



Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

Neural correlates of emotional response inhibition in obsessive-compulsive disorder: A preliminary study

Heather A. Berlin^{a,b,*}, Kurt P. Schulz^a, Sam Zhang^a, Rachel Turetzky^a, David Rosenthal^a, Wayne Goodman^{a,b}

^a Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY, USA

^b Department of Neuroscience, Icahn School of Medicine at Mount Sinai, New York, NY, USA

ARTICLE INFO

Article history:

Received 6 March 2015

Received in revised form

27 September 2015

Accepted 27 September 2015

Keywords:

Obsessive-compulsive disorder

Insula

Emotion

Inhibition

fMRI

Disgust

Contamination

ABSTRACT

Failure to inhibit recurrent anxiety-provoking thoughts is a central symptom of obsessive-compulsive disorder (OCD). Neuroimaging studies suggest inhibitory control and disgust processing abnormalities in patients with OCD. However, the emotional modulation of response inhibition deficits in OCD and their neural correlates remain to be elucidated. For this preliminary study we administered an adapted affective response inhibition paradigm, an emotional go/no-go task, during fMRI to characterize the neural systems underlying disgust-related and fear-related inhibition in nine adults with contamination-type OCD compared to ten matched healthy controls. Participants with OCD had significantly greater anterior insula cortex activation when inhibiting responses to both disgusting (bilateral), and fearful (right-sided) images, compared to healthy controls. They also had increased activation in several frontal, temporal, and parietal regions, but there was no evidence of amygdala activation in OCD or healthy participants and no significant between-group differences in performance on the emotion go/no-go task. The anterior insula appears to play a central role in the emotional modulation of response inhibition in contamination-type OCD to both fearful and disgusting images. The insula may serve as a potential treatment target for contamination-type OCD.

© 2015 Elsevier Ireland Ltd. All rights reserved.

1. Introduction

Failure to inhibit recurrent anxiety-provoking thoughts is a central feature of OCD (i.e. obsessions) (Chamberlain et al., 2005; 2006). Neural, cognitive, and clinical findings suggest that failures in cognitive and behavioral inhibition processes (indexed by, e.g., go/no-go and oculomotor tasks) are integral to the neuropsychopathology of OCD (Chamberlain et al., 2005). Neuroimaging evidence suggests that abnormal frontal–striatal–thalamic–cortical circuitry may underlie dysfunctional response inhibition in OCD (Rosenberg et al., 1997a; 1997b; Rosenberg and Keshavan, 1998; Chamberlain et al., 2005, 2006; Maltby et al., 2005; Roth et al., 2007; Lee et al., 2009).

Contamination (intense, persistent feeling of having been polluted or infected; Rachman, 2004) concerns are the most common obsessions associated with OCD (Rasmussen and Tsuang, 1986), presenting in up to 50% of OCD patients (Rachman and Hodgson, 1980; Rasmussen and Eisen, 1992). Compulsive cleaning is the

second most common compulsion of OCD (Rachman, 2004). Studies support the role of disgust in contamination-related OCD (Mancini et al., 2001; Thorpe et al., 2003; Tsao and McKay, 2004; Olatunji and Sawchuk, 2005; Olatunji et al., 2005; 2007a; Cisler et al., 2009) and the notion that disgust is distinct from other negative affective states (e.g., anxiety, depression) (Mancini et al., 2001; Woody and Tolin, 2002; Olatunji et al., 2004; Tolin et al., 2006).

Neuroimaging studies have shown that abnormalities of the same neural regions involved in disgust processing in healthy people, the insula cortex and striatum, are also involved in OCD (Phillips et al., 2000; Stein et al., 2001; Berle and Phillips, 2006). Two structural MRI studies found that OCD patients have significantly larger anterior insular cortices bilaterally compared to healthy controls (Nishida et al., 2011; Song et al., 2011). Moreover, functional imaging studies show that OCD patients with predominantly washing symptoms have increased neural responses to washing-related stimuli (Phillips et al., 2000; Mataix-Cols et al., 2004) and to disgusting pictures (Shapira et al., 2003; Schienle et al., 2005) in brain regions implicated in disgust and autonomic response processing, including the anterior insula, ventrolateral prefrontal cortex (PFC), and putamen/globus pallidus (Phillips et al., 1997; 1998; Sprengelmeyer et al., 1998; Calder et al., 2001;

* Correspondence to: Departments of Psychiatry and Neuroscience, Icahn School of Medicine at Mount Sinai One Gustave, L. Levy Place, Box 1230, New York, NY 10029, USA.

E-mail address: heather.berlin@mssm.edu (H.A. Berlin).

<http://dx.doi.org/10.1016/j.psychresns.2015.09.019>

0925-4927/© 2015 Elsevier Ireland Ltd. All rights reserved.

Critchley et al., 2004; Phillips et al., 2004; Lawrence et al., 2007). Studies have also found greater right and left insula activation to disgust-inducing images in OCD patients compared to controls, but no difference in brain activation in response to threat-inducing images (Shapira et al., 2003; Schienle et al., 2006; Stein et al., 2006; Lawrence et al., 2007).

