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Brain Activation During Response Interference in Twins Discordant or Concordant for Obsessive Compulsive Symptoms

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One of the core behavioral features associated with obsessive compulsive symptomatology is the inability to inhibit thoughts and/or behaviors. Neuroimaging studies have indicated abnormalities in frontostriatal and dorsolateral prefrontal – anterior cingulate circuits during inhibitory control in patients with obsessive compulsive disorder compared with controls. In the present study, task performance and brain activation during Stroop color-word and Flanker interference were compared within monozygotic twin pairs discordant for obsessive compulsive symptoms and between groups of pairs scoring very low or very high on obsessive compulsive symptoms, in order to examine the differential impact of non-shared environmental versus genetic risk factors for obsessive compulsive symptomatology on inhibitory control related functional brain activation. Although performance was intact, brain activation during inhibition of distracting information differed between obsessive compulsive symptom high-scoring compared to low-scoring subjects. Regions affected in the discordant group (e.g., temporal and anterior cingulate gyrus) were partly different from those observed to be affected in the concordant groups (e.g., parietal gyrus and thalamus). A robust increase in dorsolateral prefrontal activity during response interference was observed in both the high-scoring twins of the discordant sample and the high-scoring twins of the concordant sample, marking this structure as a possible key region for disturbances in inhibitory control in obsessive compulsive disorder.

■ **Keywords:** obsessive compulsive symptoms, discordant-concordant monozygotic twin design, genetic risk, environmental risk, response interference, functional MRI

Obsessive compulsive symptoms (OCS) are characterized by recurrent, persistent, and intrusive anxiety-provoking thoughts or images (obsessions) and subsequent repetitive behaviors (compulsions) performed to reduce anxiety and/or distress caused by the obsessions. When a person has these obsessions and/or performs compulsions for more than one hour a day and these thoughts and rituals significantly interfere with his/her daily life routines, the person fulfills the criteria for obsessive compulsive disorder (OCD). The lifetime prevalence of OCD is 0.5–2% (American Psychiatric Association, 1994; Grabe et al., 2000), but obsessions are much more prevalent in the general population — as high as 72% (Rachman & de Silva, 1978; Salkovskis & Harrison, 1984) and the prevalence of OC symptoms reaches up to 20% (Fullana et al., 2009).

Numerous twin (Jonnal et al., 2000; van Grootheest et al., 2005) and family studies (Hettema et al., 2001; Nestadt et al., 2000) have indicated the importance of genetic as well as environmental risk factors with regard to the etiology of OCD. Heritabilities for OCD have been estimated to be between 27–47% in adults and 45–65% in children (Jonnal et al., 2000; van Grootheest et al., 2005), and linkage and association studies have mainly pointed towards functional

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deficits of genes involved in serotonergic, glutamatergic, and dopaminergic neural signaling (for review see Nicolini et al., 2009). Potential environmental risk factors for OCD include traumatic early life experiences, perinatal problems, streptococcal infection, psychosocial stress, aspects of parenting (e.g., parental overprotection), pregnancy, divorce, and emotional neglect (Albert et al., 2000; Alonso et al., 2004; Cath et al., 2008; Geller et al., 2008; Grisham et al., 2008; Lin et al., 2007; Wilcox et al., 2008).

Over the last two decades, neuroimaging studies have indicated several neurobiological changes underlying the psychological and behavioral dysfunction of OCD. Results from structural and functional magnetic resonance imaging (sMRI/fMRI) studies mainly point to volume differences and altered regional brain activation in the ventral prefrontal cortex (PFC), dorsolateral prefrontal cortex (DLPFC), basal ganglia, anterior cingulate cortex (ACC), and thalamus (Menzies et al., 2008; Radua & Mataix-Cols, 2009; Radua et al., 2010; Rotge et al., 2009). These findings have contributed to the widely accepted neuroanatomical model of OCD involving the direct and indirect cortico-striato-thalamo-cortical (CSTC) loops (Mataix-Cols & van den Heuvel, 2006; Saxena & Rauch, 2000). The direct loop functions as a self-reinforcing feedback loop that contributes to the initiation and continuation of behaviors. The indirect loop functions as a negative feedback loop important for inhibiting and switching between behaviors. It has been hypothesized that an imbalance between these loops, resulting in a hyperactive ventral and hypoactive dorsal frontal-striatal system, might mediate OC symptomatology (Mataix-Cols & van den Heuvel, 2006; Saxena & Rauch, 2000). Although disturbance in these CSTC loops may represent the main neurological basis for OCD, several imaging studies also suggest the involvement of other brain regions, such as amygdala, hippocampus, and parietal areas in OCD (Menzies et al., 2008; Pujol et al., 2004; Valente et al., 2005). Therefore, Menzies and colleagues proposed an extended model that includes these brain areas that are functionally connected to the ventral and dorsal frontal-striatal circuits (Menzies et al., 2008).

One of the core behavioral features associated with OC symptomatology is the inability to inhibit thoughts and/or behaviors. The process of inhibitory control has been linked to frontal-striatal networks, but the ACC and its interactions with the DLPFC may also play a crucial role because this circuitry has been repeatedly linked to conflict monitoring and adjustments in control (Kerns et al., 2004; Melcher et al., 2008). Numerous imaging studies in OCD specifically focused on the neurobiological processes underlying inhibitory control by exposing both OCD patients and controls to cognitive tasks that are developed to measure inhibitory control, such as response interference in the Stroop color-word and Eriksen Flanker task (Melcher et al., 2008). Regarding task performance, in which prolonged reaction times and error rates are generally considered a direct indicator for cognitive conflict or interference, OCD patients have been repeatedly described to be in the normal range (Fitzgerald et al., 2005; Maltby et al., 2005; Nakao et al., 2005; Page et al., 2009; Viard et al., 2005; Yucel et al., 2007). However, some studies showed prolonged reaction times during high-conflict trials, suggestive for impaired inhibitory control in OCD patients (Menzies et al., 2007; van den Heuvel et al., 2005). Furthermore, of interest for the present study, Menzies et al. found delayed response inhibition on the stop-signal task in OCD patients as well as in unaffected first-degree relatives of OCD patients, suggesting familial vulnerability of this aspect of OCD (Menzies et al., 2007). Even if performance was intact, there is evidence that OCD patients show a different pattern of brain activation during the execution of tasks measuring inhibitory control. Most neuroimaging studies that investigated inhibitory control showed a higher response conflict-related increase in ACC activity in OCD patients than in controls (Fitzgerald et al., 2005; Maltby et al., 2005; Page et al., 2009; Ursu et al., 2003). Increases in regional activity during high-conflict trials has also been reported for frontal-striatal regions (orbitofrontal cortex, caudate and thalamus), as well as the DLPFC and cerebellum, and temporal and parietal regions (Maltby et al., 2005; Nakao et al., 2005; Nakao et al., 2009; Page et al., 2009; van den Heuvel et al., 2005). However, the findings regarding the direction of activation changes are not consistent, because hypoactivation of the ACC and the caudate, and temporal, and parietal regions during response interference has also been reported (Nakao et al., 2005; Nakao et al., 2009; Page et al., 2009; Yucel et al., 2007). These inconsistencies may be explained by methodological differences between studies, such as the paradigm used to measure response interference, heterogeneity of patient groups and differences in sample size, scanning modalities/parameters, and analysis methods. However, there may also be 'true' variability in the underlying neurobiology of response interference in OCD. That is, it may be that dysfunction of different brain regions may lead to highly comparable changes at the behavioral level, because these regions are part of the same brain network involved in controlling behaviors. Such heterogeneity in affected brain regions could reflect a differential influence of environmental and genetic risk factors for OCD impacting on different parts of the brain.

