	0.00**
PI Total	15	78.53	39.06	15	4.33	6.66	0.00**
DSR Total	15	50.93	19.77	15	40.00	16.35	0.13
STAI State Anxiety (*t*-score)	15	34.20	8.26	15	29.33	6.99	0.11
STAI Trait Anxiety (*t*-score)	15	46.73	10.37	15	30.67	8.34	0.00**
STAI Total (*t*-score)	15	80.93	16.47	15	60.00	14.63	0.00**
HAMD	15	3.73	2.94	15	0.27	0.80	0.00**
PANAS Total Negative Affect	15	21.73	6.20	15	11.33	2.72	0.00**
SEQ Disgust Subscale	15	0.87	0.83	15	0.13	0.35	0.01**
UPSIT Total	15	33.87	6.21	15	35.07	3.41	0.97
UPSIT Percentile	15	42.47	37.07	15	35.93	30.11	0.79
Valence Banana	15	24.07	31.41	15	23.42	25.82	0.80
Valence Vanilla	15	13.64	17.68	15	27.21	36.27	0.14
Valence Chocolate	15	7.83	42.94	15	18.40	27.45	0.51
Valence Garbage	15	−30.16	33.98	15	−31.33	31.19	0.95
Valence Feces	15	−24.17	28.24	15	−14.37	24.70	0.58
Valence Urine	15	−3.34	14.66	15	−3.71	22.09	0.54
Intensity Banana	15	43.07	16.52	15	44.09	16.64	0.82
Intensity Vanilla	14	24.18	17.10	15	40.15	22.06	0.03*
Intensity Chocolate	15	36.73	32.75	15	40.07	14.47	0.72
Intensity Garbage	15	46.65	16.14	15	45.37	22.93	0.84
Intensity Feces	15	29.83	17.25	15	26.46	23.76	0.53
Intensity Urine	15	13.57	7.68	15	17.82	13.18	0.51

Notes: Y-BOCS = Yale-Brown Obsessive Compulsive Scale; PI = Padua Inventory; DSR = Disgust Scale-Revised; STAI = State-Trait Anxiety Inventory; HAM-D = Hamilton Depression Rating Scale; PANAS = Positive and Negative Affect Schedule; SEQ=Subjective Emotion Questionnaire; UPSIT = University of Pennsylvania Smell Identification Test.

* = Significant differences found between two (OCD & HC) groups at the 0.05 level.

** = Significant differences found between two (OCD & HC) groups at the 0.01 level.

OCD patients. The years of illness in the patient group ranged from > 1 year to 44 years (M =16.8, SD =11.1).

Fifteen healthy control participants (n =15; 8 males [n =8], 7 females [n =7]) between 23 and 50 years old (M =32.67, SD =8.73) were matched with OCD patients on age, gender, education, ethnicity, employment, and IQ as measured by the WASI total score. There were no significant differences between groups on these measures at the 0.05 alpha level. One healthy control participant and three OCD patients were left-handed.

3.2. Clinical measures, odor valence and intensity, and smell identification

See Table 1 for results. As expected, compared to HC, OCD participants had significantly higher scores on clinician-rated (Y-BOCS) and self-rated (PI) OCD symptom severity scales, and greater trait anxiety (STAI), state anxiety (STAI, trend), and depression symptoms (HAM-D). OCD participants also reported experiencing disgust significantly more frequently (SEQ disgust) and had a trend toward greater disgust sensitivity (DS-R scale). In addition, OCD participants reported significantly more negative emotion (PANAS total negative affect).

There were no significant between-group differences on the UPSIT, a measure of odor identification. Pleasant odors were rated on the LHS and LMS as significantly more pleasant, $t(29)$ =8.8, $p < 0.001$, and more intense, $t(29)$ =5.5, $p < 0.001$, than unpleasant odors across the whole group. There were no significant group differences in ratings of valence or intensity, except OCD patients rated their experience of vanilla intensity as significantly less than HC, $t(27) = -2.17$, $p < 0.05$. In addition, numerically, OCD patients rated pleasant odors as less pleasant than HC (OCD mean rating: 11.3, HC mean rating: 23.1).

3.3. Neuroimaging

3.3.1. Group differences

There were no differences between OCD and healthy control groups for the unpleasant odors > rest (U > R) comparison when correcting for multiple comparisons. However, a priori ROI analysis within the insula revealed a small area in left anterior insula that was greater for OCD than HC (Fig. 2, x=−42, y=11, z=−5, Z=2.8, k=8).

