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The functional magnetic resonance imaging-based verbal fluency test in obsessive–compulsive disorder

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Clinical use of functional magnetic resonance imaging (fMRI) in obsessive–compulsive disorder (OCD) is limited by a relative absence of fMRI task development, standardization, and normative performance databases. We investigated the fMRI-based verbal fluency test (f-VFT) by quantitatively evaluating brain activation patterns in OCD participants (8 females and 4 males) compared with a normative database (16 females and 16 males). At the group level, OCD participants and references had highly similar activation in left-hemisphere language regions, including the precentral/premotor cortex, thalamus, basal ganglia, and inferior frontal gyrus/frontal operculum. At the interindividual level, however, the OCD group had highly variable activation patterns in the dorsal and ventral regions of the pre-supplementary motor area (pre-SMA) that may correspond with differences in demographic and clinical variables. Further, there were significant correlations in the OCD participants between pre-SMA dorsal and ventral activation and between dorsal pre-SMA activation and perfectionism. Our findings suggest considerable functional anatomical overlap in left-hemisphere language regions between OCD participants and references but significantly higher pre-SMA interindividual variability in OCD compared to the reference group that may be relevant in clinical fMRI application and the theoretical understanding of OCD.

Keywords: Verbal fluency; Controlled oral word association test; Obsessive–compulsive disorder; Functional neuroimaging; Neuropsychology; Pre-supplementary motor area; Individual differences; Functional magnetic resonance imaging; fMRI.

Obsessive–compulsive disorder (OCD) is a potentially debilitating neuropsychiatric condition characterized by recurrent intrusive thoughts, impulses, or obsessions that cause marked anxiety and distress extending beyond worries of real-life problems. According to the National Comorbidity Survey Replication Study, OCD has a lifetime prevalence of 1.6% (Kessler, Berglund et al., 2005) and a 1-year prevalence of 1.0% (Kessler, Chiu, Demler, Merikangas, & Walters, 2005) in the USA.

The development of neurophysiological models for OCD is an area of continuing research. Several biological markers, including candidate genes, for OCD have been proposed (Shugart et al., 2009; Wang et al., 2009; Wendland et al., 2009), although the identification of specific genes involved in OCD remains elusive (Menzies et al., 2008). The lack of clear biological markers for OCD can result in imprecise diagnosis, impede treatment innovation, and hinder the theoretical understanding of OCD. Providing a non-invasive approach assessing brain function in OCD, functional magnetic resonance imaging (fMRI) has identified several abnormalities in OCD, has been used with OCD participants to establish changes in cerebral blood flow after capsular stimulation (Nuttin et al., 2003), and is increasingly recognized as an objective and reliable endophenotypic measurement in OCD

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(Jezzard & Buxton, 2006; Menzies et al., 2007; Mitterschiffthaler, Ettinger, Mehta, Mataix-Cols, & Williams, 2006; Rauch, 2003). As such, fMRI offers the potential to better understand the neurobiology associated with OCD and to provide biological markers of OCD and its subtypes.

Although the use of fMRI in OCD is incompletely developed (Taylor, Stern, & Gehring, 2007), fMRI studies of OCD show abnormal regional brain activation in orbitofrontal-subcortical circuitry (Menzies et al., 2008; Rotge et al., 2008). However, additional abnormal activation associated with OCD in the parietal cortex (Menzies et al., 2008) suggests that models of OCD focusing primarily on orbitofrontal-subcortical circuitry may be incomplete. Further, because of known neuropsychological deficits in OCD (Burdick, Robinson, Malhotra, & Szeszko, 2008; Henry, 2006), fMRI studies based on specific and sensitive cognitive tasks (Allen & Fong, 2008a, 2008b; Menzies et al., 2008; Rotge et al., 2008) not limited to strictly off–on symptom provocation paradigms (that may produce false positive findings from non-specific correlates of anxiety) (Breiter & Rauch, 1996) with exclusive use of washing- or disgust-related material (Mitterschiffthaler et al., 2006) may provide a more precise accounting of the neurophysiology and neuropsychology of OCD. Impeding the neurophysiological and neuropsychological understanding of OCD, however, is the lack of normative performance databases by which to interpret brain activation maps in OCD (Allen & Fong, 2008a, 2008b; Brown, 2007; Desmond & Chen, 2002; Mitterschiffthaler et al., 2006; Seghier, Lazeyras, Pegna, Annoni, & Khateb, 2008). In particular, care must be taken to ensure that fMRI task development, standardization, and implementation neither inadvertently generate a bias toward the prevailing pathophysiological models of OCD (Desmond & Chen, 2002; Menzies et al., 2008; Rauch, 2000; Rotge et al., 2008) nor bias the interpretation of fMRI results in terms of their implications for clinical science (Allen & Fong, 2008a, 2008b; Desmond & Chen, 2002; Jezzard & Buxton, 2006; Maia, Cooney, & Peterson, 2008).

The recent development of fMRI-based, cognitive-testing protocols and normative activation databases based on common neuropsychological paradigms addresses many of the methodological issues (Allen & Fong, 2008a, 2008b) associated with understanding neurophysiological and neuropsychological function in OCD and may improve the investigational and clinical application of fMRI in OCD (Breiter & Rauch, 1996; Mitterschiffthaler et al., 2006). The normative activation database represents a normative brain map (i.e., distribution of activation values within functionally defined brain regions) that enables clinical quantitative assessment of specific functional brain activations (expressed in terms of a pattern of *z*-scores across regions) in clinical populations. Further, the recently developed fMRI adaptation of the classic neuropsychological phonemic fluency *FAS* test (f-VFT) has been used to reliably assess the functional integrity of brain regions of interest in participants with traumatic brain injury (Allen & Fong, 2008b). Despite deficits in verbal fluency in OCD (Henry, 2006), the f-VFT along with its normative activation database developed by Allen and Fong (2008b) has not been examined for its potential utility to understand task-induced brain activation in OCD.

In this study, we used the f-VFT to quantitatively compare brain activation patterns in OCD with previously obtained normative reference data with the objective to determine whether the f-VFT could provide a cognitive endophenotype of OCD to improve diagnostic precision in OCD and to enhance the understanding of cognitive function in OCD. Specifically, the normative data were derived from individual participants and structured for the purpose of providing statistical evaluation of individual OCD participants. Thus, rather than relying on group activation comparisons alone, the analyses in this study focused on individual differences among OCD participants with respect to a reference group with similar demographic characteristics.

Previous fMRI-based verbal fluency tasks in healthy controls suggest involvement of the left inferior frontal gyrus (IFG), the medial prefrontal cortex, including the pre-supplementary motor area (pre-SMA) (Allen & Fong, 2008b; Crosson et al., 1999), and the dorsal anterior cingulate (dAC) (Allen & Fong, 2008b; Costafreda et al., 2006). Likewise, a previous study using the *FAS* test to compare control subjects with OCD participants (Pujol et al., 1999) found primary activation in these areas for both groups, with relative hyperactivation in left IFG for OCD participants, a region implicated in neurophysiological models of OCD (Maia et al., 2008; Menzies et al., 2008; Rotge et al., 2008). Based on these studies, we hypothesized that OCD participants would exhibit greater peak activation compared to the normative data in the

medial prefrontal and left IFG during f-VFT performance. Consequent findings could potentially advance basic empirical research and support fMRI as a promising radiological application for the diagnosis, monitoring, treatment, prognosis, and theoretical understanding of OCD.

METHODS

Participants

Normative references

Thirty-two volunteers (16 male, 16 female; mean age = 25.04, $SD = 4.23$) whose fMRI data had been previously collected formed the reference group (Allen & Fong, 2008a, 2008b). All normative participants had no history of neurological impairments or significant psychological pathology as assessed by screening questionnaires developed to identify neurological and psychological disorders. Further, all normative participants had no reported past or current psychotropic medication use. All normative participants had completed at least 1 year of college and were in good academic standing at a university with high admission and continuance standards. All normative participants consented to release pre-admission records of ACT (or SAT) scores. Analysis of mean scores (with SAT converted to ACT equivalents) revealed overall high performance, with a mean of 30 ($SD = 4.30$) for females, and 29 ($SD = 2.16$) for males, with no significant difference between sexes ($t = 1.38$, $p > .1$).

OCD group

Twelve participants (8 women and 4 men) previously diagnosed with OCD were recruited from a university-affiliated community clinic and counseling center through referrals from their therapists and advertisement. As assessed after referral for study participation, all OCD participants met Diagnostic and Statistical Manual IV (DSM-IV) (American Psychiatric Association, 2000) criteria for OCD evaluated using the Structured Clinical Interview for DSM-IV (First, Spitzer, Gibbon, & Williams, 1997). Further, all the OCD participants had OCD as their primary diagnosis, a current full-scale IQ score $\geq$ 80 determined by the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999), and were on stable doses of any medication for at least 4 weeks. Exclusion criteria for OCD participants were presence of a significant medical condition or neurological disorder, history of substance abuse, bipolar disorder, schizophrenia, history of significant head injury (i.e., loss of consciousness greater than 5 minutes or significant post-concussional syndrome), pregnancy, metal implants, history of electroconvulsive therapy, or history of corticosteroid use. We did not exclude potential OCD participants with comorbid major depression, generalized anxiety disorder, or panic disorder. OCD participants' characteristics are presented in Table 1. All participants provided signed written informed consent following a complete description of the study. The appropriate institution review boards approved the study. Participants received no compensation.