Taken together, these findings suggest inhibitory control and disgust processing abnormalities in patients with OCD. However, the emotional modulation of response inhibition deficits in OCD and their neural correlates remain to be elucidated. Therefore, we employed fMRI in this preliminary study to characterize the neural systems underlying disgust and fear-related inhibition in nine OCD patients compared to ten healthy controls. We hypothesize that compared to healthy controls OCD subjects will make more commission errors in response to emotional stimuli compared to healthy controls on our emotional go/no-go task. We also predict that OCD subjects will have greater activation of insula during emotional response inhibition compared to controls.

Our approach focuses on understanding how neural circuits associated with response inhibition may become dysregulated in the context of emotion in OCD. Prior research examining inhibitory control in OCD has localized group differences to orbito-frontal–striatal circuitry; however, the use of non-emotional, neutral stimuli in those studies neglects to address the importance of emotion processing, potentially obscuring the identification of broader neural dysfunction in the disorder. This is particularly important for understanding neural mechanisms of inhibitory control in OCD, which is characterized by difficulty regulating behaviors in response to specific symptom-related stimuli that elicit fear and disgust. As such, a thorough understanding of the neural mechanisms underlying impaired response inhibition in OCD must take into account the types of emotional situations that elicit this impairment. Our use of a novel emotional go/no-go task represents an important step toward characterizing behavioral and neural functioning using an ecologically-valid measure that taps directly into symptoms of OCD.

2. Methods

2.1. Participants

Twenty participants between the ages of 18 and 65 (inclusive) were recruited for this study. The study was carried out in accordance with the Declaration of Helsinki, and written informed consent was obtained from all participants.

2.2. Screening measures and questionnaires

At screening, participants were administered the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999); exclusion criteria ($IQ \leq 70$) and the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (First et al., 1997). Participants in the OCD group were required to meet diagnostic criteria for contamination-type OCD with minimal comorbid diagnoses, while a diagnosis of any clinical disorder on the SCID-I precluded participation as a healthy control. All eligible participants were given a visual acuity test and a toxicology test, and all female applicants were tested for pregnancy. Participants who failed any of these tests were excluded. (Note: one healthy control subject had insufficient specimen for an extended toxicology panel.)

Participants were also administered the following clinical measures: Yale–Brown Obsessive Compulsive Scale (Y-BOCS) (Goodman et al., 1989), Disgust Scale – Revised (DSR) (Olatunji et al., 2007b), Hamilton Measure of Depression (HAM-D) (Hamilton, 1960), and the State-Trait Anxiety Inventory (STAI)

(Spielberger et al., 1971).

2.3. Imaging task

2.3.1. Emotion go/no-go task

The emotion go/no-go task was adapted from an established face go/no-go task (Schulz et al., 2009, 2013). The task consisted of six 5-min blocks that each began and ended with a 30-s central fixation-cross. Each block contained 72 (75%) go cues and 24 (25%) no-go cues, yielding a total of 432 go cues and 144 no-go cues. Images from the International Affective Picture System (IAPS) (Lang et al., 2008) that conveyed fear (depicting snakes, guns, and attacks), disgust (depicting roaches, garbage, feces, and vomit; and three non-IAPS images), and neutral (depicting modes of transportation) content served as cues for no-go trials. Fear and disgust images were selected based on ratings published in Mikels et al. (2005). The images were matched on ratings of arousal and dominance, but differed in ratings of valence ($F_{2, 66} = 108.44$, $p < 0.001$; Lang et al., 1997). Fear and disgust images were rated as more unpleasant than neutral images (both $p < 0.01$), but did not differ from each other ($p > 0.05$).

The fear, disgust, and neutral images were alternated as no-go trial cues across the six blocks in an ABBCCA design that was fixed for all subjects, in order to test the emotional modulation of response inhibition. IAPS images that depicted household images served as go trial cues across all six blocks. Trial cues were presented in the center of the screen for 1000 ms with an inter-stimulus interval that was pseudo-randomized from 1250 to 1750 ms (mean per block = 1500 ms) and denoted by a fixation-cross. Participants were instructed to respond as rapidly as possible to go cues using a fiber optic button system and withheld responses for no-go cues. Responses provided measures of reaction time and accuracy.

2.3.2. Image acquisition

All participants were scanned on a 3.0 T Siemens Allegra (Siemens, Erlangen, Germany) head-dedicated MRI scanner. Functional T2*-weighted images depicting the blood oxygenation level-dependent (BOLD) signal were obtained in six runs of 120 volumes each using gradient-echo echo-planar images (TR = 2500 ms, TE = 27 ms, flip angle = 82°, FOV = 240 mm, matrix = 64 × 64, slice thickness = 4 mm contiguous, in-plane resolution = 3.75 mm²). A high-resolution T2-weighted anatomical image was acquired at the same 40 slice locations with a turbo spin-echo (TSE) pulse sequence (slice thickness = 4 mm contiguous, in-plane resolution = 0.41 mm²). Images were acquired in the axial plane with slices positioned parallel to the anterior commissure–posterior commissure line.

2.3.3. Behavioral data analysis

The percentage of correct inhibitions on no-go trials served as the measure of response inhibition and was tested with a repeated-measures analysis of variance (ANOVA) that included emotion (disgust vs. fear vs. neutral) as the within-subjects factor and group (OCD vs. controls) as the between-subjects factor. Group differences in reaction time (RT) and the percentage of correct responses on go trials were tested with independent sample *t*-tests. The two-tailed *p*-value for significance was 0.05. Partial eta squared (η_p^2) and Cohen's *d* values were calculated to estimate the size of the emotion and group effects on behavioral performance. Performance data were not available from one adult with OCD due to technical difficulties.