Most brain imaging studies compare groups of affected individuals with healthy controls. These standard case-control designs cannot disentangle differences in brain function that are due to environmental risk factors from those that are due to genetic risk factors. A distinction between genetically and environmentally mediated neurobiological changes that underlie the development of OCD can be accomplished by using a discordant/concordant monozygotic (MZ) twin design (de Geus et al., 2007; den Braber et al., 2010; den Braber et al., 2011; van 't Ent et al., 2009; Wolfensberger et al., 2008). Excluding post-twinning

de novo mutations, all MZ twins begin life with identical genomes, so behavioral discordances are likely to arise from differential exposure to environmental influences. Consequently, differences in brain function between the high-risk twin and the low-risk co-twin from MZ discordant pairs reflect environmental effects on the brain, rather than effects of genetic variation. In contrast, to maximize detection of the effects of genetic risk factors for OCD, neuroimaging results can be compared between MZ twins who both score high on OC symptoms and MZ twins who both score very low on OC symptoms. These MZ concordant high-scoring and low-scoring twins likely represent either high or low familial vulnerability for OCD. This familial vulnerability could be due to shared environmental or genetic vulnerability. However, shared family environment has not been found to contribute to OC behavior in adults (Clifford et al., 1984; Jonnal et al., 2000; van Grootheest et al., 2007). Therefore, a comparison between MZ concordant high and MZ concordant low pairs on OC symptoms is likely to reveal functional activation differences due to influences of genetic risk factors.

In previous studies by our group, we applied the discordant/concordant twin design to investigate both white matter volume differences and planning-related activation changes in the brains of subjects with an environmental etiology or genetic predisposition for OC symptoms (den Braber et al., 2010; den Braber et al., 2011). The results from these studies suggest that brain regions affected in environmentally mediated OC symptoms are distinct from those affected in genetically mediated OC symptoms. Interestingly, observed white matter changes and planning-related changes in brain activity converge on the CSTC loops. Neurobiological changes in OC symptoms induced by environmental risk factors involve the dorsal frontal CSTC loop (dorsolateral prefrontal region), whereas neurobiological changes in OC symptoms induced by genetic risk factors seem to involve regions implicated in the ventral frontal CSTC loop (inferior frontal region).

The present study aimed to examine the differential impact of non-shared environmental versus genetic influences for OC symptomatology on inhibitory control related functional brain activation. To this end we compared performance and fMRI data during the Stroop color-word and the Eriksen Flanker task, between twins scoring low and twins scoring high on OC symptoms from discordant MZ pairs, and between concordant pairs where both twins scored either low or high on OC symptoms.

Methods

Participants

The twin pairs included in this study were recruited from the Netherlands Twin Register (NTR) (Boomsma et al., 2006). Surveys were sent to twin families, including the Padua Inventory Abbreviated (PI-R-ABBR) (Cath et al., 2008; van Oppen et al., 1995). Completed PI-R-ABBR questionnaires were returned by 815 MZ twin pairs (222 male, 593 female). From this sample we selected twin pairs aged between 18 and 60 years who scored discordant, concordant high or concordant low for OCS. A twin pair was classified as discordant for OC symptoms if one twin scored OCS high (> 16) and the co-twin scored OCS low (≤ 7). A twin pair was classified as concordant high for OC symptoms if both twins scored ≥ 15, with at least one twin scoring ≥ 16. A twin pair was classified as concordant low for OC symptoms if both twins scored ≤ 7. These PI-R-ABBR cut-off scores were derived from sensitivity and specificity measurements in an independent sample of OCD patients when compared to clinical controls ($n = 120$, $M = 20.7$, $SD = 8.1$; sensitivity $= .74$, specificity $= .72$ at the best cut-off point of 16); (Cath et al., 2008). For more details on sample selection refer to den Braber et al. (2010). A final sample of 71 MZ twin pairs participated in this MRI study, including 20 discordant, 23 concordant high and 28 concordant low twin pairs (Table 1). The MRI protocol could not be completed by two subjects (metal artifact, panic attack). In the final sample ($n = 140$), two twins with high OCS scores from the discordant group and five twins with high OCS scores from the concordant high group met clinical diagnosis for OCD. Furthermore, three twins with high OCS scores, one twin with a low OCS score from the discordant group, and six twins from the concordant high group used selective serotonin reuptake inhibitors.

Protocol

Participants were administered diagnostic interviews and questionnaires, including questions on demography, life events, comorbidity, type and severity of OC symptoms, tics, state anger, and state anxiety (for a detailed description of the administered diagnostic interviews and questionnaires, please refer to den Braber et al., 2010). All twins were asked to collect mucosal cell samples for DNA extraction to test zygosity. The ethical review board of the VU University Medical Center approved the study. All participants provided written informed consent.

Task Paradigms

Stroop. During the Stroop color-word task, subjects had to report the ink color of written color words. Dutch translations of the words 'red', 'yellow', 'blue', and 'green' were used that were written in any of these four colors. Word meaning and ink color could be either congruent (e.g., the word 'green' written in green) or incongruent (e.g., the word 'red' written in blue). The correct answer had to be indicated by pressing buttons: left middle finger for ink color yellow, left forefinger for green, right forefinger for red and right middle finger for blue. The task was administered in 18 blocks of similar stimulus types. Of these, 3 blocks contained congruent and 3 blocks contained incongruent color-word stimuli. In each individual block, 16 words were presented for

TABLE 1
Twin sample demographics

		Twin pairs							
		Discordant (environmental risk contrast)				Concordant (genetic risk contrast)			
		high ($n = 20$ subjects)	low ($n = 20$ subjects)			high ($n = 46$ subjects)	low ($n = 56$ subjects)		
Demographics	Female	14 pairs				17 pairs	20 pairs		
	Male	6 pairs				6 pairs	8 pairs		
	Age in years (*SD*)	35.60 (8.68)				36.00 (10.55)	37.50 (8.79)		
		mean (*SD*)	mean (*SD*)	*t*-value	*p*	mean (*SD*)	mean (*SD*)	*t*-value	*p*
Obsessive compulsive symptoms	PI-R-ABBR (0–48)	20.07 (5.03)	4.73 (1.84)	14.51	<.001	20.42 (4.56)	4.18 (2.19)	22.31	<.001
	Y-BOCS severity (0–40)	5.45 (5.62)	1.45 (2.19)	3.64	.001	7.54 (5.83)	0.95 (2.13)	6.95	<.001
Comorbidity	MINI :								
	Depression (*n*)	2	0			0	0		
	Panic disorder (*n*)	1	0			0	0		
	Agoraphobia (*n*)	2	0			0	0		
	Social disorder (*n*)	1	0			2	0		
	Post-traumatic stress disorder (*n*)	1	0			0	0		
	Generalized anxiety disorder (*n*)	3	0			7	0		
	Tic (0–8)	0.40 (0.75)	0.20 (0.41)	1.25	.214	0.30 (0.66)	0.09 (0.29)	2.03	.046
	BDI (0–39)	4.65 (7.50)	3.05 (2.80)	1.73	.089	3.50 (3.17)	1.38 (2.18)	2.47	.016
	STAI (0–60)	13.85 (8.54)	12.25 (6.13)	0.83	.409	13.37 (7.39)	8.55 (7.36)	2.91	.005
	STAS (0–30)	0.20 (0.70)	0.00 (0.00)	0.91	.365	0.46 (2.09)	0.11 (0.49)	1.09	.282