For the pleasant > rest (P > R) comparison, OCD patients showed hyperactivation of the caudate nucleus (predominantly on the right side; Fig. 3a, x=12, y=20, z=13, Z =4.0, k=97, FWE cluster level corrected p=0.01). At trend level (FWE cluster level corrected p=0.07), an area of left putamen extending into caudate nucleus and globus pallidus was also greater in the OCD group compared to the HC group for pleasant odor compared to rest blocks (x=−12, y=−1, z=10, Z =3.5, k=59). ROI analysis within the insula revealed greater activity in left anterior and posterior insula for OCD compared to HC for pleasant odors compared to rest (Fig. 3b; x=−39, y=11, z=−11, z=3.1, k=21; Fig. 3c; x=−42, y=−10, z=−2, z=2.9, k=6). There were no regions where the healthy control group showed greater activation than the OCD group for the P > R comparison, either corrected for multiple comparisons or within the insula ROI.

When comparing pleasant vs. unpleasant (P > U) directly, OCD patients showed more left anterior insula activity compared to HC within the insula ROI (x=−39, y=11, z=−11, z=2.8, k=9). There were no regions where OCD participants had greater activation than HC for the unpleasant > pleasant comparison, either at whole-brain corrected thresholds or within the insula ROI. See Table 2 for group differences in activation during the olfaction task, showing the contrasts, MNI coordinates, and z-scores of the reported findings.

3.3.2. Effects of anxiety

In order to determine whether state anxiety could be confounding the observed differences between OCD patients and HC, we conducted analyses-of-covariance (ANCOVAs) comparing the groups for the 6 clusters reported above while specifying state anxiety as a covariate. All group differences remained significant when including anxiety in the model (anterior insula, Unpleasant > Rest (U > R): $F(1,27)$ =8.2, p=0.008; caudate, Pleasant > Rest (P > R): $F(1,27)$ =26.3, $p < 0.001$; putamen, P > R: $F(1,27)$ =15.9, $p < 0.001$; anterior insula, P > R: $F(1,27)$ =13.5, p=0.001; posterior insula, P > R: $F(1,27)$ =9.9, p=0.004; anterior insula, Pleasant > Unpleasant (P > U): $F(1,27)$ =6.7, p=0.015) (See Table 2). These results indicate that group effects were not driven by differences in state anxiety.

3.4. Correlations of clinical measures and odor ratings with brain activations in OCD participants

Within the OCD group, there was a positive correlation between left anterior insula activation to *unpleasant* odors (vs. rest) and disgust sensitivity (measured by the DS-R scale, Spearman's rho =0.57, p=0.028). There was also a positive correlation between left anterior insula activation to *unpleasant* odors (vs. rest) and ratings of unpleasant odor intensity (rho =0.59, p=0.021) and an inverse correlation with ratings of odor valence (rho =−0.58, p=0.025; see Fig. 2). In other words, the greater the OCD participants' left insula activation to unpleasant odors, the more unpleasant and intense they rated those odors and the more sensitive they reported being to disgusting stimuli overall.

There was a positive correlation between caudate activation in response to *pleasant* odors (vs. rest) and self-rated OCD symptom severity as measured by the PI (rho =0.63, p=0.012). Furthermore, left *anterior* insula activation to pleasant odors (vs. rest) was positively correlated with OCD symptom severity on the PI (rho =0.64, p=0.010), trait anxiety on the STAI (rho =0.63, p=0.011), and disgust as measured by the disgust subscale of the SEQ (rho =0.59, p=0.022)]. Left *posterior* insula activation to pleasant odors was positively correlated with their intensity ratings of unpleasant odors (rho =0.54, p=0.039; see Fig. 3).

There were no significant correlations between scores on the Y-BOCS or the HAM-D scale and activation in any of the regions reported above.

4. Discussion

We investigated the function of the olfactory system in response to pleasant and unpleasant odors in OCD participants compared to matched HC using a uniquely designed, MRI-compatible olfactometer together with fMRI and measures of emotion, OCD symptomology, and disgust sensitivity. Our findings revealed abnormal hyperactivation during odor processing in OCD in regions of striatum (putamen (trend) and caudate nucleus), as well as in targeted analyses of the insula, which correlated with clinical ratings of OCD symptom severity and disgust sensitivity. By contrast, OCD patients did not appear to have a deficit in odor identification as measured by the UPSIT or in primary olfactory cortex activation in response to odors.