2.3.4. fMRI data analysis

Event-related analyses were performed with SPM8 software (<http://www.fil.ion.ucl.ac.uk/spm/>). The six functional series for

each participant were slice-time corrected, motion corrected, co-registered to the T2 anatomical volume, spatially normalized to the Montreal Neurological Institute (MNI) template, and smoothed with an 8-mm Gaussian kernel. Single-subject general linear models (GLM) were conducted to fit beta weights to regressors for the four trial events (correct no-go, correct go, incorrect no-go, incorrect go) in each run, as well as six motion parameters of no interest (Johnstone et al., 2006), convolved with the default SPM hemodynamic response function (Friston et al., 1998). The neural effect of emotion on response inhibition was tested by applying appropriate contrasts separately to the beta weights for correct no-go events cued by fear and disgust images minus correct no-go events cued by neutral images, resulting in 2 contrast maps per participant.

The two contrast images for each participant were entered into second-level group analyses conducted with random-effects GLM. Two-sample *t* tests were conducted to analyze group differences in the contrasts of interest. The resultant voxel-wise statistical maps were thresholded for significance using a cluster-size algorithm that protects against false-positive results (Hayasaka et al., 2004). The height (intensity) threshold of each activated voxel was set at a *p* value of 0.005 and the extent (cluster) threshold was fixed at $\kappa > 100$ contiguous voxels. Prior Monte Carlo simulations confirms the current voxel contiguity threshold (Schulz et al., 2013).

2.4. Questionnaire and descriptive analysis

Independent sample *t*-tests were performed to compare group differences in descriptive and questionnaire variables, using a two-tailed alpha level of 0.05.

3. Results

3.1. Demographics

Twenty subjects were recruited for this study, but one participant was excluded for failing the drug screen. The OCD group consisted of 9 participants (5 males) with clinically diagnosed contamination-type OCD (Mean age=38.33 years, SD=11.23). They were compared to 10 healthy control participants (5 male) (Mean age=38.70 years, SD=11.97) matched for age, gender, handedness education, ethnicity, employment, and IQ. There were no significant differences between groups on these measures at alpha level 0.05, except for "education level" for which OCD participants had slightly more education ($M=9.50$, $SD=1.00$) than healthy controls ($M=7.40$, $SD=1.71$), $t(12)=2.27$, $p=0.043$.

The obsessions and compulsions reported by the OCD group were grouped into the following subtypes: contamination ($n=9$), harm obsessions and/or checking compulsions ($n=8$), just right/symmetry obsessions and/or ordering, arranging and counting compulsions or perfectionism ($n=5$), and hoarding ($n=1$).

Current comorbid psychiatric diagnoses in the OCD group were (overlapping): recurrent major depressive disorder (MDD; $n=2$), a current major depressive episode (MDE; $n=2$), dysthymic disorder ($n=3$), panic disorder (without agoraphobia) ($n=1$), social phobia ($n=1$), generalized anxiety disorder ($n=2$), anorexia nervosa ($n=1$), and binge-eating disorder ($n=1$). However, OCD was the primary diagnosis for all subjects in this group.

Further, 8 patients with OCD were taking psychotropic medication (one or more of the following: Lexapro, Cymbalta, Luvox, Fluoxetine, Prozac, Klonopin, Wellbutrin, and Zoloft) and 3 patients were undergoing psychological treatment intended to improve their OCD symptoms, however the OCD group still had significant levels of symptomatology/pathology (see Table 1).

Table 1

Questionnaire means, standard deviations, and *p*-values.

Variable	OCD (N=9)		HC (N=10)		<i>p</i> -value
	Mean	SD	Mean	SD	
Y-BOCS	23.56	5.46	0.00	0.00	0.000**
DSR Core Disgust	10.61	8.28	6.18	2.47	0.124
DSR Animal Reminder	7.47	6.47	3.58	1.86	0.085
DSR Contamination Disgust	3.39	2.10	1.23	1.00	0.010**
DSR Total	20.36	13.37	10.88	4.16	0.047*
STAI State Anxiety	46.33	15.88	24.90	4.20	0.003**
STAI Trait Anxiety	51.56	9.08	29.60	5.06	0.000**
STAI Total	97.89	18.54	54.50	8.02	0.000**
HAMD	6.00	5.03	0.60	0.70	0.012*

Notes: Y-BOCS=Yale-Brown Obsessive Compulsive Scale; DSR=Disgust Scale – Revised; STAI=State-Trait Anxiety Inventory; HAMD=Hamilton Measure of Depression

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

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

3.2. Questionnaires

OCD patients scored significantly higher than healthy controls on the: Y-BOCS, $t(8.00)=12.95$, $p < 0.001$; DSR total, $t(17)=2.14$, $p < 0.05$, and DSR contamination disgust subscore, $t(17)=2.92$, $p=0.01$; STAI total, $t(6.50)=10.65$, $p < 0.001$, STAI state anxiety, $t(9.01)=3.93$, $p < 0.01$, and STAI trait anxiety, $t(17)=6.60$, $p < 0.001$; and HAMD, $t(8.28)=3.20$, $p=0.01$. See Table 1 for questionnaire means and standard deviations.

