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An fMRI study in monozygotic twins discordant for obsessive–compulsive symptoms

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Abstract

To examine neurobiological changes underlying obsessive–compulsive symptoms (OCS) we examined intrapair differences in behavior and fMRI brain activation in monozygotic twins discordant for OCS, using a Tower of London planning paradigm. Despite only mild evidence for impairment at the behavioral level, twins with OCS showed significantly decreased brain activation during planning in dorsolateral prefrontal cortex, thalamus pulvinar, and inferior parietal cortex. These findings are consistent with the hypothesis of disturbed cortico-striato-thalamo-cortical (CSTC) circuitry underlying OCS. In contrast to previous studies in patients with obsessive–compulsive disorder (OCD) we did not find robust evidence for reduced responsiveness in striatal brain regions. Together, these findings suggest that neurobiological mechanisms underlying OCS of environmental origin partly overlap with neurobiological changes in patients with OCD, where the disorder is likely caused by a combination of genetic and environmental influences. A difference between genetical and environmental etiologies may relate to the amount of reduced striatal responsiveness.

Keywords: Twins; Monozygotic; Discordant; OCS; OCD; Environmental risk; fMRI; Tower of London

1. Introduction

Obsessive–compulsive symptoms (OCS) are highly prevalent in the general population (70–80%: Rachman and de Silva, 1978). They 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 (American Psychiatric Association, 1994). Well-known obsessions are fear of contamination, pathological doubt, need for symmetry, and somatic, sexual and aggressive obsessions. Compulsions include checking, washing, counting, symmetry/precision and hoarding behavior. When obsessions and/or compulsions are performed for more than 1 h a day and significantly interfere with daily life, persons fulfill the criteria for obsessive–compulsive disorder (OCD). OCD affects about 2% of the population (Miguel et al., 2005) and is generally assessed by clinical interviews, e.g. Diagnostic and Statistical Manual of Mental Disorders: DSM-IV, fourth ed. (American Psychiatric Association, 1994). Questionnaires, such as the Padua Inventory (PI) (Sanavio, 1988) and quantitative versions of the Yale-Brown Obsessive–Compulsive Scale (Y-BOCS) (Goodman et al., 1989a,b) can be utilized to explore OC symptomatology on a more quantitative scale.

There is limited information about the etiology of OCD. Genetic factors appear to be at least partly responsible. The disorder runs in families (Nestadt et al., 2000; Hettema et al., 2001) and twin studies indicate a heritability ranging from 27% to 47% in adults and 45–65% in children (Jonnal et al., 2000; van Grootheest et al., 2005).

If genetic factors explain 27–65% of the variability in OC symptoms, as much as 35–73% should be accounted for by

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environmental stressors or adverse gene–environment interactions. Environmental risk factors suggested for OCD include streptococcal infection, perinatal problems, psychosocial stress, and familial factors such as perceived parental rearing style (Alonso et al., 2004; Miguel et al., 2005). Furthermore, several life-events, including pregnancy and divorce, may trigger OCD in people genetically predisposed to the disorder (Karno et al., 1988). A recent twin study in MZ twin pairs concordant and discordant for OC symptoms identified the following risk factors: sexual assault in women, low birth weight, and low educational level (Cath et al., 2008).

Neuroimaging studies have indicated several brain changes in OCD patients compared to unaffected controls. Structural magnetic resonance imaging (sMRI) has indicated gray matter abnormalities in the prefrontal cortex (PFC), orbitofrontal cortex (OFC), caudate nucleus, thalamus and anterior cingulate cortex (ACC) (Pujol et al., 2004; Valente et al., 2005); in line with the hypothesis of disturbed cortico-striato-thalamo-cortical (CSTC) circuitry. Consistent with the sMRI findings, functional MRI (fMRI) studies have reported increased activation of these brain structures in OCD patients during performance of cognitive tasks and after symptom provocation. For example, it was recently found that OCD patients show increased activation of frontal-striatal and medial temporal brain regions during presentation of OC related threat words in a Stroop color-word naming task (van den Heuvel et al., 2005b). In addition, in the Eriksen flanker task increased anterior cingulate activation has been observed in OCD patients (Fitzgerald et al., 2005), in agreement with the hypothesis that OCD involves overactive interference monitoring and error-processing. Besides these brain regions, increased functional activation has also been reported for parahippocampal and parietal structures (Schienle et al., 2005; Viard et al., 2005). There is also evidence for abnormally reduced activation of brain areas. A recent study indicated that OCD patients are impaired on the Tower of London (ToL) cognitive planning task (Purcell et al., 1998) and that this planning in OCD patients is associated with decreased fMRI activation of the dorsolateral prefrontal cortex (dlPFC) and caudate nucleus (van den Heuvel et al., 2005a). In summary, the overall picture points to a deficit of CSTC processing, combined with dysfunction of midbrain and brainstem systems. However, there are considerable inconsistencies regarding the brain structures involved and the direction of anatomical and functional changes. It may therefore be concluded that, until now, neuroimaging studies have been only marginal successful in reducing the observed variability in OC problem behavior associated with variations in anatomy and/or function of specific brain regions.

An important reason for the inconsistent findings might be (1) the heterogeneity of the OCD phenotype and (2) the differential impact of genetic and environmental risk factors in OC behavior that does not necessarily lead to identical neurobiological pathways underlying OC behavior. With respect to the first issue, an approach that uses more homogeneous disease dimensions, such as familial cases, cases with early onset or with only one symptom dimension, might lead to more consistent results (Miguel et al., 2005). With respect to the second issue, group analyses of affected individuals in whom OCD is caused by differences in relative contributions of genetic and environmental risk factors may produce inconsistent results.

The present study, using a monozygotic discordant twin design (Martin et al., 1997) to explore OCS-related neurobiological alterations, is a first attempt to overcome the second issue. The discordant twin design allows the investigation of between twin brain differences that are specifically due to influences of environmental risk factors. Because MZ twins begin life with identical genomes, within twin pair differences in behavior mostly reflect exposure to individual-specific environment (although these may ultimately act through modification of gene expression).