More specifically, in response to *unpleasant* odors, OCD participants had increased activation of their left anterior insula, which positively correlated with their disgust sensitivity and ratings of unpleasantness and intensity of those odors (Fig. 2). Neuroimaging studies show that compared to HC, OCD patients have greater insula activation in response to disgusting images (Shapira et al., 2003; Schienle et al., 2005; Stein et al., 2006). Our results in the olfactory domain (increased insula activation to unpleasant odors) complement previous results in the visual domain and suggest that OCD patients may in fact be more sensitive to unpleasant stimuli across sensory modalities (visual, olfactory, and perhaps also auditory, somatosensory, and gustatory domains). Further, we found that OCD participants' increased anterior insular activation to unpleasant odors correlated with their disgust sensitivity and feelings of unpleasantness and

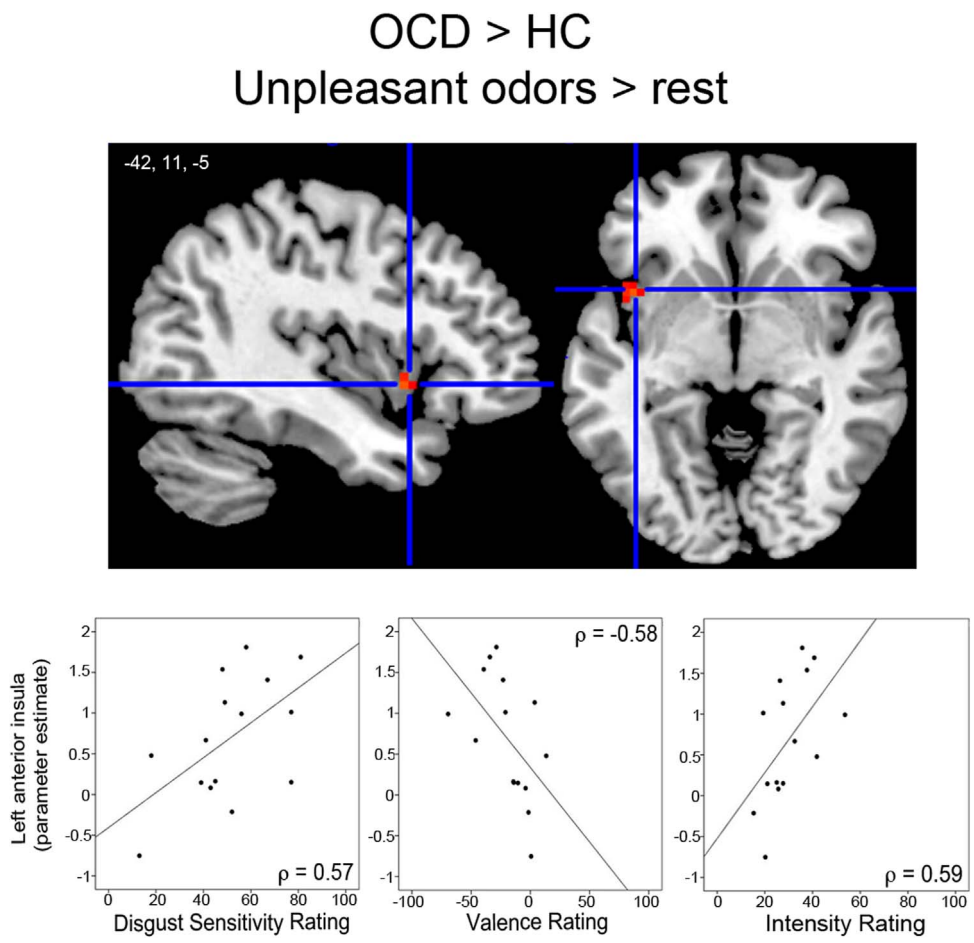

Fig. 2. ROI analysis revealed greater activation of left anterior insula in OCD patients compared to HC for the comparison of unpleasant odors vs. rest. Within the OCD group, this activation was positively correlated with ratings on the Disgust Sensitivity scale and of the intensity of unpleasant odors, and negatively correlated with the valence of unpleasant odors.

intensity of those odors, which implies that OCD patients may have abnormalities in sensory perception that may lead to, or exacerbate, their obsessions and compulsions. These results align with animal data that show that increased cortical-limbic responsiveness (i.e. sensitivity) to sensory stimuli with affective properties can trigger compulsive behaviors (McGrath et al., 1999).