Clinical measures

General intelligence in the OCD participants was estimated using the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999). At the time of scanning, all participants completed three questionnaires designed to measure the existence and severity of various OCD symptoms and features: first, the Yale–Brown Obsessive Compulsive Scale (Y-BOCS) is a structured-interview measurement designed to measure global and specific symptom severity (Goodman, Price, Rasmussen, Mazure, Delgado et al., 1989; Goodman, Price, Rasmussen, Mazure, Fleischmann et al., 1989), second, the Obsessive–Compulsive Inventory-Revised (OCI-R) is a self-report measure designed to assess the frequency and distress of particular symptom categories of OCD (Foa et al., 2002), and third, the Perfectionism Inventory (PI) is a self-report measure designed to assess perfectionism in eight areas (Concern Over Mistakes, High Standards for Others, Need for Approval, Organization, Perceived Parental Pressure, Planfulness, Rumination, and Striving for Excellence) with two sum scales (Conscientious Perfectionism and Self-Evaluative Perfectionism) and a composite index (Hill et al., 2004).

Functional imaging task – f-VFT

Full details of the f-VFT are available elsewhere (Allen & Fong, 2008b). Briefly, the f-VFT was adapted from the classic verbal-fluency neuropsychological task *FAS*, a measure of executive functioning within the domain of language

TABLE 1
OCD participant characteristics

Subject	*Age*	*Sex*	*Education*	*Comorbidity*	*Handedness*	*Medications*	*VIQ*	*PIQ*	*FSIQ*
1	25	F	15	Major depressive disorder, Specific phobia, Generalized anxiety disorder	Right	Lamictal, Citalopram, Lorazepam	132	94	113
2	21	F	15	Generalized anxiety disorder, Social Phobia, Panic disorder without agoraphobia	Right	None	125	116	123
3	18	F	12	Social phobia, Major depressive disorder	Right	Celexa	138	116	130
4	22	F	16	Major depressive disorder, Generalized anxiety disorder	Right	Effexor, Seroquel	134	127	134
5	41	F	15	Panic disorder without agoraphobia, Specific phobia, Generalized anxiety disorder	Right	Lorazepam, Provigil, Geodon, Lamictal	101	116	109
6	24	F	16	Major Depressive Disorder, Generalized anxiety disorder	Right	None	123	117	123
7	24	M	15	Social phobia	Right	Celexa	113	117	117
8	21	F	14	Attention deficit disorder, Major depressive disorder	Right	Lamictal, Lexapro, Adderall	131	123	130
9	23	M	14	None	Left	None	132	118	128
10	29	F	11	Attention deficit disorder, Major depressive disorder, Generalized anxiety disorder, Posttraumatic stress disorder	Right	Paxil, Propranolol, Clonazepam, Topomax	138	109	126
11	20	M	12	None	Right	Zoloft	138	111	128
12	15	M	9	Attention deficit disorder	Right	Effexor, Adderall	117	123	123
Mean	23.6	N/A	13.7	N/A	N/A	N/A	126.8	115.6	123.7
SD	6.5	N/A	2.2	N/A	N/A	N/A	11.6	8.4	7.4

Note: VIQ, Verbal IQ; PIQ, Performance IQ; FSIQ, Full-Scale IQ; M, male; F, female; N/A, not applicable.

production in which participants are instructed to generate as many words as possible in a limited amount of time under restricted search conditions (Allen & Fong, 2008b). Prior to the experiment, participants were informed that incorrect responses include proper names and variations of previously produced words. One challenge in adapting the standard *FAS* paradigm for fMRI use is that it requires overt vocal responses, which would create unacceptable head motion. Although some novel solutions using overt responses with 'paced' or 'compressed' paradigms have been proposed, these solutions may restrict fluency. For example, in the paced paradigm, participants are not allowed to freely generate words, as in standard fluency tests. Instead, on each trial, participants generate a single-word response and then hold that word in working memory while waiting for a designated response opportunity, typically every 4 to 6 seconds. Moreover, the total number of words participants may generate is limited by a pre-designated number of response opportunities. As such, overt designs may elicit significant brain activation associated with cognitive processes that go beyond the essence of the task, such as increased response inhibition, motor preparation, and sustained attention (Basho, Palmer, Rubio, Wulfeck, & Muller, 2007; Costafreda et al., 2006). Following previous fMRI studies of verbal fluency, therefore (Allen & Fong, 2008b; Crosson et al., 1999), our design uses covert responses.

During the f-VFT, participants viewed a back-projection screen via a system of angled mirrors in which a word generation prompt was presented: 'Think of words that begin with the letter. . .' (2 seconds). Immediately following the prompt, participants were presented a target letter cue (18 seconds) and required to covertly generate as many words as possible, under the rule restrictions, associated with that target letter until the cue disappeared. In each 20-second test block, a word-generation prompt was presented, followed by a letter cue, and an 11-second comparison block, in which participants were instructed to count covertly from 1 to 10. The f-VFT consisted of the target letters 'F', 'A', 'S', 'B', 'M', 'H', 'G', and 'L', and has a concurrent/convergent validity coefficient of 0.89 and 0.85 in samples of individuals with and without neurological/cognitive impairment, respectively (Allen & Fong, 2008b). For OCD participants, we retroactively administered the classic *FAS* verbal fluency task outside the scanner following the f-VFT.

Imaging acquisition and preprocessing procedure

All MRI sequences were acquired in a single scanning session using a 1.5-T magnetic resonance scanner (GE Twin Speed; GE Healthcare, Milwaukee, WI). Participants were explained the f-VFT task requirements just prior to scanning. Functional images were acquired at 23 contiguous axial locations using an EPI blood oxygen level-dependent (BOLD) sequence with the following critical parameters: TR = 2000; TE = 40 ms; slice thickness = 5 mm; in-plane voxel resolution = 3.75×3.75; and a 64×64 matrix of individual sample points, producing a total of 64×64×23 voxels for the entire brain coverage. Although participants in the reference group were scanned from 1 to 2 years prior to the OCD participants, their imaging data was obtained from the same MRI machine, and scanning conditions, including calibrated receiver values, were kept as uniform as possible across sessions. Conventional preprocessing and statistical analyses were performed using MRIcro and SPM5 (http://www.fil.ion.ucl.ac.uk) software packages. Preprocessing procedures included acquisition-time realignment, using sync interpolation, followed by motion correction with EPI distortion unwarping. No head movement exceeded 1-mm translation or 1° rotation displacement. After motion/distortion correction, all functional volumes were spatially normalized and resampled using the Montreal Neurological Institute templates implemented in SPM5 and spatially smoothed with an 8-mm FWHM Gaussian kernel in order to increase signal-to-noise ratio and to reduce the effects of moderate interindividual variability in brain anatomy. High resolution 3D SPGR and T_2 axial FLAIR MRI scans revealed no detectible brain abnormalities in any OCD or reference participants determined by a board-certified neuroradiologist. Participants' T-1 weighted SPGR anatomical MRIs were then coregistered and normalized to their mean functional image in order to perform participant-specific functional region analyses that take into account individual variability in cortical landmark organization.

Statistical analyses

Participant-level analyses were performed for all participants. Group-level random-effects (RFX)

analyses were performed for both the reference and OCD groups. Given the large difference in sample sizes between the groups, and the known heterogeneity of symptom severity levels and subtypes within the OCD group, no between-group inferential analyses were performed. Instead, a functional region analyses approach (Allen & Fong, 2008b) was used to extract activation profiles from each OCD participant for quantitative assessment with respect to a normative data map for the f-VFT, derived from an identical functional region extraction process using the normative participants.

Participant-level analysis

A time-series ANCOVA implemented in SPM5 was used to test each voxel, for each participant, against the null-hypothesis that changes in BOLD signal in that voxel over the duration of the experiment did not significantly correlate with the temporal sequencing of the f-VFT. A boxcar waveform convolved with a synthetic hemodynamic response function with a 4-second lag-to-peak was used to model task-related activation. The data were high-passed filtered in time, using a set of discrete cosine basis functions with a cut-off period of 128 seconds, and conditioned for temporal autocorrelations using AR1 correction. For each participant, *t*-values for the contrast test condition versus counting condition were computed for each voxel, using the parameter estimates of the ANCOVA. The resulting three-dimensional contrast map from each participant was saved for further participant-level functional region analysis as well as for random effects (RFX) group-level analysis.