We assessed differences in functional brain activation using the Tower of London task that measures the capability of cognitive planning. We aimed to investigate whether individuals with OC symptoms due to adverse environmental influences exhibit similar changes in task performance and functional brain activation during planning as previously observed in OCD patients.

2. Methods

2.1. Participants

For this study twin pairs were recruited from the Netherlands Twin Registry (NTR) (Boomsma et al., 2002). In 2002 surveys were sent to twin families including the Padua Inventory-R (PI-R) abbreviated (Sanavio, 1988; van Oppen and Arntz, 1994). Symptoms were chosen on basis of two items of each subscale with highest factor loadings in a previous validation study (van Oppen and Arntz, 1994), covering the symptom factors generally found in the PI-R dimensions of OCD, and with one additional item for each of the more equivocal obsession subscales rumination and impulses. For a detailed description of reliability and validity of the PI-R abbreviated as a screening instrument of OC behavior: (see Cath et al., 2008). Complete PI data were returned by 419 MZ twin pairs ($n = 113$ males). From this sample we selected twin pairs in the age range between 18 and 60 years, in which one twin scored high (≥ 18) and the co-twin scored low (≤ 7) on the PI-R. These cut-offs were derived from sensitivity and specificity measurements in a sample of OCD patients ($n = 120$; mean scores 20.7, S.D. 8.1; sensitivity 0.74 and specificity 0.72, when compared to clinical controls (Cath et al., 2008)). From the initial selection of 29 MZ twin pairs, 17 pairs had to be omitted: five pairs already participated in other studies of our department, one pair was found to be dizygotic, one pair used psychotropic medication, two pairs suffered from severe claustrophobia and eight pairs declined for practical reasons. Consequently, our final sample consisted of 12 MZ twin pairs discordant for OCS (fourteen females and ten males).

2.2. Protocol

Participants were administered diagnostic interviews and questionnaires, including questions on demography, life-events, comorbidity, OC symptoms and severity of OC symptoms, tics, state-anger and state-anxiety. All twins were asked to collect buccal swabs for DNA extraction to test zygosity. The ethical review board of the VU medical centre approved the study and all participants provided written informed consent.

2.3. Tower of London (ToL)

Stimuli for the ToL task consisted of images of three colored beads (red, blue, yellow), placed on three vertical rods of decreasing height (see Fig. 1). On each trial a start configuration (bottom) and final target configuration (top) were simultaneously depicted. During planning trials (Fig. 1A), subjects were requested to count the number of steps from the starting configuration to reach

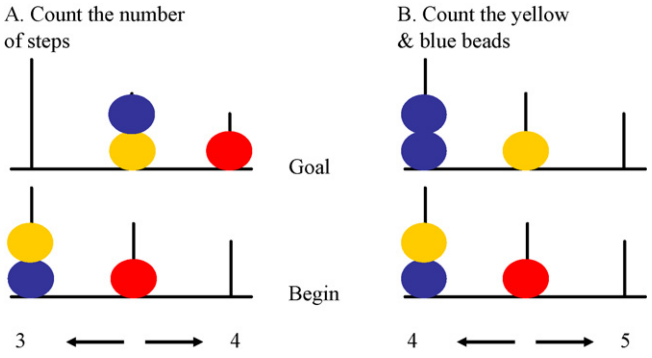

Fig. 1. Examples of Tower of London stimuli used in the present study. (A) Planning condition; (B) baseline condition (adapted from van den Heuvel et al. (2005a)).

the target configuration; with the restriction that only one bead could be moved at a time and that a bead could be moved only if there was no other bead on top. Five planning difficulty levels were included that corresponded with the minimal number of moves (1–5) actually needed to achieve the target. In addition to stimuli that required planning, baseline stimuli were included (Fig. 1B) during which subjects only had to count the total number of yellow and blue beads. With each stimulus presentation, two possible answers (one correct and one incorrect) were presented at the bottom left and right of the screen, from which the correct one had to be chosen by pressing a corresponding left or right hand button. No feedback regarding the correct answer was provided during the task.

The stimuli were presented in an event related design lasting 17 min with self-paced stimulus timing, i.e., a subsequent trial was presented on the screen immediately after the response on a previous trial, or directly after the maximum reaction time limit of 60 s. Presentation order of the stimuli was pseudo-random with a distribution frequency of the six stimulus types derived from van den Heuvel et al. (2005a). For all twins the stimulus presentation order was the same, however, the total number of trials completed by each twin depended on the twin's reaction times.

Stimuli were projected on a screen at the end of the MRI scanner table, viewed by the participant through a mirror. Two magnetic compatible response boxes were used to record the subject's performance. Prior to performance of the ToL task within the scanner, twins were made familiar with the task during a practice session on a personal computer outside the scanner. Furthermore, subjects performed a number of practice trials while being in the scanner, immediately before starting the actual task.

2.4. Image acquisition

The MRI session consisted of a structural part of about 6 min and a functional part of approximately 17 min. During the scan session the twins remained inside the scanner and were asked to minimize head-movement during and between consecutive runs. To reduce motion artifacts, the participants' 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 mm × 1.00 mm × 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 mm × 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). A total of 440 EPI volumes were scanned per subject.

2.5. 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 s), functional scans were analyzed in the context of the general linear model using delta functions convolved with a canonical hemodynamic response function. Event duration, computed as the time between stimulus and response onset, was included in the model to account for hemodynamic responses of varying lengths to each type of stimulus. Error trials and head-movement parameters were modeled as regressors of no interest. For each subject, a 'planning vs. baseline' main effect was computed in which brain activation during all planning trials was compared with brain activation during baseline trials. In addition, a main effect of 'task load' was computed using a linear contrast to identify brain regions that show MR signal intensity variation correlated with task difficulty (van den Heuvel et al., 2005a).

Differences in questionnaire- and interview data between high and low scoring twins were tested using paired sampled *t*-tests available in SPSS software (SPSS Inc., Chicago, Illinois), with significance level $p < 0.05$. For analysis of ToL task performance, reaction times and reaction accuracy (percentage of correct responses) were evaluated statistically by means of a paired MANOVA design with main variables 'task load' (the five planning difficulty levels) and 'twin OCS status' (twins scoring high on OCS vs. twins scoring low on OCS). When applicable, degrees of freedom were adjusted conforming to the method of Geisser and Greenhouse (Geisser and Greenhouse, 1958). Uncorrected degrees of freedom are reported, however, to facilitate interpretation of the statistical design.

