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ORIGINAL PAPER

Antisaccade performance in patients with obsessive–compulsive disorder and unaffected relatives: further evidence for impaired response inhibition as a candidate endophenotype

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Abstract Cognitive dysfunctions such as inhibitory deficits and visuospatial abnormalities are often found in patients with obsessive–compulsive disorder (OCD). Recent findings in unaffected relatives indicate that response inhibition and other neuropsychological functions may also constitute endophenotypes of OCD. In the present study, 30 OCD patients, 30 first-degree relatives, and 30 healthy control subjects were assessed using a comprehensive neuropsychological test battery. A subsample of 21 subjects of each group also performed an antisaccade task. The samples were matched according to age, gender, education, and verbal intelligence. The OCD patients and the unaffected OCD relatives showed increased antisaccade error rates compared with the healthy control group ($p = 0.003$, $p = 0.028$, respectively). Significantly prolonged antisaccade latencies as compared to prosaccade latencies were only found in the OCD patients compared with the healthy control group ($p = 0.019$). Only OCD patients but not the unaffected OCD relatives were impaired with regard to visuospatial functions, problem-solving, and processing speed. Antisaccade errors did not correlate with severity of OCD or depressive symptoms. This study confirms inhibitory deficits, as indicated by increased antisaccade error rates, as a candidate endophenotype of OCD. In agreement with previous findings from imaging studies, our data suggest that functional abnormalities in frontostriatal and parietal cortical regions form part of the vulnerability for OCD.

Keywords Obsessive–compulsive disorder · Endophenotype · Cognition · Neuropsychology · Antisaccade · Unaffected relatives · Response inhibition

Introduction

Obsessive–compulsive disorder (OCD) is an often chronic and debilitating psychiatric disorder affecting 1–3 % of the population worldwide [66]. Family studies in North America and Europe have shown that the disease is familial, with first-degree relatives having a fivefold higher risk on average to be affected with the same disease [20, 38, 42]. Heritability estimates based on twin studies of OCD and of OCD-related traits average around 50 % [64]. On the basis of these findings, the hunt for OCD candidate genes has started (for an overview see [39]). However, there is only modest progress in the search for contributing variants, and replication of significant findings is missing in most cases [41].

It has been reasoned that the large variability of the OCD phenotype is one major constraint of OCD genetics rendering a positive genotype–phenotype association unlikely [8, 37]. Gottesman and Gould [19] suggested an alternative design by considering endophenotypes which

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are supposed to be more closely linked to the disease-related genes and thus may be more suitable for studying genetic associations. To qualify as an endophenotype, it has to be demonstrated that these trait markers are under high heritability and are co-segregated with the disorder [19]. That is, unaffected relatives are expected to show aberrant features comparable with affected persons and in distinction from the general population [26].

Neuropsychological functions constitute promising candidate endophenotypes across several psychiatric disorders. With regard to OCD, impairments in visuospatial and executive functions have been replicated while verbal memory and other neuropsychological functions seem to be largely normal [25, 40]. For the domain of visuospatial functions, deficits in areas such as visual memory and visual organization (i.e. [12, 56]) or spatial working memory [45, 46] were reported. In executive functions, among others, impairments were reliably found with regard to set-shifting (i.e. [1]), decision making [6], and problem-solving (i.e. [62]). Some of these neuropsychological functions may qualify as an endophenotype. Recently, the first encouraging reports of deficient functioning in unaffected relatives of OCD patients were published. These preliminary studies indicated neurocognitive deficits in relatives using the Tower of London Task (TOL) [7, 13], the Wisconsin Card Sorting Test (WCST) [7, 49], the Iowa Gambling Task (IGT) [7, 65], the Rey Complex Figure Test (RCFT) [49, 57], the Delayed Alternation Task (DAT) [65], and the Stroop Test [49]. However, performance within the normal range was also reported in unaffected OCD relatives regarding some of these tasks, namely the TOL [49, 65], the WCST [65], and the RCFT [65].