Group-level analysis

Activation at the group level was analyzed using the RFX approach in which the value of the sum of the contrast weights for each voxel from each participant's ANCOVA was entered as a single data point in a second-level *t*-statistic computation, with the mean value for each voxel across participants modeled as the effect term and the variance between participants modeled as the error term (Penny, Holmes, & Friston, 2004). Significant activation peaks at the group-level are reported with a critical family-wise-error corrected *p*-value of $<.05$, and a voxel cluster extent threshold of 8.

Functional region analysis

Our procedure for establishing functional region designations and extracting activation values from individual participants was described in detail by Allen and Fong (2008a). Briefly, a parcellation scheme modified from Tzourio-Mazoyer et al. (2002) was used to designate approximately 48 functional regions for each hemisphere and then applied to each participant's structural image. Participant-individual *t*-maps from the ANCOVA estimates were smoothed (to condition outlier peaks) and overlain on each participant's custom-parcellated structural image. Activation peaks and cluster extents were analyzed for each region for each participant, yielding region reliability indices and significance inclusion thresholds. For the most part, this procedure yields similar results, in terms of significantly activated brain regions, to conventional group-level analysis. Departures from group-level analyses (e.g., RFX analysis) tend to occur in large functional brain regions (e.g., dorsolateral prefrontal cortex), with greater tendencies for intersubject variability. Following the procedures described by Tzourio-Mazoyer et al. (2002), means and standard deviations of extracted scores were computed across the normative participants and used to derive a normalized distribution of *z*-scores for each region. Following functional region analysis of each OCD participant, extracted activation values were used in two ways. First, the activation value from each functional region was converted into a *z*-score, relative to the normative distribution for that functional region, yielding an activation profile of *z*-score-levels for each participant. Second, the regional *z*-scores were entered into analyses where correlations between brain activations and demographic variables, as well as measures of *FAS*, Y-BOCS, OCI-R, and PI were investigated using Pearson's coefficient of correlation.

RESULTS

Demographic characteristics of the OCD participants

The average age of the OCD participants was 23.6 years (range 15–29 years, $SD = 6.5$ years). The average Verbal IQ was 126.8 ($SD = 11.6$), the average Performance IQ was 115.6 ($SD = 8.4$), and the average Full-scale IQ was 123.7 ($SD = 7.4$).

With the exception of one, all OCD participants were right handed, and nine of the 12 participants were on at least one psychotropic medication. Comorbidity in this sample was high. Only two participants did not have comorbidity, and comorbid diagnoses among the remaining 10 participants were major depression, generalized anxiety disorder, specific phobia, social phobia, panic disorder without agoraphobia, attention-deficit hyperactivity disorder, and posttraumatic stress disorder (Table 1).

Normative participants group-level analysis: RFX model

The group RFX activation for the normative participants is displayed in Figure 1 and summarized in Table 2. Consistent with previous studies (Costafreda et al., 2006), activation was found almost exclusively in left hemisphere language areas associated with lexical form retrieval/selection and covert articulation. Peak activations included the precentral/premotor cortex, inferior frontal gyrus/frontal operculum, basal ganglia, and thalamus. Additionally, two distinct robust activations were observed in the dorsal and ventral regions of the medial pre-supplementary motor area (pre-SMA). Functional region analyses confirmed the presence of both these peaks in normative participants.

TABLE 2
Normative participants: Group-level random-effects model activation foci ($p < .05$, FWE corrected)

Anatomical region	*MNI (x, y, z)*	*t-Score*
Medial pre-supplementary motor area		
Dorsal	−4, 4, 63	9.25
Ventral	−5, 14, 51	9.71
Left inferior frontal gyrus/Frontal operculum	−44, 32, 9	7.77
Right frontal operculum/ Anterior insula	35, 18, 3	5.07
Left precentral gyrus/Premotor area		
Superior	−30, −8, 65	7.95
Inferior	−47, 5, 30	9.24
Left thalamus	−10, −13, 13	7.01
Left basal ganglia	−15, 5, 14	6.32

Note: Premotor area, portions of superior and middle frontal gyri corresponding to BA 6.

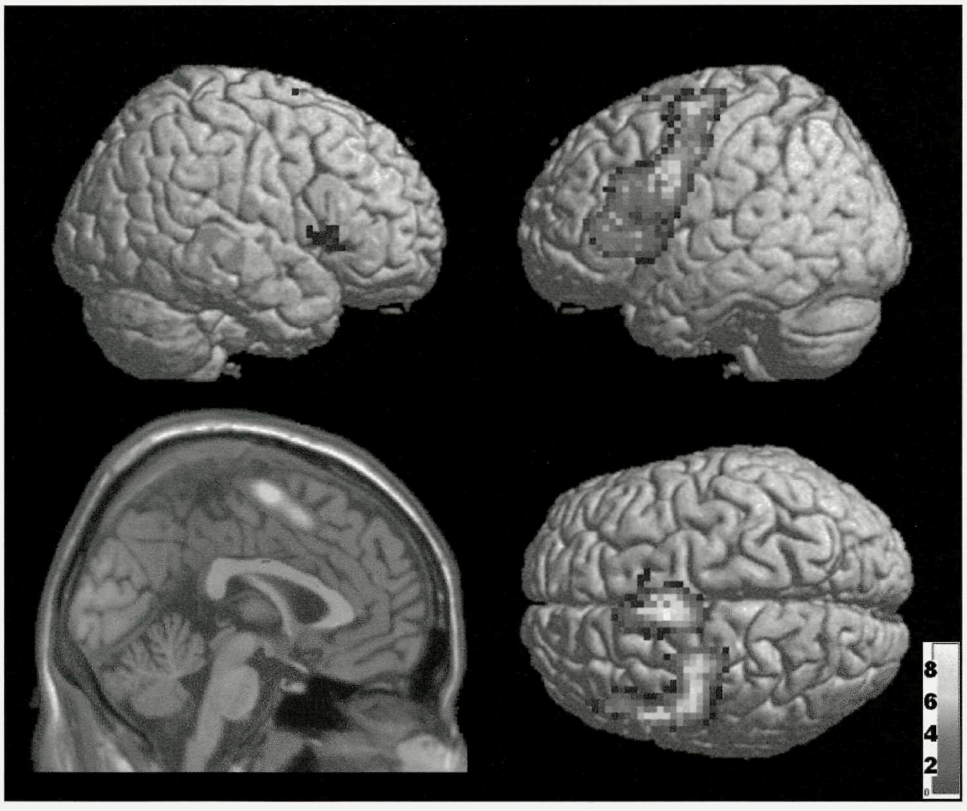

Figure 1. Normative participants: Group-level random-effects model activation foci ($p < .05$, FWE-corrected). [To view this figure in color, please visit the online version of this Journal.]

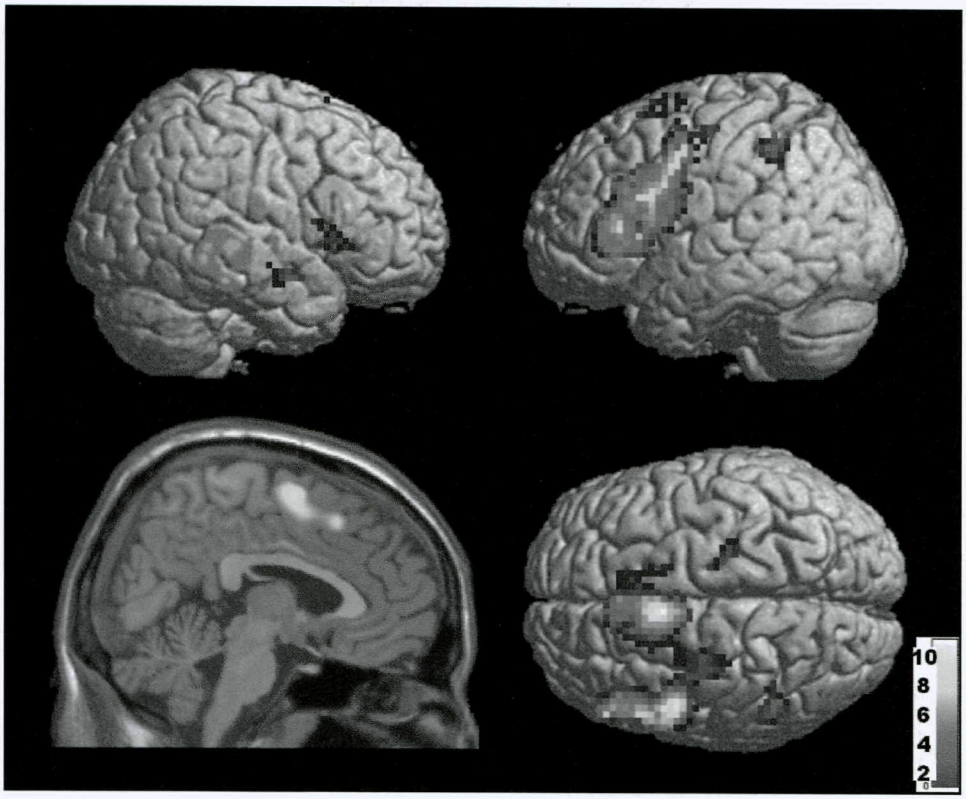

Figure 2. OCD participants: Group-level random-effects model activation foci ($p < .05$, FWE-corrected). [To view this figure in color, please visit the online version of this Journal.]