Functional MRI contrast estimates for 'planning vs. baseline' and 'task load' were entered into a second-level analysis. Main effects across twins for both contrasts were obtained by one-way ANOVA and reported at an individual voxel threshold of $p < 0.05$, corrected for multiple comparisons (false discovery rate: FDR), with minimal cluster extent of 10 voxels. Differences in contrast estimates between OCS high twins and their OCS low scoring co-twins were investigated by paired sample *t*-test, masked with the appropriate contrast main effect (mask thresholded at $p < 0.005$, uncorrected), and reported at an uncorrected individual voxel threshold of $p < 0.001$.

3. Results

3.1. Questionnaire and interview data

Demographics and data on OC symptoms of our twin sample are summarized in Table 1. In line with the initial selection criteria, scores on the PI-R abbreviated obtained in 2002 differed significantly between OCS high and low twins ($t = 8.89$, d.f. = 11, $p < 0.001$). Re-administration of this interview at the time of MRI data collection (in 2006) indicated that within twin pairs OCS differences had slightly diminished over time: mean PI-R score of the OCS high twins was decreased by 6.75 points while mean PI-R score of the OCS low group was increased by 2.66 points. Despite this, presumably reflecting an influence of current state dependence, PI-R scores remained significantly elevated in OCS high twins ($t = 2.23$, d.f. = 11, $p = 0.047$). Y-BOCS scores obtained at the time of MRI on current OCS severity were also higher in OCS high compared with low twins ($t = 2.157$, d.f. = 11, $p = 0.054$). Together, these findings indicate that within twin pair OCS discordance was stable and also present when neuroimaging was performed.

One of the OCS high twins (female) met the criterion for OCD according to the Mini-International Neuropsychiatric Interview (MINI) at the time of MRI examination. To clarify in further detail the OC symptomatology of the persons scanned, we decided to analyze the data using severity scores of current Y-BOCS data, following the definitions used in the family study

Table 1
Twin sample demographics

Twin pair	Age	Sex	OCS scores	Padua 2002	Padua current	Y-BOCS severity	Comorbidity	
1	35	F	high/low	20/5	16/15	0/2	–	/ –
2	31	F	high/low	34/0	36/3	23/0	DE; PD + AP; SP; PTSD; GAD	/ –
3	26	F	high/low	22/6	19/16	3/0	PD + AP; GAD	/ –
4	34	F	high/low	18/5	15/1	9/0	–	/ –
5	23	M	high/low	18/7	9/10	1/0	–	/ –
6	42	M	high/low	18/3	6/6	9/1	–	/ –
7	28	M	high/low	18/5	6/7	0/0	–	/ –
8	25	F	high/low	18/5	5/8	0/0	–	/ –
9	25	M	high/low	18/0	14/2	1/0	DE	/ –
10	36	M	high/low	24/5	15/3	2/0	–	/ –
11	38	F	high/low	18/6	9/6	2/2	–	/ –
12	50	F	high/low	18/6	13/8	12/6	–	/ –
Mean	32.8	7F/5M		20.3/4.4	13.6/7.1	5.2/0.9		/ –
Standard deviation	8.1			4.7/2.3	8.4/4.8	6.7/1.8		/ –

Twin sample demographics. Twin pair: twin pair number; age: age at time of MRI exam; sex: M = male, F = female; OCS scores: obsessive and compulsive symptoms measured with the 12-item Padua Inventory; high = score $\geq$18; low = score $\leq$7; Padua 2002: Padua score in 2002; Padua current: Padua score at time of MRI; Y-BOCS severity: Y-BOCS severity score at time of MRI; comorbidities: comorbidities at the time of MRI; DE = depressive episode, PD = panic disorder, AP = agoraphobia, SP = social phobia, PTSD = post traumatic stress disorder, GAD = generalized anxiety disorder. Data for OCS high and low twins within cells are separated by a forward slash ('/').

on OCD (Pauls et al., 1995), and in best estimate processes by the Tourette Syndrome Association (TSA) genetic consortium and the Obsessive Compulsive Foundation (OCF) genetic collaboration on OCD. In this method, following DSM-IV criteria, OCD is established using the Y-BOCS severity criteria, as follows: OCD is diagnosed when: OC symptoms take more than 1 h a day and persons experience distress/interference from the symptoms; subthreshold OCD is diagnosed when persons experience either distress from their OC symptoms but spend less than 1 h on the symptoms, or experience no distress from the symptoms but spend more than 1 h on the symptoms. After analyzing the data using these criteria, there were three persons in the high scoring group who fulfilled criteria of OCD (among whom the person who met OCD criteria using the MINI), and two persons fulfilled criteria of subthreshold OCD as a consequence of the time (>1 h) spent on symptoms. In the low scoring group no subjects fulfilled criteria of OCD but two persons fulfilled criteria of subthreshold OCD as a consequence of the time (>1 h) spent on the symptoms.

Comorbidity, according to the MINI and at the time of MRI, tended to be more prevalent in the OCS high twins (see Table 1: last column). However, statistical analysis did not reveal any significant within pair differences ($t = 1.42$, d.f. = 11, $p = 0.184$). Separate screening for tics ($t = .90$, d.f. = 11, $p = 0.389$), symptoms of depression (Beck's Depression Inventory Revised (BDI-R): $t = 0.73$, d.f. = 11, $p = 0.481$), or state-anxiety and state-anger (State Trait Anxiety Inventory (STAI): $t = 0.73$, d.f. = 11, $p = 0.482$; State Trait Anger Scale (STAS): $t = 1.00$, d.f. = 11, $p = 0.339$) also did not reveal significant differences between OCS high and low twins.