Note: Twin pairs = number of female and male twin pairs, Age = age at time of magnetic resonance imaging (MRI) examination, PI-R-ABBR = mean Padua Inventory Abbreviated scores, *SD* = standard deviation, Y-BOCS severity = mean Yale–Brown Obsessive–Compulsive Scale severity scores, MINI (depression, panic disorder, agoraphobia, social disorder, post-traumatic stress disorder, generalized anxiety disorder) = number of subjects with current comorbid disorder (measured using the Mini International Neuropsychiatric Interview), Tic = mean tic scores at time of MRI, BDI = mean Beck Depression Inventory scores at time of MRI, STAI = mean State Trait Anxiety Inventory scores at time of MRI, STAS = mean State Trait Anger Scale scores at time of MRI.

2 seconds, separated by small intervals of 200 ms. The other 12 blocks consisted of words with an emotional content, which were not used here (for a full description of the task we refer to van den Heuvel et al., 2005). The subjects were asked to respond to the stimuli as fast and as accurately as possible. The onset of each individual stimulus, together with the subject's response, was recorded such that the data could be analyzed in an event-related manner. Total task duration was ± 10 minutes.

Flanker. In the Flanker task, subjects had to indicate, as quickly as possible, the direction of a central target arrow (i.e. '<' left hand press; '>' right hand press) which was surrounded by four task-irrelevant flankers of the same size and shape. The direction of the Flanker arrows could be either congruent ('< < < < <' or '> > > > >') or incongruent ('< < > < <' or '> > < > >') with the direction of the central target arrow. Flankers and targets were displayed simultaneously. The task was administered in an event-related design. During the task 120 congruent and 120 incongruent trials were presented in random order. Stimuli were shown for 200 ms; the interstimulus interval consisted of a period of gray screen after each stimulus (randomized between 600 and 1600 ms) and a subsequent fixation cross for 1000 ms before the next stimulus. Total task duration was ± 10 minutes.

For both the Stroop and Flanker tasks, stimuli were projected on a screen at the end of the MRI scanner table, viewed by the participants through a mirror. Two magnet-compatible response boxes were used to record the subject's performance. Before the experiment, the subjects practiced a number of trials on a computer outside the scanner, and again inside the scanner, before the actual start of the experimental session.

Image Acquisition

The MRI session consisted of a structural part of about 6 minutes and a functional part of about 20 minutes (Stroop ± 10 minutes; Flanker ± 10 minutes). The participant remained inside the scanner and was asked to minimize head movement during and between consecutive runs. To reduce motion artifacts, the participant's head was immobilized using foam pads.

MRI was performed on a 3.0 T Intera MR system (Philips, Medical Systems, Best) with a standard SENSE receiver head coil. The anatomical scan consisted of 182 coronal slices with a 3D gradient-echo T1-weighted sequence (flip angle 8°; repetition time, TR = 9.69 ms; echo time, TE = 4.60 ms; matrix 256 × 256 pixels; voxel size, 1.00 × 1.00 × 1.20 mm). For fMRI, an echo planar imaging (EPI) sequence (flip angle 80°; TR = 2300 ms; TE = 30 ms; matrix 96 × 96 pixels; field of view 220 × 220 mm) was used, covering the

whole brain (40 axial slices; 2.29 mm × 2.29 mm in-plane resolution; 3.0 mm slice thickness). For the Stroop task a total of 260 and for the Flanker a total of 250 EPI volumes were scanned per subject.

Data Analysis

MRI data were analyzed using SPM5 (Wellcome Department of Imaging Neuroscience, London, UK). EPI scans were slice time corrected, realigned and normalized to the standard MNI (Montreal Neurological Institute) brain of SPM. Subsequently, data were resliced to 3 mm × 3 mm × 3 mm voxels and spatially smoothed using an 8 mm isotropic Gaussian kernel. After high-pass filtering (cut-off 128 seconds), functional scans were analyzed in the context of the general linear model using delta functions convolved with a canonical hemodynamic response function. Error trials and head-movement parameters were modeled as regressors of no interest. Post hoc analysis of subject motion during the scans, based on the functional scan realignment parameters, indicated that the twins with high OC symptom scores did not exhibit significantly larger head movements compared to the twins with low OC symptom scores. For each subject and task, contrast images were computed for simple main effects of congruent and incongruent trials, as well as the effect of response interference (incongruent minus congruent trials). For all contrasts, only trials with correct reactions were included.

Statistical Tests

Survey-based and interview-based variables and task performance data were investigated using a mixed-model analysis of variance (ANOVA; Mixed Models Linear menu item in SPSS; SPSS, Chicago, Illinois) with twin-pair type (discordant versus concordant) and OC symptom score (high versus low) as two fixed factors, and family as a random factor to account for within-twin pair dependence. Statistical results with regard to questionnaire and task performance data were considered significant at $p < .05$, Bonferroni corrected.

First-level functional MRI contrast estimates for 'Stroop interference' and 'Flanker interference' were entered into second-level analyses available in SPM5. Differences in contrast estimates between OCS high-scoring and OCS low-scoring twins from discordant pairs were investigated by paired sample *t*-tests. Differences in contrast estimates between concordant OCS high and concordant OCS low twin pairs were assessed using an ANOVA group comparison. To account for within-twin pair correlations of fMRI signals, first-level results of the twin and co-twin of each concordant pair were entered as repeated measures. For main task effects of selected contrasts, we set an individual voxel threshold of $p < .05$, corrected for multiple comparisons (false discovery rate: FDR), with a minimal cluster extent of 100 voxels. Group differences, masked with the appropriate main task effect (mask thresholded at $p < .05$, uncorrected), are reported at an uncorrected individual voxel threshold of $p < .005$, with a minimal cluster extent of 10 voxels.

Results

Questionnaire and Interview Data

As expected, OCS high-scoring compared to low-scoring twins in both the discordant and concordant groups showed significantly higher scores on the PI-R-ABBR and Yale-Brown Obsessive Compulsive Scale (Y-BOCS) symptom severity (see Table 1). In addition, high-scoring twins were more often diagnosed with current comorbid disorders, which were absent in the low-scoring twins.

Task Performance

Across all individuals, reaction times for both the Stroop and the Flanker task were significantly delayed after incongruent compared to congruent stimuli. [Stroop: incongruent $M = 988.92$, $SD = 167.44$ ms vs. congruent $M = 826.27$, $SD = 148.84$ ms, $F(1,139) = 279.82$, $p < .001$; Flanker: incongruent $M = 522.54$, $SD = 193.28$ ms vs. congruent $M = 527.11$, $SD = 193.10$ ms, $F(1,139) = 5.24$, $p < .05$]. In addition, for the Stroop task, percentages of trials with correct reactions were significantly reduced after incongruent stimuli [incongruent $M = 80.4$, $SD = 15.3$ vs. congruent $M = 95.0$, $SD = 6.4$, $F(1,139) = 171.02$, $p < .001$]. For the Flanker task, no significant reduction was found in percentage of trials with correct reactions after incongruent stimuli [incongruent $M = 97.8$, $SD = 4.4$ vs. congruent $M = 98.0$, $SD = 3.9$, $F(1,139) = 0.21$, $p = .649$].