OCD patients also showed greater activation of their caudate nucleus and left anterior and posterior insula in response to *pleasant* odors compared to HC. Their increased neural response to pleasant odors was positively correlated with their self-reported OCD symptom severity (caudate and left anterior insula activation correlated with PI), anxiety (left anterior insula correlated with STAI trait anxiety), feelings of disgust (left anterior insula correlated with SEQ disgust) and intensity ratings of unpleasant odors (left posterior insula correlated with intensity ratings of unpleasant odors). The activation difference in caudate nucleus (and putamen and globus pallidus at trend level) under the pleasant vs. rest condition was not expected. However these results are in line with previous studies that have shown a relationship between increased caudate and insula activation to varying types of stimuli (regardless of valence), OCD symptoms, and feelings of disgust (Schienle et al., 2005; Del Casale et al., 2011; Lapidus et al., 2014; Berlin et al., 2015).

Krusemark and Li's (2012) findings in a healthy sample emphasize an anxiety-related hypersensitivity of the primary olfactory cortex and basic olfactory perception in response to threatening olfactory stimuli. However, when we compared OCD patients to HC we did not find any evidence of hypersensitivity of their primary olfactory cortex or in basic olfactory perception in response to unpleasant olfactory stimuli. Further, we conducted ANCOVAs comparing the groups for the 6 clusters reported while specifying state anxiety as a covariate and the results indicated that group effects were not driven by differences in state anxiety. It may be that anxiety related sensitivity to threatening olfactory stimuli occurs at the basic sensory level (primary olfactory cortex) in healthy people, but that the neural mechanisms involved in hyperresponsivity to unpleasant olfactory stimuli in OCD patients instead involves secondary (higher-order) olfactory areas, like the insula cortex. This coincides with our finding of increased insula activation in response to unpleasant odors in OCD patients and no difference in primary olfactory cortex activation compared to HC.

Interestingly OCD participants had increased anterior insula activation to both pleasant and unpleasant odors, which correlated with increased self-reported disgust. In addition, OCD patients reported experiencing unpleasant odors as subjectively more unpleasant and intense in relation to their increased anterior insula response, and they experienced pleasant odors as less pleasant (numerically), and less intense in the case of vanilla, than HC. It may be that, similar to patients with major depression (Watters and Williams, 2011), OCD patients have a negative cognitive bias and experience all stimuli, regardless of sensory domain, as being slightly more negative than HC, so even “pleasurable” stimuli are experienced as less pleasant (Jhung et al., 2010), although this hypothesis is speculative and requires further investigation. Patients’ increased insular reactivity to both pleasant and unpleasant odors might reflect their propensity to experience negative emotions, which might be a vulnerability factor for OCD (Schienle et al., 2005).