3.2. Task performance

Fig. 2 shows measures of response latency (top) and response accuracy (bottom) as a function of task load. Significant main effects of the variable 'task load' (response latency: F (4, 44) = 118.58, $p < 0.001$; response accuracy: F (4, 44) = 30.04, $p < 0.001$) indicated that reaction times increased and reaction accuracy decreased with increasing task difficulty. There were no significant differences between the OCS high and low twins in response latencies and

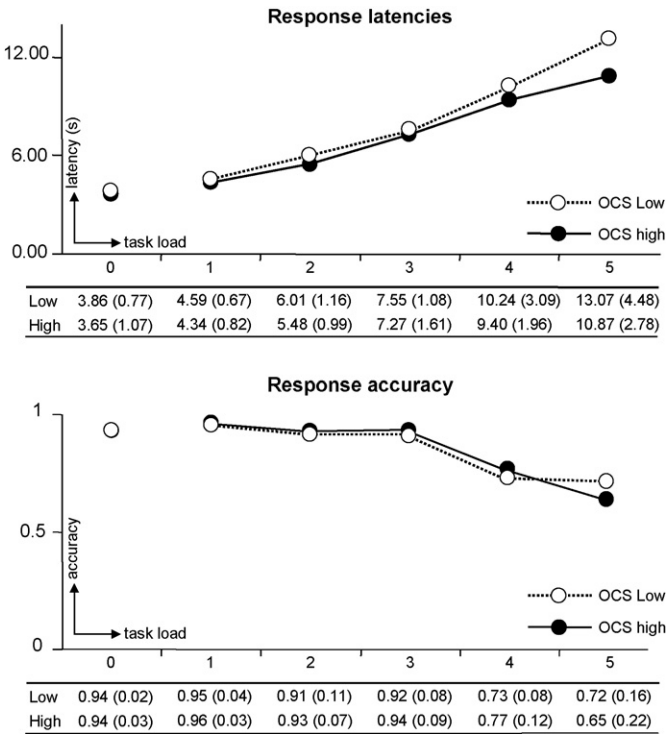

Fig. 2. ToL task performance. Top panel: mean latencies (ms) of correct responses as a function of task load levels 1, 2, 3, 4 and 5 (task load 0 = baseline condition); bottom panel: response accuracy (between 0 and 1) as a function of task load. Data for OCS high and low twins are indicated by filled and open circles, respectively.

accuracies, neither for the baseline condition (response latency: $t = 0.68$, d.f. = 11, $p = 0.514$; response accuracy: $t = -0.36$, d.f. = 11, $p = 0.725$) nor during planning ('OCS status' main effect–response latency: F (1, 11) = 1.16, $p = 0.305$; response accuracy: F (1, 11) = 0.00, $p = 0.981$; 'OCS status' by 'task load' interaction–response latency F (4, 44) = 1.07, $p = 0.380$; response accuracy: F (4, 44) = 1.42, $p = 0.262$). When comparing task performance for the two highest levels of task load (4 and 5 steps), we did find an indication of decreased response accuracy in OCS high twins for the most difficult planning condition (5 steps) ('OCS status' by 'task load' interaction: F (1, 11) = 3.61, $p = 0.084$).

3.3. Functional Imaging

3.3.1. Main effect

Regions showing increased BOLD signal for 'task vs. baseline' and 'task load' contrasts are summarized in the top and bottom panels of Fig. 3 (glass brain projections) and Tables 2 and 3, respectively. For both contrasts, clusters of increased brain activation associated with ToL planning were noted, bilaterally, in parietal cortex (Brodmann areas 7 and 40), premotor cortex (BA 6 and 8), anterior prefrontal cortex (BA 10), dorsolateral prefrontal cortex (BA 9) and cerebellum. For the 'task vs. baseline' contrast also robust task related activation was found in regions of the basal ganglia (see for example the selected anatomical overlay in the top right of Fig. 3). Basal ganglia activation was virtually absent for the 'task load' contrast (bottom right of Fig. 3).

3.4. OCS high vs. low within twin pair differences

3.4.1. 'Planning vs. baseline'

Table 4 and Fig. 4 summarize the OCS high vs. low within twin pair comparison results for the 'planning vs. baseline' contrast. Relative to their low scoring co-twins, twins who scored high on OCS exhibited clusters of decreased brain activation in the right and left premotor gyrus (clusters labeled A, B and C in Table 4 and Fig. 4), left dorsolateral prefrontal cortex (cluster labeled E) and left inferior parietal gyrus (cluster D). Increased brain activation for the OCS high twins was observed in the left precentral gyrus (cluster F), right postcentral gyrus (cluster G), right supramarginal gyrus (cluster H) and left inferior temporal gyrus (cluster I).

3.4.2. 'Task load'

For the 'task load' contrast (Table 5 and Fig. 5), clusters of decreased brain activation in OCS high compared to OCS low scoring twins were noted in the left dorsolateral prefrontal cortex (cluster labeled A in Table 5 and Fig. 5) and right pulvinar (cluster B). We found only a single cluster of relatively increased brain activation for the OCS high scoring twins in a region of the right medial frontal gyrus (cluster C).

4. Discussion

We examined behavioral performance and concurrent brain activation, measured with fMRI, during execution of the Tower of London cognitive planning task in genetically identical twins