In Table 2, response interference effects, quantified by computing differences in response latency and response accuracy between incongruent and congruent stimulus trials, are displayed separately for the discordant and concordant twin sample. Response latencies did not differ significantly between OCS high-scoring and low-scoring twins from both the discordant and concordant sample. For response accuracy, a smaller effect of response interference was found in the discordant high-risk relative to their discordant low-risk co-twins during the Flanker task.

Functional Imaging

Main Effects. Figure 1 and Table 3 show brain areas with significant fMRI-BOLD (blood-oxygen-level-dependent) activations across all subjects, during Stroop interference (Figure 1: top; Table 3: left), and Flanker interference (Figure 1, bottom; Table 3, right). In both the Stroop and Flanker tasks, response interference was associated with enhanced activation of bilateral occipital, parietal, temporal, and caudate/putamen regions, as well as several prefrontal lobe regions including the ACC, DLPFC, premotor, and inferior frontal cortices. For the Stroop task, increased activation was also noted in left and right thalamus, whereas for the Flanker task an additional cluster was observed in left and right postcentral gyrus.

TABLE 2

Response Interference Effects on Task Performance

		Stroop incongruent-congruent				***Flanker*** incongruent-congruent			
Measure	Sample	OCS High	OCS Low	F	*p*	OCS High	OCS Low	F	*p*
Response latencies	Discordant	179.29 (110.31)	145.60 (117.80)	1.69	.197	65.17 (23.59)	68.00 (28.15)	.35	.559
	Concordant	170.28 (108.61)	156.56 (122.47)	.32	.570	63.06 (21.10)	67.14 (18.79)	.61	.438
Response accuracy	Discordant	−.14 (0.08)	−.13 (0.09)	.40	.525	−.04 (0.05)	−.07 (0.07)	4.80	0.032*
	Concordant	−.18 (0.17)	−.13 (0.12)	3.03	.086	−.06 (0.04)	−.05 (0.05)	.35	.556

Note: Effects of information conflict on Stroop task (left) and Flanker task (right) behavior, measured by computing differences in response latencies (top rows) and response accuracy (bottom rows) on incongruent relative to congruent stimulus trials. OCS = obsessive compulsive symptoms. Columns F and *p* indicate results from statistical tests on OCS-related differences between selected discordant and concordant twin samples.
* = statistically significant difference.

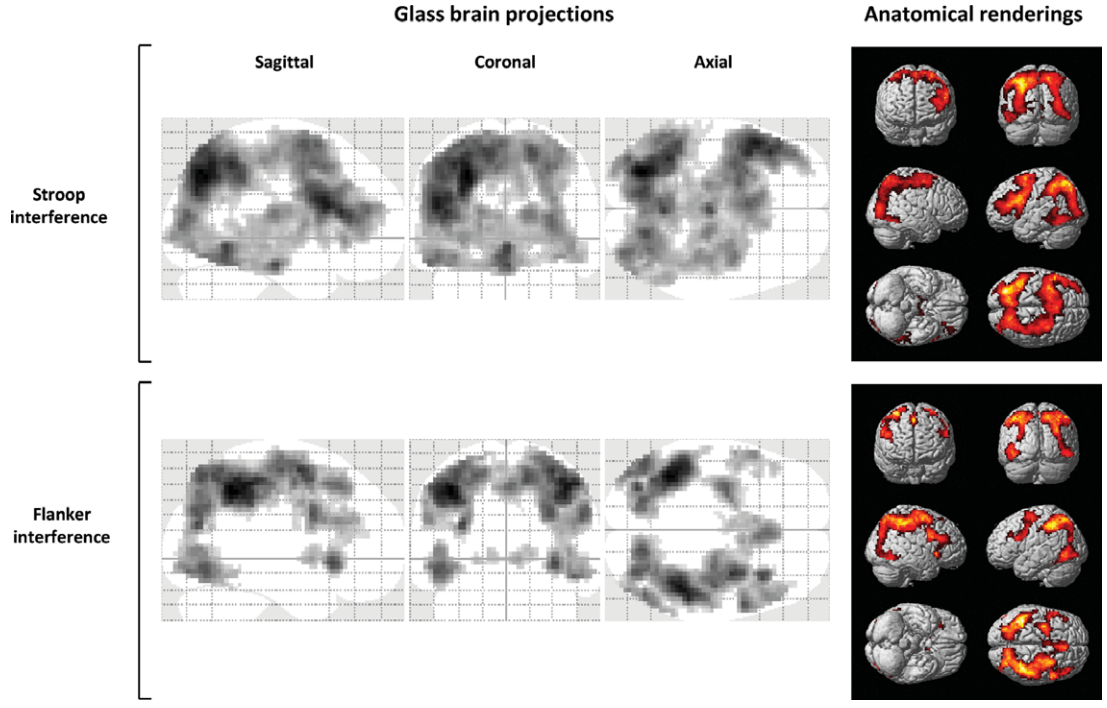

FIGURE 1

Main effects of fMRI-BOLD activation, across all participating twins. Glass brain overviews depict brain activity patterns for 'Stroop interference' (top) and 'Flanker interference' (bottom). Anatomical renderings on the right illustrate locations of functional brain activation for Stroop interference (top) and Flanker interference (bottom), across all participating twins.

Environmental Risk: OCS High-Scoring Versus Low-Scoring Twins From Discordant Pairs

Paired comparisons between the high-risk twin and the low-risk co-twin from discordant pairs revealed significant clusters of increased activation to response interference, but located in different brain regions for the Stroop and Flanker tasks. For the Stroop task, a single cluster of increased activation was found in the right DLPFC (Table 4 and Figure 2, label A). For the Flanker task, increased activation was found in the left middle temporal gyrus, left cingulate gyrus, and right cerebellum (Table 4 and Figure 2, labels B, C, and D, respectively).

High-risk discordant twins also showed an area of reduced activation during response interference, exclusively in the Stroop task, in the left precentral gyrus (Table 4 and Figure 2, label E).

Genetic Risk: Concordant High-Scoring Versus Concordant Low-Scoring Twin Pairs

Table 5 and Figure 2 (right) show clusters of OCS-related differences for brain activation to response interference between the concordant high and concordant low twin pairs. Concordant high compared to concordant low twin pairs showed several significant clusters of increased activation to response interference, again in different brain regions for the Stroop and Flanker tasks. For the Stroop task, high-risk twins from concordant pairs showed relatively increased activity in regions of the left DLPFC, left middle frontal gyrus, left precuneus, right angular gyrus, and bilateral inferior parietal gyrus (Figure 2, labels F, G, H, I, J and K, respectively). For the Flanker task, there was a single cluster of increased activation in high-risk twins in the right thalamus (Figure 2, label L).