OCD participants group-level analysis: RFX model

The group RFX activation for the 12 OCD participants (displayed in Figure 2 and summarized in Table 3) shows a highly convergent pattern of activation with the normative participants. As mentioned, a between-group inferential test for significance differences would not be appropriate. Furthermore, the within-group RFX analysis itself should be interpreted with caution, given the known heterogeneity of symptom severity levels, subtypes, comorbidities, and medications in the OCD group.

TABLE 3
OCD participants: Group-level random effects-model activation foci ($p < .05$, FWE corrected, see text for further description of threshold methods)

Anatomical region	*MNI (x, y, z)*	*t-Score*
Medial pre-supplementary motor area		
Dorsal	−5, 10, 62	11.23
Ventral	−7, 24, 45	9.10
Left inferior frontal gyrus	−50, 29, 11	7.68
Left frontal operculum/Anterior insula	−37, 15, 10	8.01
Right frontal operculum/Anterior insula	35, 18, 6	6.36
Left precentral gyrus/Premotor area		
Superior	−50, 1, 43	9.06
Inferior	−49, 16, 22	8.78
Left thalamus	−14, −8, 13	7.31
Left basal ganglia	−15, 7, 8	6.75

Note: Premotor area, portions of superior and middle frontal gyri corresponding to BA 6.

OCD Participants: Subject-level functional region analysis

Using the methods for establishing reliable functional region boundaries described elsewhere (Allen & Fong, 2008a), 10 functional regions were identified from the normative data. These regions coincide to a large degree with regions containing suprathreshold peaks on the RFX analysis, as presented in Table 3. Following functional region-based activation value extraction procedures for all 12 OCD participants, the resulting functional region activation profiles were inspected on a participant-by-participant basis for unusual or

notable patterns and trends. Specifically, each region was examined for excessive variation across participants using successive standard deviation thresholds (i.e., 1.5, 2, 2.5, 3). Based on this analysis, it was determined that all regions showed normal distributions of activation across the 12 participants, with the notable exception of two regions – the dorsal and ventral pre-SMA. Activation levels in these two regions showed highly unusual fluctuation across participants. As shown in Table 4, *z*-scores in the dorsal pre-SMA range from –1.79 to +3.84 and from –4.44 to +3.51 in the ventral pre-SMA.

Given the indications of unusual variance in pre-SMA regions in the OCD group (Figure 3), variance in *t*-scores from the functional region extraction procedure (one smoothed peak score for each participant) was analyzed for between-group differences for each region using *F* tests of equality of variances with a one-tailed *a priori* hypothesis that the OCD group showed a higher variance than the reference group. Compared with the reference group, outcomes on this analysis were significantly different for the ventral pre-SMA ($F = 7.43, p < .001$) and dorsal pre-SMA ($F = 3.65$, $p < .005$) in OCD participants, while all other functional regions were not significantly different (Table 5).

Because of the notably unusual pattern of activation variation observed in the dorsal and ventral pre-SMA in this sample of OCD participants, and suggestions that the pre-SMA is a brain structure of interest in OCD (Yucel et al., 2007), the two peaks in this region were selected as variables for further correlational analysis with demographic and clinical variables.

OCD participants: Correlational analysis

Assessed with *FAS* (1 minute per letter) outside the scanner on a different day within 12 months after fMRI imaging, OCD participants produced a mean of 25.90 words ($SD = 8.85$) and normative participants 47.10 words ($SD = 10.83$). The *FAS* performance was not significantly correlated with the dorsal ($r = .21, p > .05$) or ventral ($r = .21$, $p > .05$) pre-SMA activations, or any clinical measures or demographic data (age, education, IQ), with the exception of the OCI-R Washing index ($r = .60, p < .05$) (Table 4).

There was significant correlation in the OCD participants between dorsal and ventral activations in the pre-SMA ($r = .70$, $p < .05$), suggesting that activation magnitude in the dorsal region tends to increase with activation in the ventral region (Table 4). Additionally, there were significant positive correlations between the dorsal pre-SMA activations and the following indices: the OCI-R Washing index ($r = .63$, $p < .05$ (Table 4)), the PI Need for Approval index ($r = .59$, $p < .05$), the PI Striving for Excellence index ($r = .58$, $p < .05$), and the PI Total Score ($r = .58$, $p < .05$ (Table 4)). We found marginally significant positive correlation between the dorsal pre-SMA and the PI Concern over Mistakes index ($r = .55$, $p = .06$) and the PI Self-Evaluation index ($r = .55$, $p = .06$) (Table 6). No significant relationship was found between the ventral pre-SMA activations and any other clinical measures (Y-BOCS, OCI-R, and other PI indices), demographic data (age, education, IQ), or OCD symptom category or severity.

DISCUSSION

The present study compared brain activation of OCD participants to a reference group of healthy, demographically matched participants using the f-VFT. While the use of ACT scores as an estimate of intellectual ability in the reference group and the use of IQ scores in the OCD group precludes a direct comparison of intellectual ability between the two groups, *z*-scores based on ACT and IQ scores were similar between the reference group ($z = 1.68$) and the OCD group ($z = 1.57$), indicating generally comparable intellectual function between the two groups.

Our use of the f-VFT enabled the investigation of the functional variability of brain regions associated with phonemic fluency processes. We found that during f-VFT performance, participants with OCD, as a group, exhibited normal activations in left-hemisphere language regions, including the precentral/premotor cortex, thalamus, basal ganglia, and inferior frontal gyrus/frontal operculum. However, at the individual level, we found that OCD participants manifested highly variable activation levels in two distinct clusters: the dorsal and ventral regions of the pre-SMA. Additionally, OCD participants exhibited equivalently variable demographic and clinical symptoms, including OCD symptom severity (mild to severe), symptom category (hoarding, obsessing, washing, checking, ordering), comorbidities, and medications.

The findings of extensive overlap in brain activations between OCD participants and the reference

TABLE 4
OCD participants' pre-SMA brain activations and clinical assessment data

		Pre-SMA[1]		*Y-BOCS*			*Obsessive–Compulsive Inventory–Revised*							
Subject	*FAS*[1]	*Dorsal*	*Ventral*	*Obsession*	*Compulsion*	*Total*	*Checking*	*Hoarding*	*Neutralizing*	*Obsession*	*Ordering*	*Washing*	*Total*	*Symptom category*[2]
1	−0.29	3.84	3.28	6	6	12	1	11	3	9	6	6	36	Hoarding
2	−0.75	3.42	−0.01	8	13	21	2	6	1	8	6	8	31	Obsessing
3	0.64	−0.47	0.87	11	8	19	5	10	3	9	3	4	34	Obsessing
4	−0.47	−1.11	−4.44	7	6	13	1	4	0	5	6	0	16	Ordering
5	−1.21	1.74	2.35	14	12	26	10	4	6	6	9	4	39	Checking
6	1.19	1.44	0.26	12	12	24	9	0	0	9	3	12	33	Washing
7	−1.30	−0.42	−2.07	10	8	18	4	2	1	10	0	3	20	Obsessing
8	0.18	2.32	3.51	4	0	4	0	1	0	3	2	3	9	Washing
9	−0.29	−1.63	−1.10	4	4	8	3	5	1	3	6	3	21	Ordering
10	−1.30	−0.03	1.59	14	14	28	4	11	2	12	10	0	39	Obsessing
11	−0.56	−0.55	−2.00	8	9	17	1	5	0	8	3	0	17	Obsessing
12	−1.39	−1.79	−1.63	6	5	11	2	2	0	1	4	0	9	Ordering
Mean	−0.46	0.56	0.05[b]	8.67	8.08	16.75	3.50	5.08	1.42	6.92	4.83	3.58[a, c]	25.33	N/A
SD	0.82	1.93	2.41	3.52	4.17	7.37	3.18	3.80	1.83	3.32	2.89	3.68	11.24	N/A

Note: [1]Values are in *z*-scores; Y-BOCS, Yale–Brown Obsessive Compulsive Inventory; N/A, not applicable.
[2]As determined by the Structured Clinical Interview for DSM-IV, Yale–Brown Obsessive Compulsive Inventory, and Obsessive–Compulsive Inventory–Revised.
[a]Pearson correlation between *FAS* and Washing index, $r = .60$, two-tailed $p < .05$, uncorrected.
[b]Pearson correlation between the dorsal and ventral pre-SMA activations, $r = .70$, two-tailed $p < .05$. uncorrected.
[c]Pearson correlation between the dorsal pre-SMA and Washing index activations, $r = .63$, $p < .05$. uncorrected.