Chamberlain and colleagues suggested a model of OCD reflecting primary inhibitory deficits [8]. They proposed that failures in behavioural and cognitive inhibition form the neural base of compulsive repetitions and ongoing obsessional thoughts. This hypothesis was supported by a series of studies yielding significantly impaired inhibition processes in OCD subjects compared to healthy control subjects using a stop-signal task or go/no-go tasks [9, 35, 43]. Moreover, inhibitory deficits also qualify as candidate endophenotype. Chamberlain and co-workers reported reduced inhibition (measured by a stop-signal task) and impaired cognitive flexibility (measured by ID/ED shift task) in a group of 20 unaffected OCD relatives compared to healthy control probands [10, 35]. A recent EEG study conducted by Riesel et al. [52] analysed performance of OCD patients and their unaffected relatives in a flanker task. Similar to the stop-signal task, the flanker task asks to inhibit a prepotent but incorrect response in favour of the correct reaction. Interestingly, OCD patients and the unaffected relatives both showed an increased error-related negativity (a negative deflection after an incorrect response) compared to a healthy control group also indicating impaired performance monitoring.

Performing the antisaccade task requires inhibitory processes to suppress a reflexive saccade towards a peripheral stimulus [22]. Considering a race model, successful response inhibition of the prosaccade thus gives extra time for the computation and generation of the correct antisaccade [31]. Tien et al. [60] were the first to demonstrate significantly higher error rates in OCD patients compared to healthy controls. This finding was replicated by Rosenberg and colleagues in paediatric OCD patients and in adults with an OCD diagnosis in the absence of comorbid depression and without current medication [53, 54]. Two other studies found increased antisaccade reaction latencies but intact error rates [30, 63]. A recent study also demonstrated impairments in volitional saccade generation in OCD patients, which, however, did not lead to a higher proportion of antisaccade errors or prolonged latencies [24]. Oculomotor functions are considered heritable and stable over time, and thus could qualify as endophenotype [16, 28, 61].

We aimed to replicate the finding of impairments in OCD patients and unaffected OCD relatives in visuospatial functions (i.e. visual memory and organization) and executive functions (i.e. problem-solving), which would corroborate the potential endophenotype status of these domains. Deficits in the field of oculomotor functioning have been described in OCD patients but were not assessed in unaffected OCD relatives so far. Assuming that impaired response inhibition might be an endophenotype of OCD, we expected increased antisaccade error rates in patients and relatives, compared to healthy control subjects.

Methods and materials

Participants

The OCD families were recruited within a family study on OCD conducted at four sites across Germany [20]. This study was designed to characterize the familiarity of OCD and to identify factors related to the heterogeneity of the OCD phenotype. Additionally, blood samples were collected for genetic association analyses. The neuropsychological testing was carried out in a subsample of subjects recruited at the Departments of Psychiatry of the Universities of Bonn and Cologne while oculomotor functions were only assessed at the Department of Psychiatry of Bonn. All neuropsychological tested subjects had to be between 18 and 65 years of age. Participants were excluded when presenting with any neurological disturbance or somatic diseases affecting cognitive functions (e.g. diabetes, hypothyreosis), a lifetime history of schizophrenic or

bipolar affective disorder, and a current or lifetime history of substance abuse. In addition, participants who had undergone electroconvulsive therapy within the previous year or had a current medication of more than 0.5 mg lorazepam were excluded. An extensive clinical assessment was conducted including a screening for somatic illnesses with all study subjects to ensure diagnostic status. The German version of the Schedule for Affective Disorders and Schizophrenia (SADS, [29]), which had been extended by DSM-IV criteria for OCD spectrum disorders, was used to assess lifetime and current psychiatric status. OCD symptoms and severity were assessed using the Yale-Brown Obsessive–Compulsive Scale (Y-BOCS, [18]). The Beck Depression Inventory (BDI, [3]) was used to estimate the severity of current depressive symptoms. The clinical interviews were conducted by trained psychologists, and clinical and neuropsychological assessments were done on separate days. The study was approved by the appropriate local ethic committees of the Universities of Bonn and Cologne. All participants gave their written informed consent prior to inclusion into the study.