TABLE 3

Brain Activity for Stroop and Flanker Interference Contrasts Across Both the Discordant and Concordant Sample

			Stroop interference (incongruent-congruent)				Flanker interference (incongruent-congruent)			
			MNI coordinates				MNI coordinates			
Anatomical location	Side	BA	x	y	z	*t-value*	x	y	z	*t*- value
Frontal cortex	Left	4	−21	−24	66	2.70	−36	−24	60	3.29
	Right	4	36	−21	57	5.25	42	−15	60	6.14
	Left	6	−33	0	63	6.94	−30	−6	63	5.96
	Right	6	36	0	48	6.13	33	–3	60	6.95
	Left	8	−6	15	48	6.47	−6	18	51	3.26
	Right	8	6	18	51	3.95	6	18	51	5.61
	Left	9	−42	9	27	8.46	−54	15	27	4.83
	Right	9	–	–	–	–	54	6	30	6.15
	Left	10	−39	45	18	6.44	–	–	–	–
	Left	45	−48	18	21	9.13	−48	24	24	2.62
	Right	45	–	–	–	–	48	24	24	4.86
	Left	46	−45	33	15	7.65	−45	36	21	2.67
	Right	46	–	–	–	–	48	36	27	4.20
	Left	47	−30	30	−3	5.13	–	–	–	–
	Right	47	–	–	–	–	36	21	−3	6.46
Parietal cortex	Left	3	–	–	–	–	−57	−24	42	3.33
	Right	3	–	–	–	–	57	−24	42	2.74
	Left	7	−27	−69	42	10.13	−36	−60	54	6.40
	Right	7	18	−69	60	7.32	15	−72	54	6.33
	Left	40	−36	−51	51	8.59	−39	−48	45	8.47
	Right	40	36	−51	51	3.41	42	−42	48	7.99
Occipital cortex	Left	19	−48	−57	−12	6.30	−48	−72	6	4.93
	Right	19	33	−84	12	6.49	45	−81	−9	4.85
Temporal cortex	Left	37	−54	−54	−15	6.29	−48	−45	−18	3.03
	Right	37	51	−54	−12	4.46	60	−54	−12	4.08
ACC	Left	32	−9	24	36	3.52	−3	24	42	3.10
	Right	32	12	24	36	4.35	3	24	39	2.62
Thalamus	Left	–	−18	−21	18	5.46	–	–	–	–
	Right	–	18	−21	18	5.75	–	–	–	–
Caudate	Left	–	−15	0	21	2.90	−6	6	0	3.42
	Right	–	15	0	21	2.29	9	6	0	4.40
Putamen	Left	–	−18	0	9	5.05	−21	3	−3	3.48
	Right	–	–	–	–	–	18	9	3	3.67

Note: Anatomical locations of significant clusters for main effects of fMRI BOLD activation during Stroop interference incongruent-congruent trials (left) and Flanker interference incongruent-congruent trials (right). ACC = anterior cingulate cortex, MNI = Montreal Neurological Institute. MNI coordinates and *t*-values are listed for the voxels with the largest effect size.

TABLE 4

Environmental Risk: Brain Activation Differences Between Monzygotic Twins With High and Low Obsessive Compulsive Symptoms in the Discordant Sample

Stroop interference (incongruent - congruent)						Flanker interference (incongruent - congruent)				
		MNI coordinates					MNI coordinates			
Test	Anatomical location	x	y	z	Z score	Anatomical location	x	y	z	Z score
High > low	Right dorsolateral prefrontal gyrus	51	27	27	2.96	Left middle temporal gyrus	−48	6	−27	3.38
						Left cingulate gyrus	−9	−3	48	3.09
						Right cerebellum	15	−48	−27	3.18
High < low	Left precentral gyrus	−27	−15	54	3.53	*no significant clusters*				

Note: Differences in brain activation to trials with information conflict in discordant high compared to low risk twins. Test: test for significant increases (high > low) or decreases (high < low) in OCS high relative to OCS low scoring twins. MNI coordinates: location of voxel with largest effect size; Z score: z-value of voxel with largest effect size.

High-risk concordant twins also showed an area of reduced activation during response interference, exclusively in the Flanker task, in the left inferior parietal gyrus (Figure 2, label M).

There were 10 subjects (3 discordant high, 7 concordant high) with current comorbid disorders. Removing these subjects from the analyses did not affect the pattern of results.

Discussion

Task performance and brain activation during Stroop color-word and Flanker interference were compared within MZ twin pairs discordant for OC symptoms, and between groups of pairs scoring very low or very high on OC symptoms. These comparisons examined the differential impact of non-shared environmental versus genetic and shared environmental risk factors for OC symptomatology on