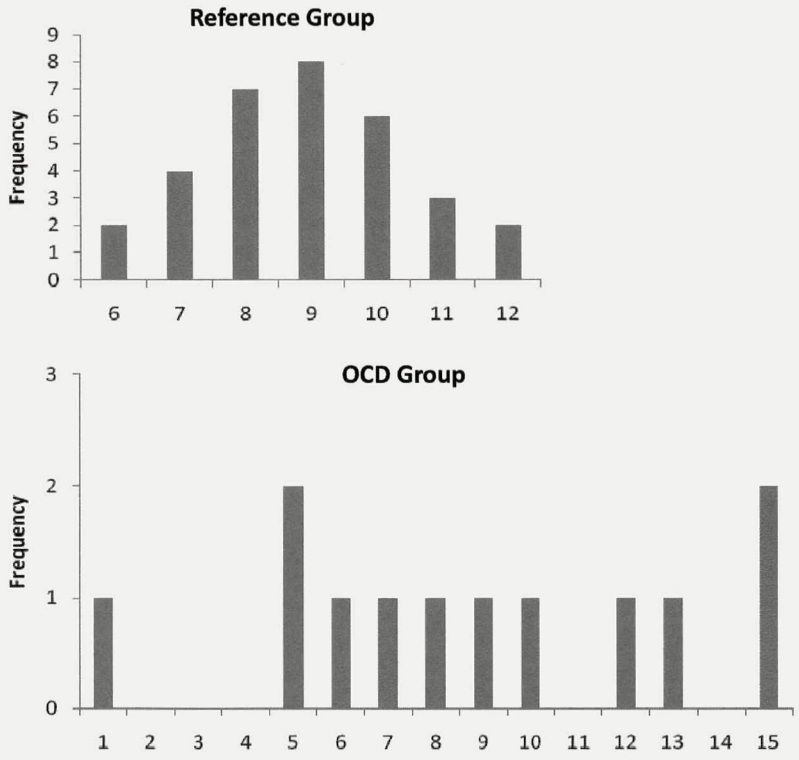

Figure 3. Variance range and distribution of extracted smoothed-peak *t*-scores in ventral pre-SMA for reference and OCD groups. *Note:* Individual *t*-scores are rounded to whole-number range bins on the *x*-axis. Number of subjects/peaks per bin is plotted on the *y*-axis.

TABLE 5
Comparison of variance between OCD and reference groups for extracted smoothed-peak *t*-scores within 10 functional regions

	OCD Group			*Reference Group*				
Functional regions	*Min.*	*Max.*	*Variance*	*Min.*	*Max.*	*Variance*	$F_{(11, 31)}$	*p*
Ventral pre-SMA	0.00	14.68	19.62	5.21	11.99	2.64	7.43	**<.001**
Dorsal pre-SMA	5.46	14.61	12.45	5.15	11.45	3.41	3.65	**<.005**
L *pars triangularis*	3.83	10.67	4.79	4.05	10.63	2.78	1.72	>.1
L frontal operculum	2.01	8.64	3.81	3.82	10.33	2.37	1.61	>.1
L inf parietal lobe	4.22	11.04	5.10	2.25	9.23	3.66	1.39	>.1
L inf precentral gyrus	4.17	10.48	4.54	4.79	13.72	3.71	1.23	>.1
L *pars opercularis*	4.38	10.90	5.29	4.69	15.16	5.43	0.97	>.1
L thalamus	2.11	7.95	2.01	2.20	8.88	3.02	0.66	>.1
L basal ganglia	3.41	7.53	2.24	1.96	8.58	2.63	0.85	>.1
L posterior temporal	2.89	6.48	1.70	2.36	11.16	3.33	0.51	>.1

Note: F-tests for equality of variances (one-tailed) reveal significant between-group differences in ventral and dorsal pre-SMA.
Min., minimum *t*-score; Max., maximum *t*-score; pre-SMA, pre-supplementary motor area; L, left; inf, inferior.

group highlight the interrelationships of the functional anatomy and degree of 'normality' of functional responses between the groups, as elicited by the f-VFT. Of particular relevance, the substantial variability in activations within the pre-SMA (compared to other regions) underscores interindividual variability as a potential source of functional variance in the OCD group that may be associated with the heterogeneity of OCD symptom severity, symptom category, comorbidities, medications, and demographic variables. Although we did not find significant correlations between

TABLE 6
OCD participants' Perfectionism Inventory Scores

Subject	*CM*	*HSO*	*NA*	*O*	*PP*	*P*	*R*	*SE*	*Consc*	*Self-Evaluative*	*Total*
1	30	11	37	16	25	27	30	22	11.10	15.79	26.88
2	35	27	34	33	34	32	26	26	16.89	16.59	33.48
3	33	21	38	11	28	26	28	15	1.59	16.38	26.97
4	29	19	28	19	29	32	30	23	13.49	15.04	28.53
5	30	21	27	29	29	30	32	26	15.24	15.32	30.57
6	39	32	37	39	39	34	31	26	18.64	18.80	37.44
7	25	18	36	11	14	23	25	25	11.39	12.95	24.35
8	31	19	35	25	13	33	26	24	14.56	13.60	28.14
9	18	15	17	25	18	32	20	15	12.34	9.48	21.82
10	40	33	33	20	30	14	35	24	13.21	17.88	31.09
11	26	19	29	19	31	33	18	24	13.80	13.32	27.12
12	8	8	8	26	8	15	12	13	8.70	4.71	13.42
Mean	28.67[d]	20.25	29.92[a]	22.75	24.83	27.58	26.08	21.92[b]	12.58	14.16[e]	27.48[c]
SD	8.87	7.51	9.12	8.45	9.45	6.95	6.57	4.76	4.35	3.87	6.03

Note: CM, Concern over Mistakes; HSO, High Standards for Others; NA, Need for Approval; O, Organization; PP, Perceived Parental Pressure; P, Planfulness; R, Rumination; SE, Striving for Excellence; Consc, Conscientious Perfectionism Sum Scales (HSO, O, P, SE); Self-Evaluative, Self-Evaluative Perfectionism Sum Scales (CM, NA, PP, R).

[a]Pearson correlation between the dorsal pre-SMA activations and NA score, $r = .59$, $p < .05$, uncorrected.

[b]Pearson correlation between the dorsal pre-SMA activations and SE score, $r = .58$, $p < .05$, uncorrected.

[c]Pearson correlation between the dorsal pre-SMA activations and Total score, $r = .58$, $p < .05$, uncorrected.

[d]Pearson correlation between the dorsal pre-SMA activations and CM score, $r = .55$, $p = .06$, uncorrected.

[e]Pearson correlation between the dorsal pre-SMA activations and Self-Evaluative score, $r = .55$, $p = .06$, uncorrected.

pre-SMA activations and many of these variables, we did find correlation between pre-SMA activation and several subscales of perfectionism and washing. Further, inconsistent functional neuroimaging findings may partly result from the heterogeneity in diagnostic classification inherent within OCD (Menzies et al., 2008; Mitterschiffthaler et al., 2006; Saxena et al., 2003), including symptom structure (Bloch, Landeros-Weisenberger, Rosario, Pittenger, & Leckman, 2008). Consistent with our findings of substantial variability in activation among the OCD participants are findings from other studies of neuropsychiatric disorders in which there is substantial individual variability in functional brain anatomy (Hariri, 2009; Hasnain, Fox, & Woldorff, 1998; Taylor et al., 2007; Xiong et al., 2000). In fact, the emphasis on 'group averages' (Robinson, 2004), as opposed to analysis of individual participants within a diagnostic group (Hariri, 2009), not only may explain the widespread abnormalities and discrepant findings in OCD (Maia et al., 2008) but also renders the clinical use of fMRI in neuropsychiatric disorders a challenging endeavor. Our findings of substantial variability within the OCD group emphasize the importance of attention to interindividual overlap and differences in interpreting fMRI activations, consistent with the well-established nomothetic and idiographic approach taken in the neuropsychological evaluation of neuropsychiatric disorders (Lezak, 1995; Strauss, Sherman, & Spreen, 2006). Taken together, each OCD participant's demographic characteristics, brain activation, and clinical characteristics highlight the notion that the underlying neural activation distributions in OCD are both continuous and interdependent, mediated by both distinct and overlapping neural activation systems. This notion is generally consistent with the fMRI findings by Mataix-Cols et al (2004), who found distinct and partially overlapping neural correlates across the symptom categories of washing, checking and hoarding. The implication is that the relevance of both distinct and overlapping individual brain activation profile may serve as important predictors of vulnerability to OCD.