3.3. Behavioral data

There were no significant differences in performance on the emotion go/no-go task between adults with OCD and healthy volunteers (Table 2). The ANOVA that assessed the percentage of correct inhibitions found no main effects of emotion ($F_{2, 32}=0.32$, $p=0.73$, $\eta_p^2=0.02$) or group ($F_{1, 16}=0.004$, $p=0.95$, $\eta_p^2 < 0.01$), and no emotion \times group interaction ($F_{2, 32}=2.22$, $p=0.13$, $\eta_p^2=0.14$). There were also no group differences in the percentage of correct responses ($t_{16}=1.96$, $p=0.07$, Cohen's $d=0.87$) or RT ($t_{16}=-0.51$, $p=0.07$, Cohen's $d=0.23$).

3.4. fMRI data

Neural activation for the successful inhibition of responses to disgust images (correct disgust no-go events minus correct neutral no-go events) was seen throughout frontal cortex and cerebellum in adults with OCD, but was limited to pre-supplementary motor and inferior temporal areas in healthy volunteers (see Supplementary Table 1). As shown in Fig. 1, direct comparison of the two groups revealed significantly greater activation in anterior insula

Table 2

Measures of performance on the emotion go/no-go task.

Measure	Control (N=10)	OCD (N=8) ^a
<i>No-go trials</i>		
Correct inhibitions (%)		
Disgust cues	97.1 \pm 3.3	95.3 \pm 9.2
Fear cues	97.9 \pm 3.4	96.6 \pm 6.5
Neutral cues	95.2 \pm 7.5	98.7 \pm 1.6
<i>Go trials</i>		
Correct responses (%)	98.0 \pm 3.3	86.1 \pm 19.0
Reaction time (ms)	610 \pm 78	632 \pm 112

^a Data were unavailable from one participant.

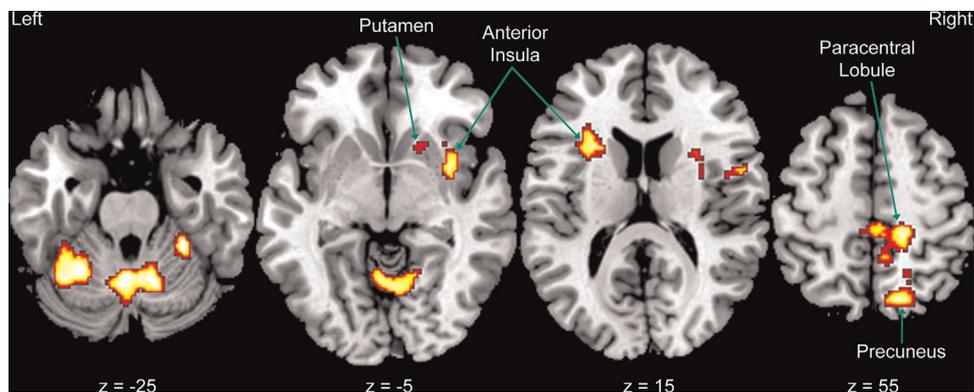


Fig. 1. Regions of significantly greater activation for the inhibition of responses to disgust images (correct disgust no-go events minus correct neutral no-go events) in participants with OCD compared to healthy controls. Figures are thresholded at $p < 0.005$ (corrected for multiple comparisons with a cluster threshold > 100 voxels). Numbers at bottom indicate z coordinates in the Montreal Neurological Institute brain template space.

bilaterally, as well as right putamen, paracentral lobule, precuneus, and bilateral cerebellum in OCD participants compared to healthy controls.

The inhibition of responses to fear images (correct fear no-go events minus correct neutral no-go events) also engendered extensive frontal, temporal, parietal, and subcortical activation in adults with OCD but more limited frontotemporal activation in healthy volunteers (see [Supplementary Table 2](#)). Direct comparison of the two groups found that adults with OCD showed significantly greater activation in right anterior insula, as well as anterior cingulate cortex, motor cortex, left superior temporal gyrus, right fusiform gyrus, precuneus, and brainstem compared to healthy volunteers ([Fig. 2](#)). There was no evidence of activation in amygdala in either adults with OCD or healthy volunteers, even when a small volume correction was used to account for the small size of the structure.

4. Discussion

Our results provide preliminary evidence of neural abnormalities associated with the inhibition of responses to emotional stimuli in contamination-type OCD. Although there were no significant between-group differences in the behavioral measure of response inhibition on the emotion go/no-go task, there were significant between-group differences in neural activation. Our data shows that inhibiting a response to both disgusting and fearful images requires more neural activation in OCD patients than in healthy controls. Patients with OCD also missed more responses on the go/no-go task than healthy controls; this difference did not reach significance in the small sample, but points to a more

general deficit in attention that may have contributed to the group differences in activation for response inhibition.

The insula in particular appears to play a central role in the emotional modulation of response inhibition in OCD to both fearful and disgusting images. Our finding that the anterior insula is activated during both fear- and disgust-related inhibition suggests 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](#)). Along these lines, the insula has been shown to be involved in affective tasks regardless of the specific emotion, and [Damasio et al. \(2000\)](#) suggests the insula plays a key role in a circuit that monitors “ongoing internal emotional states” (i.e., feelings) ([Schienle et al., 2002](#)). In fact, some have referred to the insula as the “limbic integration cortex” ([Augustine, 1996; Phan et al., 2002](#)).