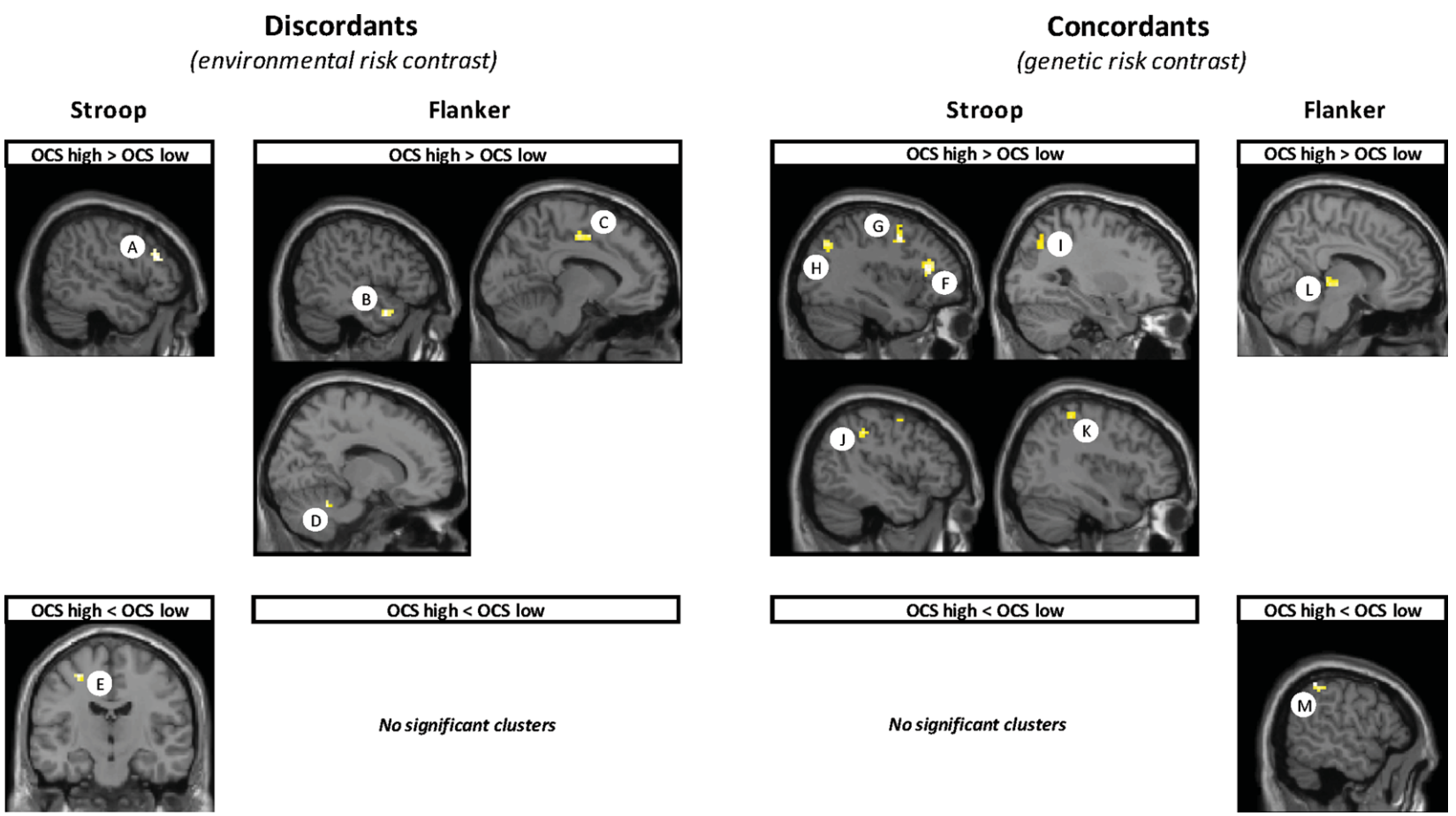

FIGURE 2

Most significant clusters, overlaid on MR sections, from statistical evaluations of OCS-related differences in brain activation to Stroop and Flanker trials with response interference. Left panels: hyperactivations (top row) and hypoactivations (bottom row) for discordant high compared to low-risk twins (environmental contrast). Right panels: hyperactivations (top row) and hypoactivations (bottom row) for concordant high-risk twins compared to low-risk twins (genetic contrast). OCS = obsessive-compulsive symptoms, A = Right dorsolateral prefrontal gyrus, B = Left middle temporal gyrus, C = Left cingulate gyrus, D = Right cerebellum, E = Left precentral gyrus, F = Left dorsolateral prefrontal gyrus, G = Left middle frontal gyrus, H = Left precuneus, I = Right angular gyrus, J = Left inferior parietal gyrus, K = Right inferior parietal gyrus, L = Right thalamus, M = Left inferior parietal gyrus.

TABLE 5

Genetic Risk: Brain Activation Differences Between Monzygotic Twins With High and Low Obsessive Compulsive Symptoms in the Concordant Sample

Stroop interference (incongruent - congruent)						*Flanker interference (incongruent - congruent)*				
		MNI coordinates					MNI coordinates			
Test	Anatomical location	x	y	z	Z score	Anatomical location	x	y	z	Z score
High > low	Left dorsolateral prefrontal gyrus	−36	30	15	3.73	Right thalamus	9	−21	−3	3.14
	Left middle frontal gyrus	−33	0	45	3.68					
	Left precuneus	−33	−66	36	3.39					
	Right angular gyrus	30	−66	36	2.86					
	Left inferior parietal gyrus	−45	−36	42	3.32					
	Right inferior parietal gyrus	39	−39	57	3.15					
High < low	*no significant clusters*					Left inferior parietal gyrus	−54	−45	51	3.30

Note: Differences in brain activation to trials with information conflict in concordant high compared to low risk twins.

inhibitory control related functional brain activation. Shared family environment has never been reported to influence OC behavior in adult twin studies (Clifford et al., 1984; Jonnal et al., 2000; van Grootheest et al., 2007). Therefore, familial risk factors for this trait were taken to translate mainly to genetic risk.

Analysis of task-related behavior indicated classical effects of response interference on response latencies and response accuracy for both the Stroop and Flanker tasks. In line with previous studies, task performances of twins high and low on OC symptoms were comparable, with the exception of marginally reduced interference in high-scoring compared to low-scoring twins of the discordant sample during the Flanker task, which was mainly due to the fact that high-scoring twins made fewer errors during incongruent trials than their low-scoring co-twins.

The fMRI main effects of our study indicated that highly similar brain processes were active during Stroop and Flanker task performance. Brain areas involved include bilateral occipital, parietal, temporal, and caudate/putamen regions, as well as several frontal lobe regions including the ACC, the DLPFC, and the premotor and inferior frontal cortices. These results highly overlap with findings from previous studies that investigated response interference using these paradigms (Kerns et al., 2004; van den Heuvel et al., 2005; van 't Ent et al., 2009). OC symptom status clearly affected this pattern of brain activation, with increased conflict-related DLPFC activity in high-risk compared to low-risk twins from both the discordant and concordant samples during the Stroop task. It has been hypothesized that evaluative and control functions are represented by a dorsolateral prefrontal – anterior cingulate cortical circuit, where the ACC is involved in detecting the occurrence of conflict and the DLPFC in performance adjustments (Melcher et al., 2008). A study that examined predictions of this conflict hypothesis indeed showed more ACC activity in high-conflict correct trials and error trials, which was associated with adjustments in behavior on the next trial that reflect improved control (Kerns et al., 2004). In addition, this study showed that trials exhibiting the largest adjustments in behavior following conflict were associated with increased activity in the DLPFC. Furthermore, previous studies provided evidence for hyperactivity in this dorsolateral prefrontal anterior cingulate circuit during cognitive control in OCD patients compared to healthy controls (Maltby et al., 2005; Schlosser et al., 2010) and showed that OCD patients exhibited enhanced dorsal ACC to DLPFC connectivity, in agreement with the hypothesis that OCD is related to an overactive control system (Schlosser et al., 2010). During Stroop interference there was no evidence for increased conflict-related activity in the ACC in our study, but increased conflict-related activity in the ACC was observed in OCS high-scoring compared to low-scoring twins from the discordant sample during Flanker interference. In addition, this increase in ACC activity during response interference was accompanied by a better performance of the OC symptom high-scoring twins compared to their low-scoring co-twins.

While the ACC was not significantly more activated in high-scoring versus low-scoring twins during Stroop interference, the DLPFC, involved in performance adjustments, showed increased conflict-related activity in the OCS high-scoring twins from discordant OCS pairs as well as in twins from concordant OCS pairs. This finding suggests that, although the degree of color-word conflict detection was the same, OCS high-scoring subjects have a higher propensity to adjust their behavior following conflict compared to low-scoring subjects. This supports the assumption of an overactive control network in OC symptomatology. As the DLPFC was affected in both the high-scoring twins from discordant and concordant pairs, it seems to act as a final common pathway for both genetic and environmental risk factors for OC symptomatology. Deviant DLPFC activity during inhibitory control may be closely correlated with the actual behavioral deficits of the disorder.

Response conflict-related brain alterations in OCS high-scoring compared to low-scoring twins were also observed

in several other regions of the brain. Regions affected in the discordant group were different from those observed in the concordant group. Brain regions showing different activation patterns in twins with high OC symptoms scores compared with those with low OC symptoms scores that were present in only the discordant group and, therefore, are likely related to environmental risk factors for OC symptomatology include the precentral gyrus (Stroop), middle temporal gyrus and cerebellum (Flanker). Brain regions showing different activation patterns in twins with high OC symptoms scores compared with those with low OC symptoms scores that were present in only the concordant group and, therefore, are likely related to genetic risk factors for OC symptomatology include the middle frontal gyrus, precuneus, angular gyrus, parietal gyrus (Stroop), and thalamus (Flanker).