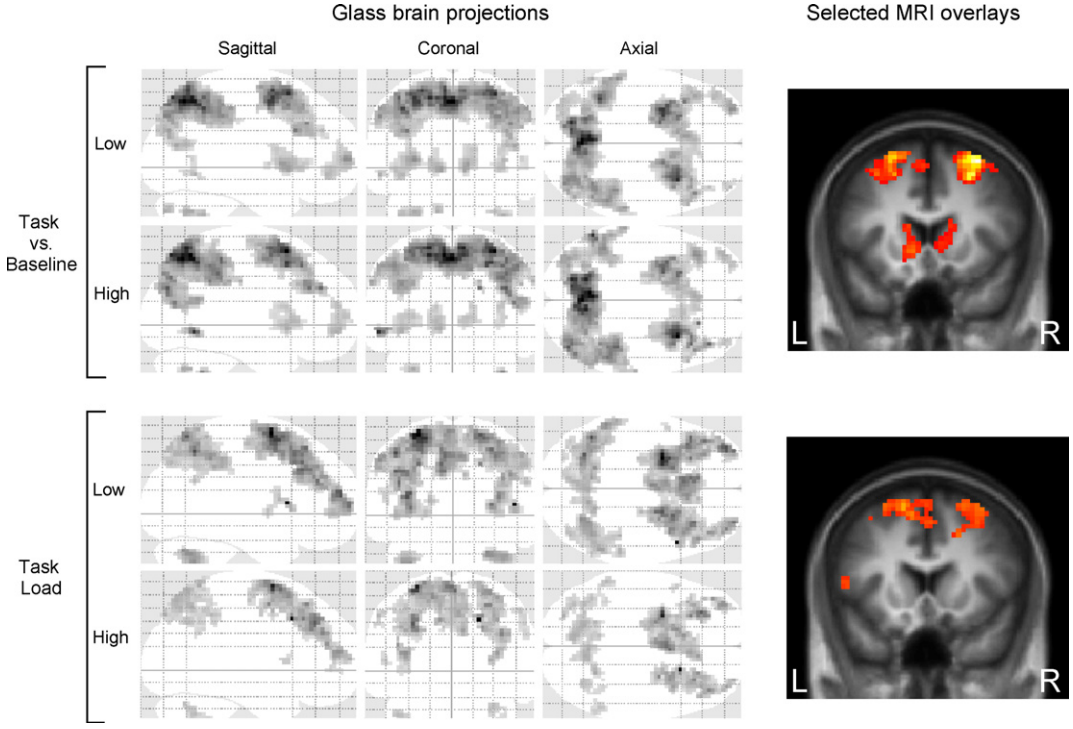

Fig. 3. Brain regions showing increased BOLD signal during ToL cognitive planning. Glass brain overviews on the left depict brain activity patterns for 'task vs. baseline' (top) and 'task load' (bottom) contrasts in OCS low (low) and high (high) scoring twins. Selected anatomical overlays on the right illustrate the difference in functional activation of basal ganglia structures between 'task vs. baseline' (top) and 'task load' (bottom) contrasts. Functional activations for OCS high twins are shown, overlaid on an averaged structural MRI across all twins.

Table 2
Brain regions showing significant BOLD signal increase for the 'planning vs. baseline' contrast

	Anatomical location	BA	OCS low ($n = 12$)						OCS high ($n = 12$)					
			MNI coordinates			Z score	p-value	# voxels	MNI coordinates			Z score	p-value	# voxels
			x	y	z				x	y	z			
PC	Left parietal cortex	7/40	0	−66	54	5.98	0.000	2363	−6	−60	57	5.78	0.000	2416
	Right parietal cortex	7/40	33	−78	42	4.73			9	−63	63	5.51		
PM	Left premotor cortex	6	−30	3	57	5.53	0.000	471	−24	3	63	5.00	0.000	470
	Right premotor cortex	6	33	15	60	5.63	0.000	855	33	15	60	5.78	0.000	612
PFC	Left anterior prefrontal cortex	10	−30	60	6	4.61	0.000	158	−39	54	−6	3.89	0.000	93
	Left dlPFC	9	−36	21	30	4.89	0.000	106	−39	33	33	4.43	0.000	107
	Right anterior prefrontal cortex	10	39	60	6	3.81	0.676	20	36	57	15	3.48	0.000	612
	Right dlPFC	9	45	30	36	4.71	0.000	855	21	33	30	4.80	0.946	13
CBL	Left cerebellum	–	−30	−60	−36	4.13	0.009	62	−30	−66	−36	3.97	0.143	34
	Right cerebellum	–	39	−51	−39	4.05	0.020	54	39	−51	−39	4.46	0.834	16
BG	Left caudate nucleus	–	−9	15	0	4.33	0.000	109	−9	15	−3	3.99	0.000	128
	Left globus pallidus	–	−15	0	3	3.29			–	–	–	–	–	–
	Right caudate nucleus	–	12	9	3	4.35	0.000	151	12	21	6	3.56	0.002	75

Brain regions showing significant BOLD signal increase after applying the 'planning vs. baseline' contrast for OCS low (left) and OCS high (right) twins. Anatomical location: location of cluster (PC = parietal cortex; TC = temporal cortex; PM = premotor cortex; PFC = prefrontal cortex; CBL = cerebellum; BG = basal ganglia); BA: Brodmann area; MNI coordinates (mm): location of voxel with largest effect size; Z score: z-value of voxel with largest effect size; p-value: cluster p-value; # voxels: number of voxels in cluster. For cases where regional differences correspond to local maxima within a large interconnected cluster, cluster p-value and number of voxels are displayed in single, merged, cells.

discordant for obsessive–compulsive symptoms. Differences in task performance and fMRI activation between twins scoring high and low on OCS were expected to be indicative of neurobiological changes related to the environmentally mediated risk for OCD.

Although impaired ToL planning at the behavioral level, as reported earlier in OCD patients (van den Heuvel et al., 2005a), was evident in our sample only by a tendency towards decreased reaction accuracy for the highest planning difficulty level (five planning steps), comparison of fMRI data indicated several areas with decreased brain activation during ToL performance in OCS high scoring twins.

In agreement with van den Heuvel et al. (2005a) we observed reduced brain activity in regions of the dlPFC for both 'task vs. baseline' and 'task load' contrasts. The dlPFC is importantly involved in executive functions including cognitive planning, inhibitory control and decision making (Rosenberg and Keshavan, 1998; Faw, 2003; Newman et al., 2003; Remijnse et al., 2006). Furthermore, decreased dlPFC activity is compatible with the neuroanatomical model of OCD that

Table 3
Brain regions showing significant BOLD signal increase for the 'task load' contrast