$N = 32$ unaffected relatives with analyzable neuropsychological data were included in the present study. Oculomotor data recordings were only done in Bonn and were thus available only from $n = 21$ relatives. To compare cognitive functioning in these relatives, we investigated an OCD patient group and a healthy control group. The group of unaffected relatives and both comparison groups were parallelized (groupwise) with regard to age, gender distribution, education, and premorbid verbal intelligence resulting in a neuropsychological sample of $n = 90$ subjects ($n = 30$ of each group) and an antisaccade sample of $n = 63$ subjects ($n = 21$ of each group). All subjects of the antisaccade sample were included in the larger neuropsychological sample.

Of the 30 first-degree relatives included in the analyses, $n = 15$ were parents, $n = 11$ were siblings, and $n = 4$ were children of OCD-affected patients. None of the relatives had ever experienced any OCD symptoms as was assured by the clinical interview. In five cases, other psychiatric conditions were diagnosed (depressive disorders: $n = 2$, tic disorder: $n = 1$, anxiety disorders: $n = 5$).

All included OCD patients fulfilled DSM-IV-criteria of OCD at the time of testing. The OCD patients were not related to the unaffected relatives included in the present study. Seven of them were outpatients, and 23 were inpatients of the Departments of Psychiatry, universities of Bonn and Cologne. Two OCD patients refused to submit to a detailed diagnostic interview. However, both fulfilled DSM-IV-criteria of OCD as confirmed by two independent clinicians and were therefore included in the OCD group. In 20 cases (67 %), comorbid illnesses were diagnosed (depressive disorders, $n = 8$; anxiety disorders, $n = 14$; tic disorder, $n = 3$; somatoform disorder/hyochondriasis, $n = 2$; OCD spectrum disorders, $n = 2$). Twenty-two OCD patients (73 %) were on stable medication at the time of assessment (SSRIs, $n = 10$; SSRIs plus other antidepressants, $n = 12$).

The control subjects had been randomly chosen from the city address registers and were subsequently contacted by mail. Others were recruited via public notices. Control subjects were admitted to the study only if they had no history of neurological or psychological disturbances (as evident from the psychiatric interview SADS). The OCD patients and the healthy control subjects of the present study partly overlap with a previous study [50].

Saccadic tasks

All stimuli were presented on a 17-inch monitor positioned about 41 cm from the eyes of the participant. The task consisted of two prosaccade and two antisaccade blocks, respectively, with 30 trails per block (5 practice trials plus 25 test trials). One trial involved a central fixation stimulus with a duration of 1,500, 2,000, 2,500, or 3,000 ms, respectively (randomized presentation), and a 800-ms peripheral location target (16°) which overlapped with the central fixation stimulus for 200 ms. Instructions in the prosaccade condition were to focus on the stimulus in the centre and then follow the peripheral target as closely as possible. In the antisaccade condition, the participants were instructed to quickly redirect their gaze towards the side of the screen opposite to the target.

Oculomotor recordings were obtained using an electro-oculographic recording technique. Head movements were minimized by a chin-rest. We used five Ag/AgCl electrodes for EOG recordings. Two electrodes on the outer canthi of the eyes measured horizontal eye movements (HEOG). Vertical EOG recordings on the right eye were used to facilitate the identification and removal of blinks from the EOG record. The ground electrode was placed on the glabella. Experimental stimuli were presented using ERTS® (BeriSoft Corporation, Frankfurt, Germany). The EOG was recorded using Neuro Scan Labs™ with a Synamps® 5083 amplifier controlled by Acquire® software package (Neurosoft Inc., Sterling USA). EOG data were digitized at 250 Hz. Brain vision analyzer was used to preprocess the EOG recordings. The raw data were segmented relative to the trigger marker positions starting 200 ms before the onset of a trigger marker and ending 800 ms after a trigger marker. Next, the data were filtered with a low pass filter set at 30 Hz and with a notch filter of 50 Hz, and baseline correction was employed. Saccadic eye movements were analysed by a rater (A.V.) blind to the diagnostic group (OCD patient, OCD relative, and control