An environmentally mediated increase in temporal activity and a genetically mediated increase in parietal activity have also been observed in a previous study by our group that used the discordant/concordant twin design to study OC symptom-related brain alterations during a cognitive planning paradigm (den Braber et al., 2010). OCD-related alterations in temporal and parietal cortices have been found by others as well, and have therefore been included in an extended model for OCD (Menzies et al., 2008). An altered function of these regions might, through their functional connections with the ventral and dorsal PFC, lead to an imbalance of the direct and indirect pathway of the CSTC networks, which could subsequently induce OC behavior. Abnormalities in thalamic volume and function in OCD have been extensively reported (Menzies et al., 2008). The thalamus is implicated in the CSTC model of OCD. It is the key region in modulating subcortical input to the frontal cortex, stimulates output of frontal brain regions, and plays a crucial role in the processing of sensory inputs, thereby mediating behaviors, emotion, and cognition (Sherman & Guillery, 2002). Therefore, disturbances within this structure are likely to be coupled to the cognitive and behavioral deficits seen in OCD patients. Further research into the association between these structures and the control network is warranted.

A total of 10 subjects included in this study had comorbid diagnoses which could have confounded our result. Although excluding these subjects did not change the patterns of results, comorbid traits that do not meet threshold for clinical diagnoses in the remaining subjects with high levels of OC symptoms may have influenced the results. This is a limitation of the design used, as the selection for high levels of OC symptoms will by necessity lead to co-selection for comorbid traits.

In summary, the present study demonstrates decreases as well as increases in brain activation during the inhibition of distracting information in OCS high-scoring compared to low-scoring subjects. A robust increase in DLPFC activity during response interference was observed in both the high-scoring twins of the discordant sample as well as the high-scoring twins of the concordant sample, marking this structure as a possible key region for disturbances in inhibitory control in OCD.

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References

Albert, U., Maina, G., Bogetto, F., & Ravizza, L. (2000). The role of recent life events in the onset of obsessive-compulsive disorder. *CNS Spectrums, 5*, 44–50.

Alonso, P., Menchon, J. M., Mataix-Cols, D., Pifarre, J., Urretavizcaya, M., Crespo, J. M., Jiménez, S., Vallejo, G., & Vallejo, J. (2004). Perceived parental rearing style in obsessive-compulsive disorder: Relation to symptom dimensions. *Psychiatry Research, 127*, 267–278.

American Psychiatric Association (1994). *Diagnostic and statistical manual of mental disorders: DSM-IV* (4th ed.). Washington, DC: Author.

Boomsma, D. I., de Geus, E. J., Vink, J. M., Stubbe, J. H., Distel, M. A., Hottenga, J. J., Posthuma, D., van Beijsterveldt, T. C., Hudziak, J. J., Bartels, M., & Willemsen, G. (2006). Netherlands Twin Register: From twins to twin families. *Twin Research and Human Genetics, 9*, 849–857.

Cath, D. C., van Grootheest, D. S., Willemsen, G., van Oppen, P., & Boomsma, D. I. (2008). Environmental factors in obsessive-compulsive behavior: Evidence from discordant and concordant monozygotic twins. *Behavior Genetics, 38*, 108–120.

Clifford, C. A., Murray, R. M., & Fulker, D. W. (1984). Genetic and environmental influences on obsessional traits and symptoms. *Psychological Medicine, 14*, 791–800.

de Geus, E. J., van 't Ent, D., Wolfensberger, S. P., Heutink, P., Hoogendijk, W. J., Boomsma, D. I., & Veltman, D. J. (2007). Intrapair differences in hippocampal volume in monozygotic twins discordant for the risk for anxiety and depression. *Biological Psychiatry, 61*, 1062–1071.

den Braber, A., van 't Ent, D., Boomsma, D. I., Cath, D. C., Veltman, D. J., Thompson, P. M., & de Geus, E. J. (2011). White matter differences in monozygotic twins discordant or concordant for obsessive-compulsive symptoms: A combined diffusion tensor imaging/voxel-based morphometry study. *Biological Psychiatry, 70*, 969–977.

den Braber, A., van 't Ent, D., Cath, D. C., Wagner, J., Boomsma, D. I., & de Geus, E. J. (2010). Brain activation during cognitive planning in twins discordant or concordant for obsessive-compulsive symptoms. *Brain, 133*, 3123–3140.

Fitzgerald, K. D., Welsh, R. C., Gehring, W. J., Abelson, J. L., Himle, J. A., Liberzon, I., & Taylor, S. F. (2005). Error-related hyperactivity of the anterior cingulate cortex in obsessive-compulsive disorder. *Biological Psychiatry, 57*, 287–294.

Fullana, M. A., Mataix-Cols, D., Caspi, A., Harrington, H., Grisham, J. R., Moffitt, T. E., & Poulton, R. (2009). Obsessions and compulsions in the community: Prevalence, interference, help-seeking, developmental stability, and co-occurring psychiatric conditions. *American Journal of Psychiatry, 166*, 329–336.

Geller, D. A., Wieland, N., Carey, K., Vivas, F., Petty, C. R., Johnson, J., Reichert, E., Pauls, D., & Biederman, J. (2008). Perinatal factors affecting expression of obsessive compulsive disorder in children and adolescents. *Journal of Child and Adolescent Psychopharmacology, 18*, 373–379.

Grabe, H. J., Meyer, C., Hapke, U., Rumpf, H. J., Freyberger, H. J., Dilling, H., & John, U. (2000). Prevalence, quality of life and psychosocial function in obsessive-compulsive disorder and subclinical obsessive-compulsive disorder in northern Germany. *European Archives of Psychiatry and Clinical Neuroscience, 250*, 262–268.

Grisham, J. R., Anderson, T. M., & Sachdev, P. S. (2008). Genetic and environmental influences on obsessive-compulsive disorder. *European Archives of Psychiatry and Clinical Neuroscience, 258*, 107–116.

Hettema, J. M., Neale, M. C., & Kendler, K. S. (2001). A review and meta-analysis of the genetic epidemiology of anxiety disorders. *American Journal of Psychiatry, 158*, 1568–1578.

Jonnal, A. H., Gardner, C. O., Prescott, C. A., & Kendler, K. S. (2000). Obsessive and compulsive symptoms in a general population sample of female twins. *American Journal of Medical Genetics, 96*, 791–796.

Kerns, J. G., Cohen, J. D., MacDonald, A. W., III, Cho, R. Y., Stenger, V. A., & Carter, C. S. (2004). Anterior cingulate conflict monitoring and adjustments in control. *Science, 303*, 1023–1026.

Lin, H., Katsovich, L., Ghebremichael, M., Findley, D. B., Grantz, H., Lombroso, P. J., King, R. A., Zhang, H., & Leckman, J. F. (2007). Psychosocial stress predicts future symptom severities in children and adolescents with Tourette syndrome and/or obsessive-compulsive disorder. *Journal of Child Psychology and Psychiatry, 48*, 157–166.

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*, 495–503.

Mataix-Cols, D., & van den Heuvel, O. A. (2006). Common and distinct neural correlates of obsessive-compulsive and related disorders. *Psychiatric Clinics of North America, 29*, 391–410, viii.

Melcher, T., Falkai, P., & Gruber, O. (2008). Functional brain abnormalities in psychiatric disorders: Neural mechanisms to detect and resolve cognitive conflict and interference. *Brain Research Reviews, 59*, 96–124.