Functional neuroimaging studies have identified interindividual brain activation variability as important markers of the pathophysiology of anxiety disorders (Hariri, 2009). Relative to other brain regions, our findings of considerable variability in the pre-SMA hyperactivations in the OCD group, particularly the dorsal region, is therefore a next step in identifying potential neurobiological sources of interindividual variability in OCD. The pattern and region of variability may appear unexpected at the outset because the pre-SMA regions have been generally associated with complex motor control function (Picard & Strick, 1996). Nonetheless,

several important fMRI studies have focused on the contribution of the pre-SMA to the execution of word production, specifically semantic fluency (name a 'flower' or an 'animal') (Alario, Chainay, Lehericy, & Cohen, 2006; Crosson et al., 1999; Tremblay & Gracco, 2006). Moreover, there is growing recognition that pre-SMA activations in human and animal studies are associated with cognitive control (i.e., executive function), including response inhibition, set-shifting, rule learning, and conflict or error-monitoring (Isoda & Hikosaka, 2007; Lau, Rogers, Haggard, & Passingham, 2004; Nachev, 2006; Nachev, Kennard, & Husain, 2008; Nachev, Wydell, O'Neill, Husain, & Kennard, 2007), for which the classic phonemic fluency task and f-VFT were putatively designed to measure (Allen & Fong, 2008b; Strauss et al., 2006). The relationships between the pre-SMA region and cognitive control are further supported by human and animal studies of disruption or lesions in the confined pre-SMA region that resulted in inhibited behavioral response (Floden & Stuss, 2006; Nachev et al., 2007; Rushworth, Hadland, Paus, & Sipila, 2002) and increased response error rate (Drewe, 1975; Nakamura, Sakai, & Hikosaka, 1999; Picton et al., 2007). Indeed, a recent study found robust pre-SMA hyperactivation in the OCD group compared with matched controls in response to an inhibitory/intereference task (Yucel et al., 2007). However, it should be noted that we did not consistently find pre-SMA hyperactivation across all OCD participants, likely due to interindividual clinical or endophenotypic variability.

We found significant correlation between the dorsal and ventral pre-SMA activations in the OCD group. Because no study has directly investigated the functional subregions of the pre-SMA, we can only speculate that activations in these pre-SMA subregions may be functionally connected in OCD. That is, in OCD patients, high dorsal pre-SMA activation was related to high ventral pre-SMA activation, whereas low dorsal pre-SMA activation was related to low ventral pre-SMA activation. Clearly, additional studies are needed in examining the functional anatomy of the pre-SMA subregions and its relation to OCD and its subtypes.

There are few published findings about pre-SMA activations and behavioral correlates in OCD. The substantial activation variability across individuals in this region provided an appropriate avenue to retrospectively conduct correlational analyses between the dorsal and ventral activation in the pre-SMA and clinical and demographic measures. We found that the magnitude of the dorsal pre-SMA BOLD response to f-VFT positively correlated with participants' perfectionism, as indexed by the proximal (Concerns over Mistakes, Need for Approval, and Striving for Excellence) and composite (Self-Evaluation and Total Score) indicators of the Perfectionism Inventory, as well as washing tendencies as indexed by the OCI-R. Previous studies have established that perfectionism is a significant contributor to obsessive beliefs in OCD (Moretz & McKay, 2009; Taylor, McKay, & Abramowitz, 2005), even after accounting for other symptoms, including depression (Wu & Cortesi, 2009). As such, perfectionism may be a key dimension in OCD along which obsession varies and by which OCD can be subtyped. To our knowledge, no group studies to date have examined the associations between functional brain activations and perfectionism in OCD. Although our functional region analyses provide preliminary evidence for a correlation between obsessive–compulsive perfectionism and washing and pre-SMA activation in response to the f-VFT, it is important to note that there is appreciable interindividual variability in other clinical variables in our sample (e.g., symptom severity, category, medications and comorbidities), making the generalization of our findings imprecise, a limitation compounded to the low statistical power in this study because of small sample size. However, the interindividual clinical variability in our sample also underscores the salience of the finding of high interindividual variation in task-induced activation in the dorsal and ventral pre-SMA regions. The patient sample all met criteria for OCD. Had we relied simply on group averages, we would have concluded that there were no differences in activation patterns between the reference group and OCD participants, when in fact the OCD participants showed considerable variation compared to the reference group in task-induced dorsal and ventral pre-SMA activation, variation in activation suggesting that the dorsal and ventral pre-SMA regions may be relevant in understanding OCD in certain subtypes of OCD patients. Thus, our findings should be extended or complemented by future studies including a larger sample examining the relationships between perfectionism, brain activations, clinical variables (e.g., symptom severity, category, medications and comorbidities), and OCD at both group and interindividual levels is needed.

Although the OCD subjects performed worse on the *FAS* than did the reference group, we did

not find a significant correlation between the OCD participants' pre-SMA hyperactivations and *FAS* performance. This may be due to the low power in our study, a clinically heterogeneous sample, anxiety levels (characteristic of OCD) inside the scanner, and/or the fact that participants' *FAS* performance data was retroactively collected within 12 months following their brain scans. Nonetheless, *FAS* performance was below a *z*-score of zero (range between –1.4 and 1.2) in 9 out of 12 OCD participants compared to the reference group, suggesting variable phonemic fluency performance in OCD. This variable phonemic fluency performance may partly explain previous conflicting reports of either normal or impaired verbal fluency performances in OCD (Bannon, Gonsalvez, Croft, & Boyce, 2006; Henry, 2006; Mataix-Cols et al., 2006). Further, performance on the *FAS* was not significantly correlated with any clinical measures or demographic data (age, education, IQ), with the exception of the OCI-R Washing index, in contrast to the significant positive correlations between the dorsal pre-SMA activations and the OCI-R Washing index, the PI Need for Approval index, the PI Striving for Excellence index, and the PI Total Score. Even though we found no significant associations between the ventral pre-SMA activations and any other clinical measures (Y-BOCS, OCI-R, and other PI indices), demographic data (age, education, IQ), or OCD symptom or severity our findings together suggest that the dorsal and ventral pre-SMA may be a region of interest for better understanding OCD and its associated neurobiology.

The findings of variable pre-SMA activations in our sample are not necessarily in contrast to a number of existing fMRI studies that found hyperactive dorsal anterior cingulate gyrus (dAC) (Maltby, Tolin, Worhunsky, O'Keefe, & Kiehl, 2005; Nabeyama et al., 2008; Nachev, 2006; Rotge et al., 2008; Ursu, Stenger, Shear, Jones, & Carter, 2003), a subregion of the medial prefrontal cortex involved in response inhibition, and conflict- or error-monitoring in OCD (Maia et al., 2008). In OCD patients, hyperactivation in the dAC appears to extend into the pre-SMA (Yucel et al., 2007), raising the question whether the pre-SMA region has a central or peripheral etiology of OCD. However, due to inconsistent labeling schemes across studies, many previous studies of cognitive control processes reported dAC activation peaks that would clearly fall within the pre-SMA regions (Brown & Braver, 2005; Nachev et al., 2008) according to our labeling scheme. Nonetheless, cytoarchitecture studies have found that the dAC and pre-SMA, together with the SMA proper, are reciprocally connected with the primary motor cortex and involved in motor planning (Biber, Kneisley, & LaVail, 1978; Braak, 1976; Vogt & Vogt, 2003), suggesting that these regions may be structurally and functionally linked. Additionally, the pre-SMA and the dAC are parts of a wider frontal cognitive-motor network (Dum & Strick, 2002) involved in conflict monitoring (Taylor et al., 2007). Further, studies of conflict monitoring show significant variability in localizing the dAC by as much as 6 cm and extending into the pre-SMA region (Taylor et al., 2007). As such, future neuroimaging studies may need careful anatomical labeling and examination of the relationships between pre-SMA and dAC activations, and their behavioral correlates, in OCD.

Our findings of variable pre-SMA activations in response to the f-VFT task provide preliminary evidence of altered medial frontal functioning in OCD. Our findings complement an fMRI study in which deficits of verbal fluency, but not of naming and comprehension, remained 1 year after surgical removal of the pre-SMA region of a woman with drug-resistant epilepsy (Deblieck et al., 2003). Further, fMRI has been used in parceling out the pre-SMA region from the medial prefrontal cortex in identifying epilepsy surgery candidates (Chassagnon, Minotti, Kremer, Hoffmann, & Kahane, 2008) and in presurgical evaluation of patients with intractable, partial motor seizures (Hanakawa et al., 2001). While clinical fMRI in OCD needs considerably more study at this juncture, our current findings of significantly varied pre-SMA activation levels in response to the f-VFT protocol highlight initial efforts in applying fMRI for individualized diagnosis, treatment, and prognosis, as well as advancing empirical research in OCD.

Limitations in our current clinical fMRI study include the use of a single cognitive protocol of the f-VFT and the focus of our functional region analysis on the pre-SMA, inferior frontal gyrus, frontal operculum, precentral gyrus, thalamus, and basal ganglia in both the OCD and reference groups. Nevertheless, our functional region-based investigation focusing on the effects of a specific signaling region on the brain circuitry in OCD was driven by the standardized f-VFT protocol, development of a normative f-VFT brain activation database, and an *a priori* hypothesis based on prior

evidence. Continued large-scale, whole-brain mapping of OCD at group and individual levels using a sequence of standardized cognitive tasks is needed in future studies. Second, we did not systematically quantify the amount between the neural overlap and variability for each individual in response to f-VFT. Future studies quantifying interindividual neural variability in OCD may provide a valuable extension to this study.