Along these lines, Berlin et al. (2015) found that participants with

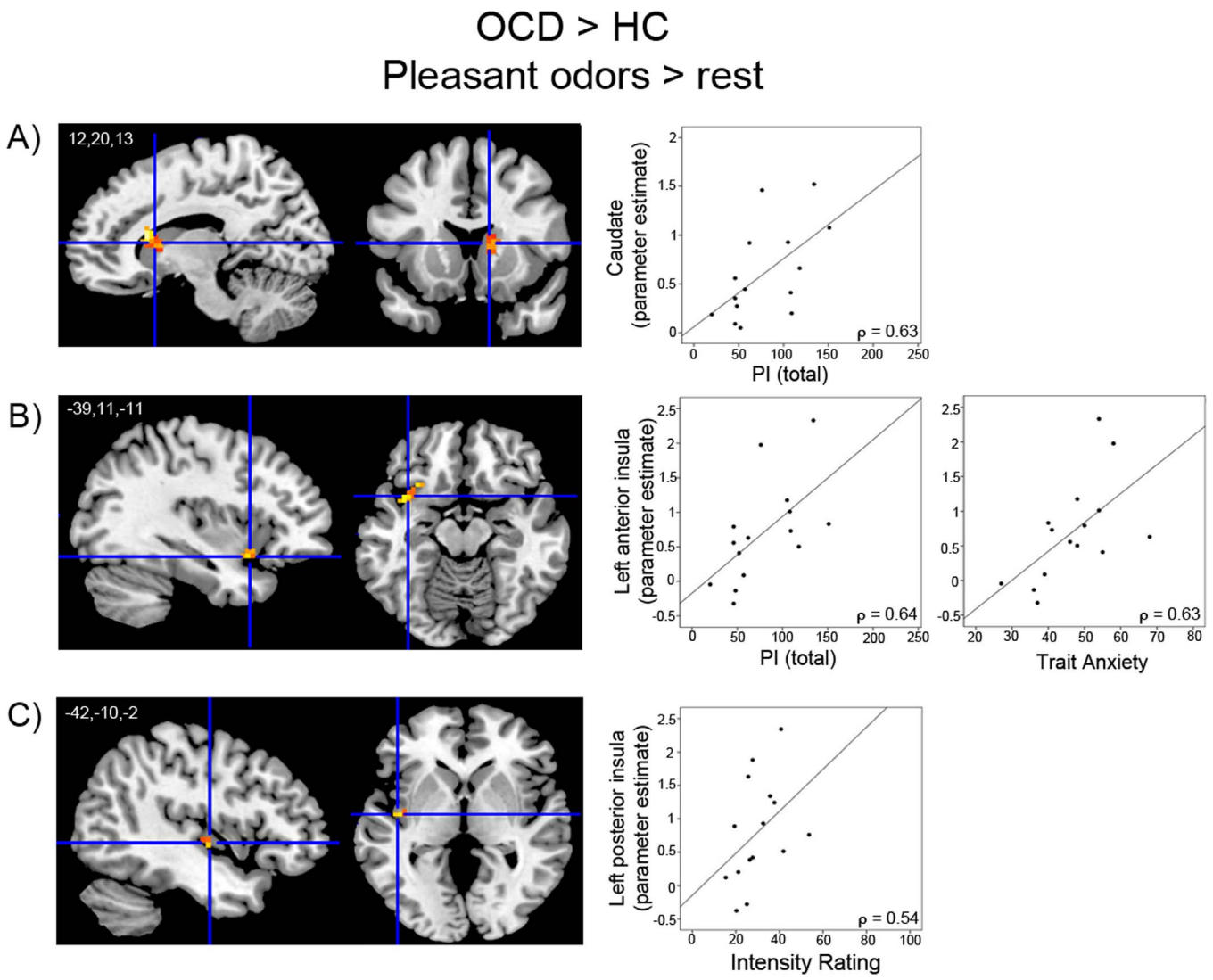

Fig. 3. (A) Greater activation in caudate nucleus for OCD patients compared to HC for pleasant odors (vs. rest), which was positively correlated with self-rated OCD symptoms on the Padua inventory (PI). (B) Greater activation in left anterior insula for OCD patients compared to HC for pleasant odors (vs. rest), which was positively correlated with self-rated OCD symptom severity (PI) and trait anxiety (STAI). C) Greater left posterior insula activation for OCD patients compared to HC for pleasant odors (vs. rest), which was positively correlated with intensity ratings of unpleasant odors.

OCD had significantly greater anterior insula cortex activation when inhibiting responses to both disgusting (bilateral), and fearful (right-sided) images, compared to HC. And there was no evidence of increased amygdala activation in OCD to fearful or disgusting images, compared to HC. The finding that the anterior insula is activated during both fear- and disgust-related inhibition in OCD patients implies that this region may not be implicated specifically in disgust processing (Schienle et al., 2002, 2005). Instead, the insula may play a more general role in modulating the influence of emotions on cognitive functions (Goldin et al., 2008). In fact, the insula has been shown to be involved in affective tasks regardless of the exact emotion, and it may play an important role in a circuit that monitors “ongoing internal emotional states” (i.e., feelings) (Schienle et al., 2002; Damasio et al., 2000). Some have even referred to the insula as the “limbic integration cortex” (Augustine, 1996; Phan et al., 2002). Research also reveals that cognitive strategies that modulate the arousal associated with emotions do so via the insula (Grecucci et al., 2013a, 2013b). Therefore, an alternative interpretation of the present study's findings of increased insula activation to both pleasant and unpleasant olfactory stimuli in OCD is that patients have more difficulty regulating the emotions triggered by sensory stimuli, whether positive or negative, than HC. Studies with larger sample sizes are needed to further explore OCD patients’ abnormal neural response to pleasant stimuli and its relationship to OCD symptoms at both the neural and cognitive/behavioral levels.