Menzies, L., Achard, S., Chamberlain, S. R., Fineberg, N., Chen, C. H., Del Campo, N., Sahakian, B. J., Robbins, T. W., & Bullmore, E. (2007). Neurocognitive endophenotypes of obsessive-compulsive disorder. *Brain, 130*, 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 and Biobehavioral Reviews, 32*, 525–549.

Nakao, T., Nakagawa, A., Yoshiura, T., Nakatani, E., Nabeyama, M., Sanematsu, H., Togao, O., Yoshioka, K., Tomita, M., Kuroki, T., & Kanba, S. (2009). Duration effect of obsessive-compulsive disorder on cognitive function: A functional MRI study. *Depression and Anxiety, 26*, 814–823.

Nakao, T., Nakagawa, A., Yoshiura, T., Nakatani, E., Nabeyama, M., Yoshizato, C., Kudoh, A., Tada, K., Yoshioka, K., & Kawamoto, M. (2005). A functional MRI comparison of patients with obsessive-compulsive disorder and normal controls during a Chinese character Stroop task. *Psychiatry Research, 139*, 101–114.

Nestadt, G., Samuels, J., Riddle, M., Bienvenu, O. J., III, Liang, K. Y., LaBuda, M., Walkup, J., Grados, M., & Hoehn-Saric, R. (2000). A family study of obsessive-compulsive disorder. *Archives of General Psychiatry, 57*, 358–363.

Nicolini, H., Arnold, P., Nestadt, G., Lanzagorta, N., & Kennedy, J. L. (2009). Overview of genetics and obsessive-compulsive disorder. *Psychiatry Research, 170*, 7–14.

Page, L. A., Rubia, K., Deeley, Q., Daly, E., Toal, F., Mataix-Cols, D., Giampietro, V., Schmitz, N., & Murphy, D. G. (2009). A functional magnetic resonance imaging study of inhibitory control in obsessive-compulsive disorder. *Psychiatry Research, 174*, 202–209.

Pujol, J., Soriano-Mas, C., Alonso, P., Cardoner, N., Menchon, J. M., Deus, J., & Vallejo, J. (2004). Mapping structural brain alterations in obsessive-compulsive disorder. *Archives of General Psychiatry, 61*, 720–30.

Rachman, S., & de Silva, P. (1978). Abnormal and normal obsessions. *Behaviour Research and Therapy, 16*, 233–248.

Radua, J., & Mataix-Cols, D. (2009). Voxel-wise meta-analysis of grey matter changes in obsessive-compulsive disorder. *British Journal of Psychiatry, 195*, 393–402.

Radua, J., van den Heuvel, O. A., Surguladze, S., & Mataix-Cols, D. (2010). Meta-analytical comparison of voxel-based morphometry studies in obsessive-compulsive disorder vs other anxiety disorders. *Archives of General Psychiatry, 67*, 701–711.

Rotge, J. Y., Guehl, D., Dilharreguy, B., Tignol, J., Bioulac, B., Allard, M., Burbaud, P., & Aouizerate, B. (2009). Meta-analysis of brain volume changes in obsessive-compulsive disorder. *Biological Psychiatry, 65*, 75–83.

Salkovskis, P. M., & Harrison, J. (1984). Abnormal and normal obsessions—a replication. *Behavior Research and Therapy, 22*, 549–552.

Saxena, S., & Rauch, S. L. (2000). Functional neuroimaging and the neuroanatomy of obsessive-compulsive disorder. *Psychiatry Clinics of North America, 23*, 563–586.

Schlosser, R. G., Wagner, G., Schachtzabel, C., Peikert, G., Koch, K., Reichenbach, J. R., & Sauer, H. (2010). Fronto-cingulate effective connectivity in obsessive compulsive disorder: A study with fMRI and dynamic causal modeling. *Human Brain Mapping, 31*, 1834–1850.

Sherman, S. M., & Guillery, R. W. (2002). The role of the thalamus in the flow of information to the cortex. *Philosophical Transactions of the Royal Society of London Series B-Biological Sciences, 357*, 1695–1708.

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. *Psychological Science, 14*, 347–353.

Valente, A. A., Jr., Miguel, E. C., Castro, C. C., Amaro, E., Jr, Duran, F. L., Buchpiguel, C. A., Chitnis, X., McGuire, P. K., & Busatto, G. F. (2005). Regional gray matter abnormalities in obsessive-compulsive disorder: A voxel-based morphometry study. *Biological Psychiatry, 58*, 479–87.

van den Heuvel, O. A., Veltman, D. J., Groenewegen, H. J., Witter, M. P., Merkelbach, J., Cath, D. C., van Balkom, A. J., van Oppen, P., & van Dyck, R. (2005). Disorder-specific neuroanatomical correlates of attentional bias in obsessive-compulsive disorder, panic disorder, and hypochondriasis. *Archives of General Psychiatry, 62*, 922–933.

van Grootheest, D. S., Cath, D. C., Beekman, A. T., & Boomsma, D. I. (2005). Twin studies on obsessive-compulsive disorder: A review. *Twin Research and Human Genetics, 8*, 450–458.

van Grootheest, D. S., Cath, D. C., Beekman, A. T., & Boomsma, D. I. (2007). Genetic and environmental influences on obsessive-compulsive symptoms in adults: A population-based twin-family study. *Psychological Medicine, 37*, 1635–1644.

van Oppen, P., Hoekstra, R. J., & Emmelkamp, P. M. (1995). The structure of obsessive-compulsive symptoms. *Behavior Research and Therapy, 33*, 15–23.

van 't Ent, D., van Beijsterveldt, T. C., Derks, E. M., Hudziak, J. J., Veltman, D. J., Todd, R. D., Boomsma, D. I., & de Geus, E. J. (2009). Neuroimaging of response interference in twins concordant or discordant for inattention and hyperactivity symptoms. *Neuroscience, 164*, 16–29.

Viard, A., Flament, M. F., Artiges, E., Dehaene, S., Naccache, L., Cohen, D., Mazet, P., Mouren, M. C., & Martinot, J. L. (2005). Cognitive control in childhood-onset obsessive-compulsive disorder: A functional MRI study. *Psychological Medicine, 35*, 1007–1017.

Wilcox, H. C., Grados, M., Samuels, J., Riddle, M. A., Bienvenu, O. J., III, Pinto, A., Cullen, B., Wang, Y., Shugart, Y. Y., Liang, K. Y., & Nestadt, G. (2008). The association between parental bonding and obsessive compulsive disorder in offspring at high familial risk. *Journal of Affective Disorders, 111*, 31–39.

Wolfensberger, S. P., Veltman, D. J., Hoogendijk, W. J., Boomsma, D. I., & de Geus, E. J. (2008). Amygdala responses to emotional faces in twins discordant or concordant for the risk for anxiety and depression. *Neuroimage, 41*, 544–552.

Yucel, M., Harrison, B. J., Wood, S. J., Fornito, A., Wellard, R. M., Pujol, J., Clarke, K., Phillips, M. L., Kyrios, M., Velakoulis, D., & Pantelis, C. (2007). Functional and biochemical alterations of the medial frontal cortex in obsessive-compulsive disorder. *Archives of General Psychiatry, 64*, 946–955.