	Anatomical location	BA	OCS low ($n = 12$)						OCS high ($n = 12$)					
			MNI coordinates			Z score	p-value	# voxels	MNI coordinates			Z score	p-value	# voxels
			x	y	z				x	y	z			
PC	Left parietal cortex	7/40	−45	−57	51	4.83	0.000	795	−27	−81	45	3.82	0.000	123
	Right parietal cortex	7/40	54	−51	48	3.89	0.000	299	24	−54	69	3.93	0.000	384
PM	Left premotor cortex	6	−27	3	66	5.41	0.000	2255	−27	3	69	5.28	0.000	693
	Right premotor cortex	6	21	3	66	4.72			27	0	54	4.41	0.000	471
PFC	Left anterior prefrontal cortex	10	−36	57	15	4.78			−36	54	15	4.26	0.000	242
	Left dlPFC	9	−45	27	36	4.63			−30	36	39	4.81		
	Right anterior prefrontal cortex	10	30	63	9	4.42			36	57	15	4.10	0.000	471
	Right dlPFC	9	45	33	33	4.08			24	33	36	4.24		
CBL	Left cerebellum	–	−33	−57	−39	4.10	0.001	97	−42	−57	−36	3.63	0.132	27
	Right cerebellum	–	27	−66	−30	4.15	0.000	160	33	−66	−27	3.56	0.014	45
BG	Left putamen	–	−18	9	12	3.52	0.179	36	–	–	–	–	–	–

Brain regions showing significant BOLD signal increase after applying the 'task load' contrast for OCS low (left) and OCS high (right) twins.

Table 4
Clusters with differences in brain activity between OCS high and low twins: 'planning vs. baseline' contrast

Test	Cluster label	Anatomical location	BA	MNI coordinates			Z score	p-value	# voxels
				x	y	z			
high < low	A	Right frontal gyrus	6	15	−3	63	4.17	0.000	29
	B		8	15	24	48	3.07	0.001	9
	C	Left frontal gyrus	6	−30	0	51	3.01	0.001	15
	E		9	−36	21	30	3.14	0.001	4
	D	Left inferior parietal gyrus	40	−39	−51	48	3.32	0.000	17
high > low	F	Left precentral gyrus	6	−21	−15	69	3.10	0.001	6
	G	Right post central gyrus	1	36	−39	69	3.32	0.000	6
	H	Right supramarginal gyrus	40	51	−54	21	3.35	0.000	22
	I	Left inferior temporal gyrus	37	−48	−57	−3	3.64	0.000	16

Clusters with regional brain activity differences between OCS high and low scoring twins for the 'planning vs. baseline' contrast. Test: test for significant increases/decreases in OCS high relative to OCS low twins. Cluster label: alphabetical cluster label as displayed in anatomical overlays of Fig. 4. dlPFC = dorsolateral prefrontal cortex.

proposes a disturbance of cortico-striato-thalamo-cortical circuitry (Rosenberg and Keshavan, 1998; Singer and Minzer, 2003; Mataix-Cols and van den Heuvel, 2006).

For the contrast 'task load', an additional area of reduced activation was found in the pulvinar of the right thalamus. Although decreased responsiveness of thalamic regions was absent in the study by van den Heuvel et al. (2005a), OCD related changes for the pulvinar (Viard et al., 2005) as well as other regions of the thalamus have been found in several other neuroimaging studies. Structural MRI studies have reported OCD related volumetric increases of thalamic regions (Gilbert et al., 2000; Kim et al., 2001; Atmaca et al., 2007). Functional MRI studies have indicated changes for thalamic regions as well, although in contrast to our findings, these generally point to increased rather than decreased metabolism associated with the disorder (Chen et al., 2004; Mataix-Cols et al., 2004; Schienle et al., 2005). Results of PET/SPECT studies are inconclusive. Some perfusion studies showed increased thalamic regional cerebral blood flow (rCBF) (Alptekin et al., 2001; Saxena et al., 2001, 2004; Lacerda et al., 2003), whereas others report thalamic rCBF decreases (Lucey et al., 1995; Busatto et al., 2001). One PET ligand study demonstrated reduced thalamic serotonin transporter (SERT) availability in OCD patients compared to healthy controls (Hesse et al., 2005). The pulvinar of the posterior thalamus is presumably involved in the integration of sensory information, visuo-spatial processing and visual selective attention (Laberge and Buchsbaum, 1990; Kastner and Pinsk, 2004; Michael and Buron, 2005; Buchsbaum et al., 2006). Together with the dlPFC, the thalamus is implicated in the CSTC circuit. It is the key region in modulating subcortical input to frontal cortex, stimulates output of frontal brain regions, and plays a crucial role in the processing of sensory inputs thereby mediating both behaviors, emotion and cognition (Sherman and Guillery, 2002). Disturbances within this structure could therefore easily be coupled to the cognitive and behavioral deficits seen in OCD patients.

Finally, reduced brain activity related to OCS included premotor and inferior parietal regions. Similar to van den Heuvel et al. (2005a), activation changes in these brain regions were present exclusively in the 'task vs. baseline' contrast. Given that the 'task vs. baseline' contrast (as compared to 'task load') tests for all brain areas needed for correct planning, as well as the fact that premotor and parietal areas are involved in basic functions of motor response preparation (Hoshi and Tanji, 2000; Mars et al., 2007) and visuo-spatial processing (Cabeza and Nyberg, 2000), it is likely that these brain regions mainly support proper task execution rather than higher-order planning itself (Lazeron et al., 2000). For example, involvement of premotor regions might reflect differences in internal imagery of movement of the beads during planning (Rowe et al., 2001). Involvement of the parietal lobes during cognitive planning has been found previously (Lazeron et al., 2000; van den Heuvel et al., 2003), and parietal cortex abnormalities associated with OCD also have been reported. Anatomical studies indicated OCD related parietal gray matter (Valente et al., 2005; Menzies et al., 2007) and white matter (Szeszko et al., 2005; Kitamura et al., 2006) reductions. Furthermore PET, SPECT as well as MEG studies reported decreased parietal activation in OCD patients compared to unaffected controls (Lucey et al., 1995; Kwon et al., 2003; Ciesielski et al., 2005). The dlPFC receives somatosensory and visuo-spatial information from the parietal lobes (Faw, 2003) and activation of the inferior parietal lobes has shown to be correlated with prefrontal activity (Baker et al., 1996; Dagher et al., 1999). Therefore reduced parietal cortex function may result in functional changes of the dlPFC which in turn could eventuate in OC symptoms. Parietal dysfunction may also relate to general problems in visuo-spatial ability and nonverbal memory which have been proposed as impaired cognitive domains in OCD patients (Savage et al., 1999a,b; Lazeron et al., 2000).