Research also suggests that cognitive strategies that modulate the arousal associated with emotions do so via the insula ([Grecucci et al., 2013a, 2013b](#)). Therefore, the increased insula activation OCD patients demonstrated in our study during both fear- and disgust-related inhibition may indicate that they have more difficulty regulating their emotions in order to perform a cognitive/behavioral task (in this case inhibition) than healthy controls. Participants with OCD appeared to need increased insula activation to perform the emotional go–no-go on par with healthy controls. Whether this reflects an increased emotional response to aversive stimuli, difficulty in modulating emotions to aversive stimuli, or a more general deficit in attention, as evidenced by the large but non-significant number of missed responses on go trials, remains to be elucidated.

The failure to find amygdala activation in either group of

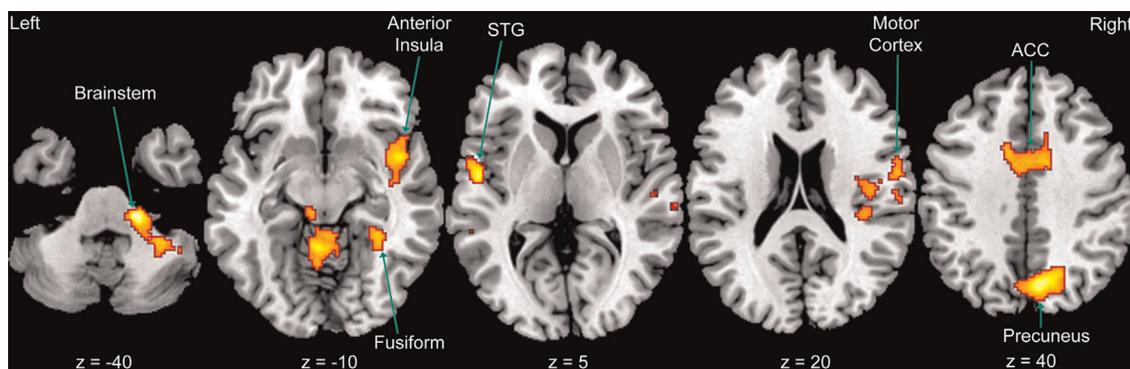


Fig. 2. Regions of significantly greater activation for the inhibition of responses to fear images (correct fear no-go events minus correct neutral no-go events) in participants with OCD compared to healthy controls. Figures are thresholded at $p < 0.005$ (corrected for multiple comparisons with a cluster threshold > 100 voxels). Numbers at bottom indicate z coordinates in the Montreal Neurological Institute brain template space. ACC, anterior cingulate cortex; STG, superior temporal gyrus.

participants may reflect the attentional processing demands of the emotion go/no-go task, the difficulty with imaging the region (e.g., susceptibility artifacts; LaBar et al., 2001), and/or simply Type II error. Tasks requiring participants to focus on, label, and respond (or not) to emotional stimuli have been shown to diminish amygdala responses to disgusting and fearful images (Costafreda et al., 2008). Furthermore, the small sample size in this pilot study may have limited the power to detect such subtle effects, but does not detract from our findings of significant group differences in activation for response inhibition. The results must therefore be considered preliminary until confirmed in larger studies.

We excluded patients from the OCD group if they had current or lifetime DSM-IV-TR diagnosis of bipolar disorders or psychotic disorder/psychosis, or current or recent (within six months) DSM-IV-TR diagnosis of substance/alcohol abuse or dependence or a positive urine screen indicating substance/alcohol use. However, we did not exclude individuals in the OCD patient group with other psychiatric disorders. We view this sampling method as advantageous since most individuals with OCD present with at least one comorbid disorder, major depression being the most common (Overbeek et al., 2002; Pallanti et al., 2011). By not excluding for common comorbidities we have greater confidence that our sample is more representative of OCD in the general population. In addition, we did not exclude OCD patient who were undergoing psychopharmacological or psychological treatments aimed at alleviating their OCD symptoms as this provides a more ecologically valid sample. And despite these treatments, our OCD sample still had significant OCD symptomology (see Table 1).

This is the first study, to our knowledge, to examine emotional response inhibition in OCD patients using fMRI. Our findings suggest that the insula may serve as a potential target for treating contamination-type OCD. For example, deep transcranial magnetic stimulation therapy could be used to target and modulate OCD patients' increased insula activation to aversive stimuli. Or real-time fMRI, i.e. neurofeedback, of insula activation could be used to help OCD patients decrease their own insula activation in response to aversive stimuli.

Contributors

Dr. Heather A. Berlin was the PI for this study and was involved in it's design and execution, data analysis, and paper write-up. Dr. Kurt P. Schulz oversaw the neuroimaging protocol, and was involved in data analysis and paper write-up. Sam Zhang, Rachel Turetzky, and David Rosenthal helped with subject recruitment, running subjects through the protocol, maintaining the database, data analysis and paper write-up. Wayne Goodman was involved in the study conceptualization and oversight of the study.

Conflicts of interest

Dr. Heather A. Berlin, Dr. Kurt P. Schulz, Sam Zhang, Rachel Turetzky, and David Rosenthal report no conflicts of interest. Dr. Wayne Goodman reports research funding from Roche, Simon Foundation and NIMH.