In this small fMRI study using a verbal task in OCD compared to a reference group, we found considerable interindividual overlap and variability, particularly in the pre-SMA, in neural signaling in response to the f-VFT cognitive task, suggesting that OCD may be mediated by variability within the normative range of neural systems and behavior. Clinical measures of perfectionism correlated with pre-SMA activation, and activation patterns in the dorsal and ventral regions of the pre-SMA in OCD were highly correlated. Clinical use of fMRI to understand individual neural differences and overlap in OCD may inform clinically and theoretically relevant issues and assist in developing individualized diagnosis, monitoring, treatment, and prognosis.

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REFERENCES

Alario, F. X., Chainay, H., Lehericy, S., & Cohen, L. (2006). The role of the supplementary motor area (SMA) in word production. *Brain Research*, *1076*(1), 129–143.

Allen, M. D., & Fong, A. K. (2008a). Clinical application of standardized cognitive assessment using fMRI. I. Matrix reasoning. *Behavioral Neurology*, *20*(3), 127–140.

Allen, M. D., & Fong, A. K. (2008b). Clinical application of standardized cognitive assessment using fMRI. II. Verbal fluency. *Behavioral Neurology*, *20*(3), 141–152.

American Psychiatric Association (2000). *Diagnostic and statistical manual of mental disorders – 4th edition, text revision* (4th ed.). Washington, DC: Author.

Bannon, S., Gonsalvez, C. J., Croft, R. J., & Boyce, P. M. (2006). Executive functions in obsessive-compulsive disorder: State or trait deficits? *Australian and New Zealand Journal of Psychiatry*, *40*(11–12), 1031–1038.

Basho, S., Palmer, E. D., Rubio, M. A., Wulfeck, B., & Muller, R. A. (2007). Effects of generation mode in fMRI adaptations of semantic fluency: Paced production and overt speech. *Neuropsychologia*, *45*(8), 1697–1706.

Biber, M. P., Kneisley, L. W., & LaVail, J. H. (1978). Cortical neurons projecting to the cervical and lumbar enlargements of the spinal cord in young and adult rhesus monkeys. *Experimental Neurology*, *59*(3), 492–508.

Bloch, M. H., Landeros-Weisenberger, A., Rosario, M. C., Pittenger, C., & Leckman, J. F. (2008). Meta-analysis of the symptom structure of obsessive-compulsive disorder. *American Journal of Psychiatry*, *165*(12), 1532–1542.

Braak, H. (1976). A primitive gigantopyramidal field buried in the depth of the cingulate sulcus of the human brain. *Brain Research*, *109*(2), 219–223.

Breiter, H. C., & Rauch, S. L. (1996). Functional MRI and the study of OCD: From symptom provocation to cognitive-behavioral probes of cortico-striatal systems and the amygdala. *Neuroimage*, *4*(3 Pt 3), S127–138.

Brown, G. G. (2007). Functional magnetic resonance imaging in clinical practice: Look before you leap. *Neuropsychology Review*, *17*(2), 103–106.

Brown, J. W., & Braver, T. S. (2005). Learned predictions of error likelihood in the anterior cingulate cortex. *Science*, *307*(5712), 1118–1121.

Burdick, K. E., Robinson, D. G., Malhotra, A. K., & Szeszko, P. R. (2008). Neurocognitive profile analysis in obsessive-compulsive disorder. *Journal of the International Neuropsychological Society*, *14*(4), 640–645.

Chassagnon, S., Minotti, L., Kremer, S., Hoffmann, D., & Kahane, P. (2008). Somatosensory, motor, and reaching/grasping responses to direct electrical stimulation of the human cingulate motor areas. *Journal of Neurosurgery*, *109*(4), 593–604.

Costafreda, S. G., Fu, C. H., Lee, L., Everitt, B., Brammer, M. J., & David, A. S. (2006). A systematic review and quantitative appraisal of fMRI studies of verbal fluency: Role of the left inferior frontal gyrus. *Human Brain Mapping*, *27*(10), 799–810.

Crosson, B., Sadek, J. R., Bobholz, J. A., Gokcay, D., Mohr, C. M., Leonard, C. M., et al. (1999). Activity in the paracingulate and cingulate sulci during word generation: An fMRI study of functional anatomy. *Cerebral Cortex*, *9*(4), 307–316.

Deblieck, C., Pesenti, G., Scifo, P., Fazio, F., Bricolo, E., Lo Russo, G., et al. (2003). Preserved functional competence of perilesional areas in drug-resistant epilepsy with lesion in supplementary motor cortex: fMRI and neuropsychological observations. *Neuroimage*, *20*(4), 2225–2234.

Desmond, J. E., & Chen, S. H. (2002). Ethical issues in the clinical application of fMRI: Factors affecting the validity and interpretation of activations. *Brain Cognition*, *50*(3), 482–497.

Drewe, E. A. (1975). Go – no go learning after frontal lobe lesions in humans. *Cortex*, *11*(1), 8–16.

Dum, R. P., & Strick, P. L. (2002). Motor areas in the frontal lobe of the primate. *Physiology & Behavior*, *77*(4–5), 677–682.

First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. B. (1997). *Structured Clinical Interview for DSM-IV Axis I disorders*. Washington, DC: American Psychiatric Press.

Floden, D., & Stuss, D. T. (2006). Inhibitory control is slowed in patients with right superior medial frontal damage. *Journal of Cognitive Neuroscience*, *18*(11), 1843–1849.

Foa, E. B., Huppert, J. D., Leiberg, S., Langner, R., Kichic, R., Hajcak, G., et al. (2002). The Obsessive-Compulsive Inventory: Development and validation of a short version. *Psychological Assessment*, *14*(4), 485–496.

Goodman, W. K., Price, L. H., Rasmussen, S. A., Mazure, C., Delgado, P., Heninger, G. R., et al. (1989). The Yale-Brown Obsessive Compulsive Scale. II. Validity. *Archives of General Psychiatry*, *46*(11), 1012–1016.

Goodman, W. K., Price, L. H., Rasmussen, S. A., Mazure, C., Fleischmann, R. L., Hill, C. L., et al. (1989). The Yale-Brown Obsessive Compulsive Scale. I. Development, use, and reliability. *Archives of General Psychiatry*, *46*(11), 1006–1011.

Hanakawa, T., Ikeda, A., Sadato, N., Okada, T., Fukuyama, H., Nagamine, T., et al. (2001). Functional mapping of human medial frontal motor areas. The combined use of functional magnetic resonance imaging and cortical stimulation. *Experimental Brain Research*, *138*(4), 403–409.

Hariri, A. R. (2009). The neurobiology of individual differences in complex behavioral traits. *Annual Review of Neuroscience*, *32*, 225–247.

Hasnain, M. K., Fox, P. T., & Woldorff, M. G. (1998). Intersubject variability of functional areas in the human visual cortex. *Human Brain Mapping*, *6*(4), 301–315.

Henry, J. D. (2006). A meta-analytic review of Wisconsin Card Sorting Test and verbal fluency performance in obsessive-compulsive disorder. *Cognitive Neuropsychiatry*, *11*(2), 156–176.

Hill, R. W., Huelsman, T. J., Furr, R. M., Kibler, J., Vicente, B. B., & Kennedy, C. (2004). A new measure of perfectionism: The Perfectionism Inventory. *Journal of Personal Assessment*, *82*(1), 80–91.

Isoda, M., & Hikosaka, O. (2007). Switching from automatic to controlled action by monkey medial frontal cortex. *Nature Neuroscience*, *10*(2), 240–248.

Jezzard, P., & Buxton, R. B. (2006). The clinical potential of functional magnetic resonance imaging. *Journal of Magnetic Resonance Imaging*, *23*(6), 787–793.

Kessler, R. C., Berglund, P., Demler, O., Jin, R., Merikangas, K. R., & Walters, E. E. (2005). Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry*, *62*(6), 593–602.

Kessler, R. C., Chiu, W. T., Demler, O., Merikangas, K. R., & Walters, E. E. (2005). Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry*, *62*(6), 617–627.

Lau, H. C., Rogers, R. D., Haggard, P., & Passingham, R. E. (2004). Attention to intention. *Science*, *303*(5661), 1208–1210.

Lezak, M. D. (1995). *Neuropsychological assessment* (3rd ed.). New York, NY: Oxford University Press.

Maia, T. V., Cooney, R. E., & Peterson, B. S. (2008). The neural bases of obsessive-compulsive disorder in children and adults. *Developmental Psychopathology*, *20*(4), 1251–1283.