Our results also indicated clusters of increased functional brain activation related to OCS. Regional fMRI signal increments in OCS high compared to low scoring twins were found in the right postcentral gyrus, left precentral gyrus, right supramarginal gyrus and left inferior temporal gyrus, and in the right medial frontal gyrus for the 'task load' contrast. Post/precentral, supramarginal and medial frontal gyrus regions primarily relate to brain areas involved in sensory (Iwamura, 1998), and motor and premotor (Chouinard and Paus, 2006) processing, while the inferior temporal lobe has been

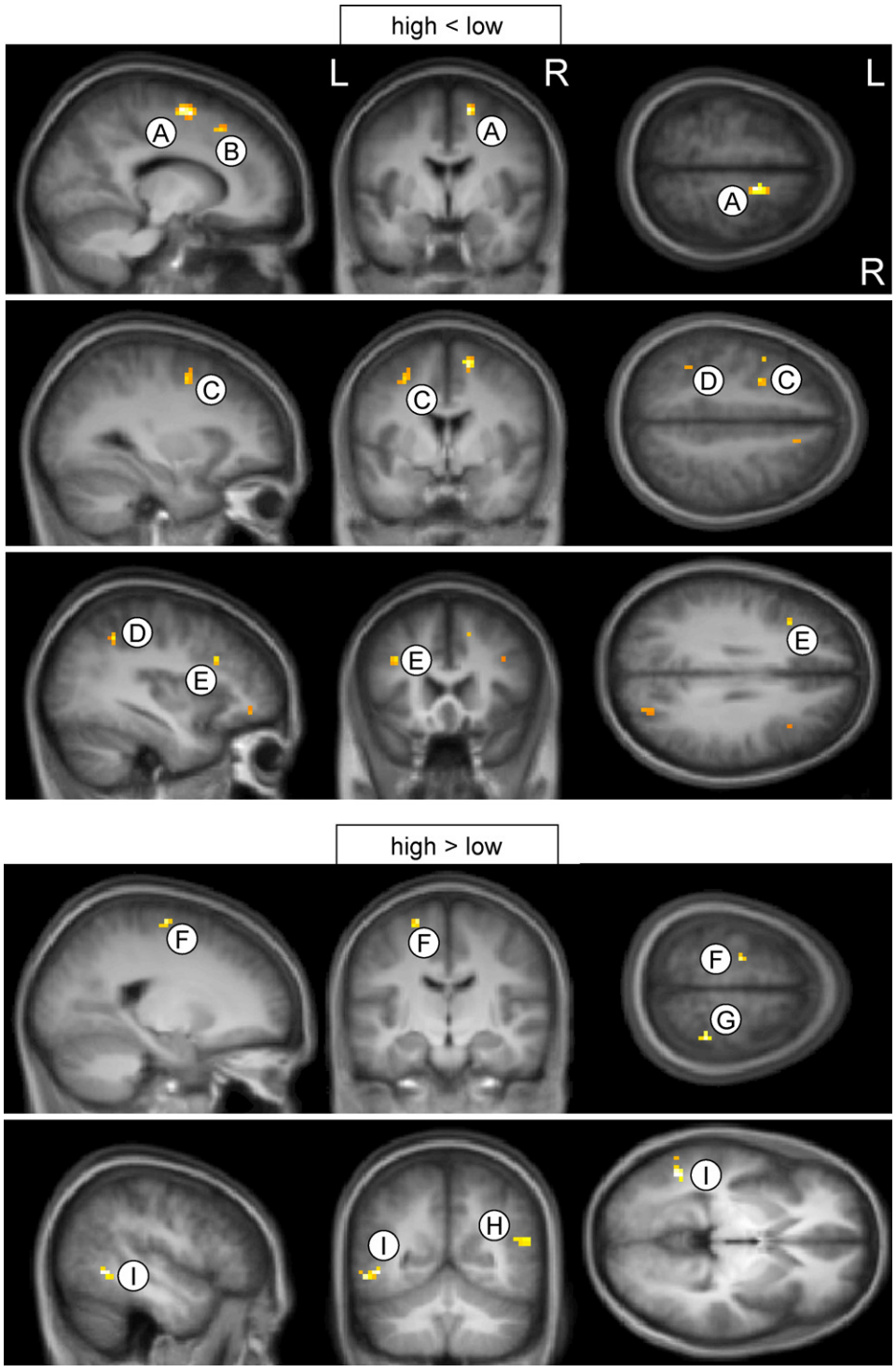

Fig. 4. Brain regions showing reduced (top panels) and increased (bottom panels) BOLD signal in OCS high vs. low twins for the 'planning vs. baseline' contrast. Clusters of significant difference are overlaid on an averaged structural MRI across all twins.

implicated in the ventral visual stream associated with object and word recognition (Goodale and Milner, 1992; Nobre et al., 1994). It is therefore likely that these brain regions mainly relate to basic processing that supports proper planning execution, rather than higher-order cognitive planning. For the temporal lobes, functional activation changes in OCD patients have been reported earlier (Adler et al., 2000; Mataix-Cols et al., 2004; van den Heuvel et al., 2005a), although generally not in inferior temporal parts. Increased responsiveness of brain areas may be indicative of increased arousal or mechanisms that act to compensate for functional deficits elsewhere in the brain.