Acknowledgment

This study was supported by a grant from the International OCD Foundation. Dr. Andrew Gilbert assisted with grant submission, James Fisher assisted with subject recruitment and research coordination and Jai Bhatt assisted with data entry.

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.psychresns.2015.09.019>.

References

- Augustine, J.R., 1996. Circuitry and functional aspects of the insular lobe in primates including humans. *Brain Res. Brain Res. Rev.* 22, 229–244.
- Berle, D., Phillips, E.S., 2006. Disgust and obsessive-compulsive disorder: an update. *Psychiatry* 69, 228–238.
- Calder, A.J., Lawrence, A.D., Young, A.W., 2001. Neuropsychology of fear and loathing. *Nat. Rev. Neurosci.* 2, 352–363.
- Chamberlain, S.R., Blackwell, A.D., Fineberg, N.A., Robbins, T.W., Sahakian, B.J., 2005. The neuropsychology of obsessive compulsive disorder: the importance of failures in cognitive and behavioural inhibition as candidate endophenotypic markers. *Neurosci. Biobehav. Rev.* 29, 399–419.
- Chamberlain, S.R., Fineberg, N.A., Blackwell, A.D., Robbins, T.W., Sahakian, B.J., 2006. Motor inhibition and cognitive flexibility in obsessive compulsive disorder and trichotillomania. *Am. J. Psychiatry* 163, 1282–1284.
- Cisler, J.M., Olatunji, B.O., Lohr, J.M., 2009. Disgust, fear, and the anxiety disorders: a critical review. *Clin. Psychol. Rev.* 29, 34–46.
- Costafreda, S.G., Brammer, M.J., David, A.S., Fu, C.H., 2008. Predictors of amygdala activation during the processing of emotional stimuli: a meta-analysis of 385 PET and fMRI studies. *Brain Res. Rev.* 58, 57–70.
- Critchley, H.D., Wiens, S., Rotshtein, P., Öhman, A., Dolan, R.J., 2004. Neural systems supporting interoceptive awareness. *Nat. Neurosci.* 7, 189–195.
- Damasio, A.R., Grabowski, T.J., Bechara, A., Damasio, H., Ponto, L.L., Parvizi, J., Hichwa, R.D., 2000. Subcortical and cortical brain activity during the feeling of self-generated emotions. *Nat. neurosci.* 3, 1049–1056.
- First, M., Spitzer, R., Gibbon, M.J.W., 1997. *User's Guide for the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID)*. American Psychiatric Press, Washington, D.C.
- Friston, K.J., Fletcher, P., Josephs, O., Holmes, A., Rugg, M.D., Turner, R., 1998. Event-related fMRI: characterizing differential responses. *NeuroImage* 7, 30–40.
- Goldin, P.R., McRae, K., Ramel, W., Gross, J.J., 2008. The neural bases of emotion regulation: reappraisal and suppression of negative emotion. *Biol. Psychiatry* 63, 577–586.
- Goodman, W.K., Price, L.H., Rasmussen, S.A., Mazure, C., Fleischmann, R.L., Hill, C.L., Heninger, G.R., Charney, D.S., 1989. The Yale–Brown Obsessive Compulsive Scale. I. Development, use, and reliability. *Arch. Gen. Psychiatry* 46, 1006–1011.
- Greucci, A., Giorgetta, C., Bonini, N., Sanfey, A.G., 2013a. Reappraising social emotions: the role of inferior frontal gyrus, temporo-parietal junction and insula in interpersonal emotion regulation. *Front. Hum. Neurosci.* 7, 523.
- Greucci, A., Giorgetta, C., Van't Wout, M., Bonini, N., Sanfey, A.G., 2013b. Reappraising the ultimatum: an fMRI study of emotion regulation and decision making. *Cereb. Cortex* 23, 399–410.
- Hamilton, M., 1960. A rating scale for depression. *J. Neurol., Neurosurg. Psychiatry* 23, 56–62.
- Hayasaka, S., Phan, K.L., Liberzon, I., Worsley, K.J., Nichols, T.E., 2004. Nonstationary cluster-size inference with random field and permutation methods. *NeuroImage* 22, 676–687.
- Johnstone, T., Ores Walsh, K.S., Greischar, L.L., Alexander, A.L., Fox, A.S., Davidson, R. J., Oakes, T.R., 2006. Motion correction and the use of motion covariates in multiple-subject fMRI analysis. *Hum. Brain Mapp.* 27, 779–788.
- LaBar, K.S., Gitelman, D.R., Mesulam, M.M., Parrish, T.B., 2001. Impact of signal-to-noise on functional MRI of the human amygdala. *Neuroreport* 12, 3461–3464.
- Lang, P.J., Bradley, M.M., Cuthbert, B.N., 2008. *International Affective Picture System (IAPS): Affective Ratings of Pictures and Instruction Manual*. Technical Report A-8. University of Florida, Gainesville, FL.
- Lang, P.J., Bradley, M.M., Cuthbert, B.N., 1997. *International Affective Picture System (IAPS): Technical Manual and Affective Ratings*. NIMH Center for the Study of Emotion and Attention, U.o.F., Gainesville, FL.
- Lawrence, N.S., An, S.K., Mataix-Cols, D., Ruths, F., Speckens, A., Phillips, M.L., 2007. Neural responses to facial expressions of disgust but not fear are modulated by washing symptoms in OCD. *Biol. Psychiatry* 61, 1072–1080.
- Lee, H.J., Yost, B.P., Telch, M.J., 2009. Differential performance on the go/no-go task as a function of the autogenous-reactive taxonomy of obsessions: findings from a non-treatment seeking sample. *Behav. Res. Ther.* 47, 294–300.
- Maltby, N., Tolin, D.F., Worhunsky, P., O'Keefe, T.M., K.A., K., 2005. Dysfunctional action monitoring hyperactivates frontal-striatal circuitry in obsessive-compulsive disorder: an event-related fMRI study. *NeuroImage* 24, 495–503.
- Mancini, F., Gagnani, A., D'Olimpio, F., 2001. The connection between disgust and obsessions and compulsions in a non-clinical sample. *Personal. Individ. Differ.* 31, 1173–1180.
- Mataix-Cols, D., Wooderson, S., Lawrence, N., Brammer, M.J., Speckens, A., Phillips, M.L., 2004. Distinct neural correlates of washing, checking, and hoarding symptom dimensions in obsessive-compulsive disorder. *Arch. Gen. Psychiatry* 61, 564–576.
- Mikels, J.A., Fredrickson, B.L., Larkin, G.R., Lindberg, C.M., Maglio, S.J., Reuter-Lorenz, P.A., 2005. Emotional category data on images from the International Affective