subject). A visually controlled computer algorithm detected saccades as signals exceeding 2 SD of the baseline variation lasting for at least 20 ms, taking the onset of such a deviation as onset of the saccade and recording its direction and onset latency. Trials containing blinks occurring around stimulus presentation were excluded from the analyses. Any saccade movement towards the peripheral stimulus in the antisaccade condition was considered an antisaccade error. Latencies of the correct prosaccades and antisaccades were measured as time (ms) between target presentation and saccade initiation.

Neuropsychological test battery

The MWT-B (Mehrfachwahl-Wortschatz-Intelligenztest, [27]), a standardized German vocabulary test, was used to calculate our subjects' level of verbal intelligence. In addition to the antisaccade task, a comprehensive neuropsychological test battery was applied measuring a wide range of cognitive functions. To increase reliability, we aggregated seventeen major test parameters into seven cognitive domains based on theoretical assumptions and on face validity [58]. Single test scores of all probands were standardized according to the mean and standard deviation of the healthy control group (Glass Δ). Cognitive domain scores were computed as the mean z scores belonging to a particular domain with negative scores indicating impairments. A detailed description of the neuropsychological tests is given elsewhere [50] (see also suppl. material). Table 1 depicts the specified cognitive domains.

Statistical analysis

All statistical analyses were conducted using SPSS (version 18.0). Group differences on demographic and clinical characteristics such as age, verbal intelligence, and BDI scores were tested using univariate analyses of variances (ANOVA). Fisher's chi-square tests were used to compare sex ratios among groups. Group differences in antisaccade errors and neuropsychological domains were tested with univariate ANOVAs with group as independent variable. Pro- and antisaccade latencies of the correct trials were tested with repeated measurement ANOVAs with task condition (pro- or antisaccade) as within-subject factor and group as between-subject factor and reaction times as dependent variables. We employed square root transformation of the antisaccade error rate to assure normal distribution. Following Mataix-Cols et al. [32], Y-BOCS symptom dimension scores were derived by principal component analysis of the Y-BOCS categories in 244 OCD patients included in the family study. All analyses were computed using an alpha of $p < 0.05$.

Results

Demographic and clinical characteristics

As depicted in Table 2, the groups of the antisaccade sample were comparable in terms of age, sex ratio, education, and estimated premorbid verbal intelligence. However, both OCD patients and the first-degree relatives

Table 1 Cognitive domains and single test parameters

Cognitive domain	Single test parameters
Verbal fluency	Number of S—words over 2 min
	Number of A—words over 2 min
	Number of N—words over 2 min
Visual organization	RCFT: copy score
	RCFT: organization score
	VOT: number of correct answers
Visual memory	RCFT: delayed recall
Problem-solving	TOL: efficiency score
Visual working memory	Deviation from presented stimulus after 5 s delay
	Deviation from presented stimulus after 15 s delay
Processing speed	TMT A: latency in s
	TMT B: latency in s
Verbal memory	AVLT: correct total learning trials 1–5
	AVLT: correct recall after interference
	AVLT: correct recall after delay
	AVLT: correct recognition

AVLT auditory verbal learning test, *RCFT* rey complex figure test, *VOT* visual organization test, *TOL* tower of London, *TMT* trail making test