Functional neuroimaging studies have conventionally used visual stimuli to investigate dysfunction in the neural networks implicated in OCD. In contrast, olfaction has never been applied to this paradigm. To our knowledge, this is the first study to examine olfaction in OCD patients using fMRI. Our novel findings further elucidate the neural underpinnings of OCD, and may contribute to the development of more effective methods of treatment. Specifically, our findings indicate abnormal functioning in OCD patients’ higher-order olfactory regions, e.g. the insula, related to processing the valence associated with odors (but not in secondary olfactory areas related to odor identification since OCD patients did not have a deficit on the UPSIT). Thus, our results suggest the use cognitive treatment methods to modulate OCD patients’ increased disgust response to primary sensory stimuli. For example, exposure response prevention therapy could be aimed at desensitizing OCD patients to malodors specifically – with habituation of olfactory stimuli being a treatment target – together with cognitive restructuring. Further, our findings suggest that the insula may serve as

Table 2
Group differences in activation during olfaction task.

Condition/region (side)	k	x	y	z	Max z	F/p values for ANCOVA
	OCD > HC					
Unpleasant > Rest						
Anterior insula (L)[a]	8	−42	11	−5	2.8	F=8.2, p=0.008
Pleasant > Rest						
Caudate nucleus (B)[b]	97	12	20	13	4.0	F=26.3, p < 0.001
Putamen (L)[c]	59	−12	−1	103.5	3.5	F=15.9, p < 0.001
Anterior insula (L)[a]	21	−39	11	−11	3.1	F=13.5, p=0.001
Posterior insula (L)[a]	6	−42	−10	−2	2.9	F=9.9, p=0.004
Unpleasant > Pleasant						
Nothing						
Pleasant > Unpleasant						
Anterior insula (L)[a]	9	−39	11	−11	2.8	F=6.7, p=0.015

Notes: k=number of voxels; L=left; R=right; B=both hemispheres; coordinates are in MNI space. There were no regions where HC > OCD in either whole-brain or ROI analyses. All group differences listed above remain significant after including state anxiety as a covariate in post-hoc analyses of covariance.

[a] ROI analyses (uncorrected p < 0.01).

[b] whole-brain corrected (FWE, p < 0.05).

[c] trend-level whole-brain corrected (FWE, p=0.07).

a potential treatment target for OCD. For example, deep transcranial magnetic stimulation therapy could be used to target and modulate OCD patients' increased insula activation to unpleasant (and pleasant) stimuli. Finally, real-time fMRI (i.e., neurofeedback of insula activation) could be used to help OCD patients decrease their own insula activation in response to both unpleasant (and pleasant) images and odors.

One limitation of these results is that several insula clusters were small and not significant at corrected thresholds, so our conclusions are drawn with caution. However, we report results from the ROI analysis in the insula because it was motivated by strong prior evidence of the importance of the insula in OCD and in disgust processing (see introduction). The importance of these insula findings is further bolstered by the association we found between insula activity and several clinical scales, which measure OCD symptomology, disgust sensitivity, and frequency of disgust feelings. Thus, although further research with larger sample sizes will be needed to replicate the present results, these data identify novel effects in OCD and provide an important step toward elucidating the relationship between insula activity and clinical symptoms.

The results of this study warrant further study with larger sample sizes, which will allow us to examine olfactory processing differences between OCD subtypes, specifically between those with contamination type versus non-contamination type OCD. More research is needed to better understand the relationship between OCD symptomology and sensory perception, and how disgust-related neural networks operate in OCD, in order to better characterize the role sensitivity to, and cognitive interpretation of, stimuli plays in the pathophysiology of this disorder. Understanding the neural circuitry of higher-order sensory processing abnormalities in OCD will likely lead to the development of more effective methods of early detection and treatment. For example, sensitivity to odors, as measured by subjective ratings of intensity and valence and hyperactivation of specific neural circuits, may eventually be used as a noninvasive early marker of OCD, much like olfactory sensitivity is used as a marker in Alzheimer's Disease (Doty et al., 1987).

Contributors

Dr. Heather A. Berlin was the Principle Investigator for this study and was involved in its design and execution, data analysis, and paper write-up. Drs. Cheuk Tang and Johnny Ng were involved in the study design, olfactometer engineering, running participants through the neuroimaging protocol, and data analysis. Dr. Emily R. Stern was involved in the data analysis and paper write-up. Sam Zhang, Rachel Turetzky, and David Rosenthal helped with participant recruitment, running participants through the protocol, maintaining the database, data analysis and the paper write-up. Dr. Wayne Goodman was involved in the study conceptualization and oversight of the study.

Conflict of interest

Dr. Heather A. Berlin, Dr. Emily R. Stern, Dr. Johnny Ng, Sam Zhang, David Rosenthal, Rachel Turetzky, and Dr. Cheuk Tang report no conflicts of interest. Dr. Wayne Goodman reports research funding from Roche, Simon Foundation and NIMH.

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