- Picture System. *Behav. Res. Methods* 37, 626–630.
- Nishida, S., Narumoto, J., Sakai, Y., Matsuoka, T., Nakamae, T., Yamada, K., Nishimura, T., Fukui, K., 2011. Anterior insular volume is larger in patients with obsessive-compulsive disorder. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* 35, 997–1001.
- Olatunji, B.O., Lohr, J.M., Sawchuk, C.N., Tolin, D.F., 2007a. Multimodal assessment of disgust in contamination-related obsessive-compulsive disorder. *Behav. Res. Ther.* 45, 263–276.
- Olatunji, B.O., Sawchuk, C.N., 2005. Disgust: characteristic features, social implications, and clinical manifestations. *J. Soc. Clin. Psychol.* 24, 932–962.
- Olatunji, B.O., Sawchuk, C.N., Arrindell, W., Lohr, J.M., 2005. Disgust sensitivity as a mediator of the sex difference in contamination fears. *Personal. Individ. Differ.* 38, 713–722.
- Olatunji, B.O., Sawchuk, C.N., Lohr, J.M., de Jong, P.J., 2004. Disgust domains in the prediction of contamination fear. *Behav. Res. Ther.* 42, 93–104.
- Olatunji, B.O., Williams, N.L., Tolin, D.F., Abramowitz, J.S., Sawchuk, C.N., Lohr, J.M., Elwood, L.S., 2007b. The Disgust Scale: item analysis, factor structure, and suggestions for refinement. *Psychol. Assess.* 19, 281–297.
- Overbeek, T., Schruers, K., Vermetten, E., Griez, E., 2002. Comorbidity of obsessive-compulsive disorder and depression: prevalence, symptom severity, and treatment effect. *J. Clin. Psychiatry* 63, 1106–1112.
- Pallanti, S., Grassi, G., Sarrecchia, E.D., Cantisani, A., Pellegrini, M., 2011. Obsessive-compulsive disorder comorbidity: clinical assessment and therapeutic implications. *Front. Psychiatry* 2, 70.
- Phan, K.L., Wager, T., Taylor, S.F., Liberzon, I., 2002. Functional neuroanatomy of emotion: a meta-analysis of emotion activation studies in PET and fMRI. *NeuroImage* 16, 331–348.
- Phillips, M.L., Marks, I.M., Senior, C., Lythgoe, D., O'Dwyer, A.M., Meehan, O., Williams, S.C., Brammer, M.J., Bullmore, E.T., McGuire, P.K., 2000. A differential neural response in obsessive-compulsive disorder patients with washing compared with checking symptoms to disgust. *Psychol. Med.* 30, 1037–1050.
- Phillips, M.L., Williams, L.M., Heining, M., Herba, C.M., Russell, T., Andrew, C., Bullmore, E.T., Brammer, M.J., Williams, S.C., Morgan, M., Young, A.W., Gray, J.A., 2004. Differential neural responses to overt and covert presentations of facial expressions of fear and disgust. *NeuroImage* 21, 1484–1496.
- Phillips, M.L., Young, A.W., Scott, S.K., Calder, A.J., Andrew, C., Giampietro, V., Williams, S.C., Bullmore, E.T., Brammer, M., Gray, J.A., 1998. Neural responses to facial and vocal expressions of fear and disgust. *Proc. R. Soc. Lond., B Biol. Sci.* 265, 1809–1817.
- Phillips, M.L., Young, A.W., Senior, C., Brammer, M., Andrew, C., Calder, A.J., Bullmore, E.T., Perrett, D.I., Rowland, D., Williams, S.C., Gray, J.A., David, A.S., 1997. A specific neural substrate for perceiving facial expressions of disgust. *Nature* 389, 495–498.
- Rachman, S., 2004. Fear of contamination. *Behav. Res. Ther.* 42, 1227–1255.
- Rachman, S., Hodgson, R.J., 1980. *Obsessions and Compulsions*. Prentice Hall, Englewood Cliffs, NJ.
- Rasmussen, S.A., Eisen, J.L., 1992. The epidemiology and clinical features of obsessive compulsive disorder. *Psychiatr. Clin. N. Am.* 15, 743–758.
- Rasmussen, S.A., Tsuang, M.T., 1986. Clinical characteristics and family history in DSM-III obsessive-compulsive disorder. *Am. J. Psychiatry* 143, 317–322.
- Rosenberg, D.R., Averbach, D.H., O'Hearn, K.M., Seymour, A.B., Birmaher, B., Sweeney, J.A., 1997a. Oculomotor response inhibition abnormalities in pediatric obsessive-compulsive disorder. *Arch. Gen. Psychiatry* 54, 831–838.