Maltby, N., Tolin, D. F., Worhunsky, P., O'Keefe, T. M., & Kiehl, K. A. (2005). Dysfunctional action monitoring hyperactivates frontal-striatal circuits in obsessive-compulsive disorder: An event-related fMRI study. *Neuroimage*, *24*(2), 495–503.

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. *Archives of General Psychiatry*, *61*(6), 564–576.

Mataix-Cols, D., Rahman, Q., Spiller, M., Alonso, M. P., Pifarre, J., Menchon, J. M., et al. (2006). Are there sex differences in neuropsychological functions among patients with obsessive-compulsive disorder? *Applied Neuropsychology*, *13*(1), 42–50.

Menzies, L., Achard, S., Chamberlain, S. R., Fineberg, N., Chen, C. H., del Campo, N., et al. (2007). Neurocognitive endophenotypes of obsessive-compulsive disorder. *Brain*, *130*(Pt 12), 3223–3236.

Menzies, L., Chamberlain, S. R., Laird, A. R., Thelen, S. M., Sahakian, B. J., & Bullmore, E. T. (2008). Integrating evidence from neuroimaging and neuropsychological studies of obsessive-compulsive disorder: The orbitofronto-striatal model revisited. *Neuroscience Biobehavioral Reviews*, *32*(3), 525–549.

Mitterschiffthaler, M. T., Ettinger, U., Mehta, M. A., Mataix-Cols, D., & Williams, S. C. (2006). Applications of functional magnetic resonance imaging in psychiatry. *Journal of Magnetic Resonance Imaging*, *23*(6), 851–861.

Moretz, M. W., & McKay, D. (2009). The role of perfectionism in obsessive-compulsive symptoms: 'not just right' experiences and checking compulsions. *Journal of Anxiety Disorders*, *23*(5), 640–644.

Nabeyama, M., Nakagawa, A., Yoshiura, T., Nakao, T., Nakatani, E., Togao, O., et al. (2008). Functional MRI study of brain activation alterations in patients with obsessive-compulsive disorder after symptom improvement. *Psychiatry Research*, *163*(3), 236–247.

Nachev, P. (2006). Cognition and medial frontal cortex in health and disease. *Current Opinion in Neurology*, *19*(6), 586–592.

Nachev, P., Wydell, H., O'Neill, K., Husain, M., & Kennard, C. (2007). The role of the pre-supplementary motor area in the control of action. *Neuroimage*, 36(Suppl 2), T155–163.

Nachev, P., Kennard, C., & Husain, M. (2008). Functional role of the supplementary and pre-supplementary motor areas. *Nature Reviews Neuroscience*, *9*(11), 856–869.

Nakamura, K., Sakai, K., & Hikosaka, O. (1999). Effects of local inactivation of monkey medial frontal cortex in learning of sequential procedures. *Journal of Neurophysiology*, *82*(2), 1063–1068.

Nuttin, B. J., Gabriels, L. A., Cosyns, P. R., Meyerson, B. A., Andreewitch, S., Sunaert, S. G., et al. (2003). Long-term electrical capsular stimulation in patients

with obsessive-compulsive disorder. *Neurosurgery*, *52*(6), 1263–1272.

Penny, W. D., Holmes, A. P., & Friston, K. J. (2004). Random effects analysis. In R. S. J. Frackowiak, K. J. Friston, C. Frith, R. Dolan, C. J. Price, S. Zeki, J. Ashburner & W. D. Penny (Eds.), *Human brain function* (2nd ed.). Oxford, UK: Academic Press.

Picard, N., & Strick, P. L. (1996). Motor areas of the medial wall: A review of their location and functional activation. *Cerebral Cortex*, *6*(3), 342–353.

Picton, T. W., Stuss, D. T., Alexander, M. P., Shallice, T., Binns, M. A., & Gillingham, S. (2007). Effects of focal frontal lesions on response inhibition. *Cerebral Cortex*, *17*(4), 826–838.

Pujol, J., Torres, L., Deus, J., Cardoner, N., Pifarre, J., Capdevila, A., et al. (1999). Functional magnetic resonance imaging study of frontal lobe activation during word generation in obsessive-compulsive disorder. *Biological Psychiatry*, *45*(7), 891–897.

Rauch, S. L. (2000). Neuroimaging research and the neurobiology of obsessive-compulsive disorder: Where do we go from here? *Biological Psychiatry*, *47*(3), 168–170.

Rauch, S. L. (2003). Neuroimaging and neurocircuitry models pertaining to the neurosurgical treatment of psychiatric disorders. *Neurosurgery Clinics of North America*, *14*(2), 213–223, vii–viii.

Robinson, R. (2004). FMRI beyond the clinic: Will it ever be ready for prime time? *PLoS Biology*, *2*(6), e150.

Rotge, J. Y., Guehl, D., Dilharreguy, B., Cuny, E., Tignol, J., Bioulac, B., et al. (2008). Provocation of obsessive-compulsive symptoms: A quantitative voxel-based meta-analysis of functional neuroimaging studies. *Journal of Psychiatry Neuroscience*, *33*(5), 405–412.

Rushworth, M. F., Hadland, K. A., Paus, T., & Sipila, P. K. (2002). Role of the human medial frontal cortex in task switching: A combined fMRI and TMS study. *Journal of Neurophysiology*, *87*(5), 2577–2592.

Saxena, S., Brody, A. L., Ho, M. L., Zohrabi, N., Maidment, K. M., & Baxter Jr, L. R. (2003). Differential brain metabolic predictors of response to paroxetine in obsessive-compulsive disorder versus major depression. *American Journal of Psychiatry*, *160*(3), 522–532.

Seghier, M. L., Lazeyras, F., Pegna, A. J., Annoni, J. M., & Khateb, A. (2008). Group analysis and the subject factor in functional magnetic resonance imaging: Analysis of fifty right-handed healthy subjects in a semantic language task. *Human Brain Mapping*, *29*(4), 461–477.

Shugart, Y. Y., Wang, Y., Samuels, J. F., Grados, M. A., Greenberg, B. D., Knowles, J. A., et al. (2009). A family-based association study of the glutamate transporter gene SLC1A1 in obsessive-compulsive disorder in 378 families. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, *150B*, 886–892.

Strauss, E., Sherman, E. M. S., & Spreen, O. (2006). *A compendium of neuropsychological tests: Administration, norms and commentary* (3rd ed.). New York, NY: Oxford University Press.

Taylor, S., McKay, D., & Abramowitz, J. S. (2005). Hierarchical structure of dysfunctional beliefs in obsessive-compulsive disorder. *Cognitive Behavior Therapy*, *34*(4), 216–228.

Taylor, S. F., Stern, E. R., & Gehring, W. J. (2007). Neural systems for error monitoring: Recent findings and theoretical perspectives. *Neuroscientist*, *13*(2), 160–172.

Tremblay, P., & Gracco, V. L. (2006). Contribution of the frontal lobe to externally and internally specified verbal responses: fMRI evidence. *Neuroimage*, *33*(3), 947–957.

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., et al. (2002). Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage*, *15*(1), 273–289.

Ursu, S., Stenger, V. A., Shear, M. K., Jones, M. R., & Carter, C. S. (2003). Overactive action monitoring in obsessive-compulsive disorder: Evidence from functional magnetic resonance imaging. *Psychology Science*, *14*(4), 347–353.

Vogt, B. A., & Vogt, L. (2003). Cytology of human dorsal midcingulate and supplementary motor cortices. *Journal of Chemical Neuroanatomy*, *26*(4), 301–309.

Wang, Y., Samuels, J. F., Chang, Y. C., Grados, M. A., Greenberg, B. D., Knowles, J. A., et al. (2009). Gender differences in genetic linkage and association on 11p15 in obsessive-compulsive disorder families. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, *150B*(1), 33–40.

Wechsler, D. (1999). *Wechsler Abbreviated Scale of Intelligence*. San Antonio, TX: The Psychological Corporation.

Wendland, J. R., Moya, P. R., Timpano, K. R., Anavitarte, A. P., Kruse, M. R., Wheaton, M. G., et al. (2009). A haplotype containing quantitative trait loci for SLC1A1 gene expression and its association with obsessive-compulsive disorder. *Archives of General Psychiatry*, *66*(4), 408–416.

Wu, K. D., & Cortesi, G. T. (2009). Relations between perfectionism and obsessive-compulsive symptoms: Examination of specificity among the dimensions. *Jouranl of Anxiety Disorders*, *23*(3), 393–400.

Xiong, J., Rao, S., Jerabek, P., Zamarripa, F., Woldorff, M., Lancaster, J., et al. (2000). Intersubject variability in cortical activations during a complex language task. *Neuroimage*, *12*(3), 326–339.

Yucel, M., Harrison, B. J., Wood, S. J., Fornito, A., Wellard, R. M., Pujol, J., et al. (2007). Functional and biochemical alterations of the medial frontal cortex in obsessive-compulsive disorder. *Archives of General Psychiatry*, *64*(8), 946–955.