When contrasting the present findings with the ToL planning in OCD patients as reported by van den Heuvel et al. (2005a),

Table 5
Clusters with differences in brain activity between OCS high and low twins: 'task load' contrast

Test	Cluster label	Anatomical location	BA	MNI coordinates			Z score	*p*-value	# voxels
				x	*y*	*z*			
high < low	A	Left frontal gyrus	46	−48	39	18	3.95	0.000	14
	B	Right pulvinar	–	18	−36	9	3.07	0.001	6
high > low	C	Right medial frontal gyrus	8	21	30	36	3.24	0.001	11

Clusters with regional brain activity differences between OCS high and low twins for the 'task load' contrast. Cluster label: alphabetical cluster label as displayed in Fig. 5.

an interesting difference is observed with respect to responsiveness of the caudate nuclei. van den Heuvel et al. (2005a) found decreased activation of the caudate nuclei in OCD patients compared to controls, whereas a comparable difference was absent in our intrapair twin comparisons. Functional changes of the caudate are in line with the general theory of a dysfunction of prefrontal-basal ganglia circuitry in OCD (Pauls et al., 1986; van den Heuvel et al., 2005a). The dissimilarity between our results and those of van den Heuvel et al. (2005a) may indicate a difference between neurobiological changes underlying OCS due to combined genetic and environmental influences and due to pure environmental influences. OCD patients represent a group in which OCD is caused by genetic, environmental, and combined influences. In discordant MZ twin pairs, neurobiological changes can only be due to environmental stressors. However, we cannot rule out alternative explanations, such as the limited sample size possibly obscuring between-group differences, and the possibility that basal ganglia abnormalities are more severe in clinically diagnosed OCD patients. In this respect, we should also note that post-hoc analyses revealed a cluster of relatively reduced activation for the OCS high twins in the right caudate for the 'planning vs. baseline' contrast, similar to van den Heuvel et al. (2005a), but only after lowering the statistical threshold to $p = 0.01$, uncorrected.

Finally, due to the limited sample size of this study, we were unable to analyze our data at a level of symptom dimensions.

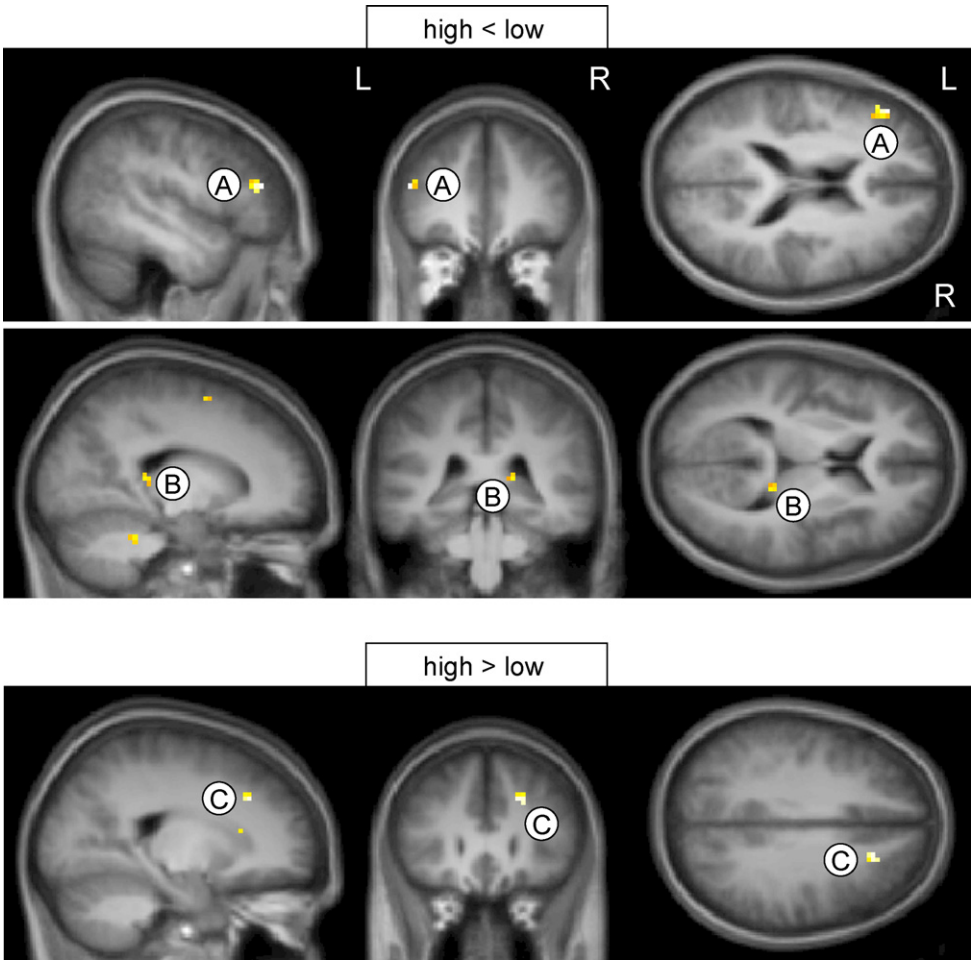

Fig. 5. Clusters with significantly reduced (top) and increased (bottom) BOLD signal in OCS high vs. low twins, for the 'task load' contrast.

Previous studies have indicated washing behavior to be related to activation of caudate and ventral striatal regions, and checking to activation of dorsal regions (Mataix-Cols et al., 2004). Our whole group analyses did not reveal any of these patterns. Future studies, using a larger sample size, should address this issue.

In the present sample for MRI we did not find significant intrapair differences on life-events or data on health (including birth order and birth weight) between the high and low scoring co-twins. However, our sample was drawn from a larger population of OCS high–low discordant twin pairs previously selected for behavioral characterization (Cath et al., 2008). Statistical analysis on survey data (self-reports including: life-events, life style factors and data on health, taken at six time points between 1991 and 2002) in that study indicated as risk factors: low educational level, sexual assault at a young age and low birth weight (low birth weight was significant only as a shared environment factor in the comparison with twin pairs concordant high and low for OCS).

Taken together, our findings suggest that neurobiological changes underlying the environmentally mediated risk for OCS partly overlap with the neurobiological abnormalities reported in OCD patients where the disorder likely originates from a combination of adverse genetic and environmental influences. A possible difference between genetically and environmentally mediated backgrounds may relate to functional changes of the striatum, which appear to be less pronounced in environmentally mediated OCS. In future work, we will directly explore differences between the genetic and environmental neurobiology of OC behavior by comparing results from our intrapair OCS discordant twin comparisons with changes in fMRI brain scans during cognitive planning between MZ twin pairs concordant high and MZ twin pairs concordant low for OCS; a contrast particularly suited for identifying basic neural mechanisms behind OCS primarily due to genetic risks.

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