- Rosenberg, D.R., Dick, E.L., O'Hearn, K.M., Sweeney, J.A., 1997b. Response-inhibition deficits in obsessive-compulsive disorder: an indicator of dysfunction in frontostriatal circuits. *J. Psychiatry Neurosci.* 22, 29–38.
- Rosenberg, D.R., Keshavan, M.S., 1998. Toward a neurodevelopmental model of obsessive-compulsive disorder. *Biolog. Psychiatry*, 43.
- Roth, R.M., Saykin, A.J., Flashman, L.A., Pixley, H.S., West, J.D., Mamourian, A.C., 2007. Event-related functional magnetic resonance imaging of response inhibition in obsessive-compulsive disorder. *Biol. Psychiatry* 62, 901–909.
- Schienze, A., Schäfer, A., Hermann, A., Walter, B., Stark, R., Vaitl, D., 2006. fMRI responses to pictures of mutilation and contamination. *Neurosci. Lett.* 393, 174–178.
- Schienze, A., Schäfer, A., Stark, R., Walter, B., Vaitl, D., 2005. Neural responses of OCD patients towards disorder-relevant, generally disgust-inducing and fear-inducing pictures. *Int. J. Psychophysiol.* 57, 69–77.
- Schienze, A., Stark, R., Walter, B., Blecker, C., Ott, U., Kirsch, P., Sammer, G., Vaitl, D., 2002. The insula is not specifically involved in disgust processing: an fMRI study. *NeuroReport* 13, 2023–2026.
- Schulz, K.P., Clerkin, S.M., Fan, J., Halperin, J.M., Newcorn, J.H., 2013. Guanfacine modulates the influence of emotional cues on prefrontal cortex activation for cognitive control. *Psychopharmacology* 226, 261–271.
- Schulz, K.P., Clerkin, S.M., Halperin, J.M., Newcorn, J.H., Tang, C.Y., Fan, J., 2009. Dissociable neural effects of stimulus valence and preceding context during the inhibition of responses to emotional faces. *Hum. Brain Mapp.* 30, 2821–2833.
- Shapira, N.A., Liu, Y., He, A.G., Bradley, M.M., Lessig, M.C., James, G.A., Stein, D.J., Lang, P.J., Goodman, W.K., 2003. Brain activation by disgust-inducing pictures in obsessive-compulsive disorder. *Biol. Psychiatry* 54, 751–756.
- Song, A., Jung, W.H., Jang, J.H., E., K., Shim, G., Park, H.Y., Choi, C.H., S., K.J., 2011. Disproportionate alterations in the anterior and posterior insular cortices in obsessive-compulsive disorder. *PLoS One* 6, e22361.
- Spielberger, C.D., Gorsuch, R.L., Lushere, R.E., 1971. *State-Trait Anxiety Inventory*. Consulting Psychologists Press, Palo Alto, CA.
- Sprengelmeyer, R., Rausch, M., Eysel, U.T., Przuntek, H., 1998. Neural structures associated with recognition of facial expressions of basic emotions. *Proc. R. Soc. Lond., B Biol. Sci.* 265, 1927–1931.
- Stein, D.J., Arya, M., Pietrini, P., Rapoport, J.L., Swedo, S.E., 2006. Neurocircuitry of disgust and anxiety in obsessive-compulsive disorder: a positron emission tomography study. *Metab. Brain Dis.* 21, 267–277.
- Stein, D.J., Liu, Y., Shapira, N.A., Goodman, W.K., 2001. The psychobiology of obsessive-compulsive disorder: how important is the role of disgust? *Curr. Psychiatry Rep.* 3, 281–287.
- Thorpe, S.J., Patel, S.P., Simonds, L.M., 2003. The relationship between disgust sensitivity, anxiety and obsessions. *Behav. Res. Ther.* 41, 1397–1409.
- Tolin, D.F., Woods, C.M., Abramowitz, J.S., 2006. Disgust sensitivity and obsessive-compulsive symptoms in a nonclinical sample. *J. Behav. Ther. Exp. Psychiatry* 37, 30–40.
- Tsao, S.D., McKay, D., 2004. Behavioral avoidance tests and disgust in contamination fears: distinctions from trait anxiety. *Behav. Res. Ther.* 42, 207–216.
- Wechsler, D., 1999. *Wechsler Abbreviated Scale of Intelligence*, 3rd ed. The Psychological Corporation, San Antonio, TX.
- Woody, S.R., Tolin, D.F., 2002. The relationship between disgust sensitivity and avoidant behavior: studies of clinical and nonclinical samples. *J. Anxiety Disord.* 16, 543–559.