Table 2 Demographic and clinical characteristics of the samples

	Antisaccade sample			*p*	Neuropsychological sample			*p*
	OCD	REL	CON		OCD	REL	CON	
N	21	21	21		30	30	30	
Age [mean (SD)]	38.9 (6.9)	43.3 (15.4)	41.2 (13.0)	0.510	40.6 (7.7)	42.1 (14.3)	42.7 (12.6)	0.782
Sex (m:f)	10:11	11:10	8:13	0.639	15:15	12:18	9:21	0.287
Years of education [mean (SD)]	14.9 (2.01)	13.7 (2.85)	14.7 (2.72)	0.256	14.5 (2.64)	13.9 (2.36)	14.6 (2.62)	0.535
IQ [mean (SD)]	114.7 (12.8)	115.0 (16.2)	116.6 (12.4)	0.888	116.1 (13.8)	116.9 (14.0)	117.1 (12.5)	0.954
Y-BOCS								
Total	17.21 (8.3)	0.03 (0.2)	0 (0)		17.75 (9.6)	0.03 (0.2)	0 (0)	
Obsession	8.11 (5.2)	0.03 (0.2)	0 (0)		8.57 (5.6)	0.03 (0.2)	0 (0)	
Compulsions	9.11 (4.9)	0 (0)	0 (0)		9.18 (5.3)	0 (0)	0 (0)	
BDI	11.86 (8.71)	5.95 (3.97)	1.95 (2.31)	<0.001	13.10 (10.35)	5.83 (4.05)	2.30 (2.38)	<0.001

OCD OCD patients, *REL* unaffected OCD relatives, *CON* healthy control group, *IQ* premorbid verbal intelligence (MWT-B), *Y-BOCS* Yale-Brown Obsessive–Compulsive Scale, *BDI* Beck Depression Scale

were significantly more depressed as indicated by BDI scores compared to the healthy control group [$F(1,40) = 25.35$, $p < 0.001$, $\eta_p^2 = 0.38$; $F(1,40) = 15.93$, $p < 0.001$, $\eta_p^2 = 0.26$, respectively]. The groups of the larger neuropsychological sample were also parallel with regard to age, gender distribution, education, and premorbid intelligence (Table 2). As in the antisaccade sample, OCD patients and the unaffected relatives showed significantly elevated depression scores compared to the healthy control subjects [$F(1,58) = 31.02$, $p < 0.001$, $\eta_p^2 = 0.35$; $F(1,58) = 16.96$, $p < 0.001$, $\eta_p^2 = 0.23$, respectively].

Before testing for potential endophenotypes, we correlated saccadic and neuropsychological performance of the OCD patients and the unaffected OCD relatives with OCD and depression severity. In the OCD patients, reduced verbal memory was related to higher BDI scores ($r = -0.38$, $p = 0.036$). In the unaffected relatives, prosaccade latencies were negatively correlated with BDI score ($r = -0.47$, $p = 0.030$). OCD severity measured with the Y-BOCS was not correlated with any neuropsychological domain or oculomotor parameter in both groups ($p > 0.05$). Oculomotor performance was not correlated with neuropsychological domains in the OCD patients. In the unaffected relatives, longer antisaccade latencies were significantly related to reduced lexical fluency ($r = -0.55, p = 0.009$). With regard to OCD dimensions (derived from Y-BOCS checklist categories, [32]), no significant correlation with any of the identified OCD dimension (washing, hoarding, symmetry, obsessions) and oculomotor functions was found in the OCD patients ($p > 0.05$). In the neuropsychological OCD sample, high obsession dimension scores were negatively correlated with the verbal memory domain ($r = -0.42$, $p = 0.026$). However, when Bonferroni correction was applied to control for multiple computations, no correlation remained significant ($p > 0.05$).

Examination of potential endophenotypes

Next, we analysed oculomotor functions as potential endophenotypes. Following the rationale of candidate endophenotypes, we first compared neuropsychological performance and antisaccade parameters in OCD patients and the healthy control group. In a second step, we aimed to confirm significant differences indicating a potential endophenotype in the first-degree relatives in contrast to the healthy control subjects.

OCD patients showed significantly more antisaccade errors compared to the healthy control subjects [$F(1,40) = 10.14$, $p = 0.003$, $\eta_p^2 = 0.20$]. An increased antisaccade error rate was also found in the unaffected relatives compared to the healthy control subjects [$F(1,40) = 5.20$, $p = 0.028$, $\eta_p^2 = 0.12$]. This higher rate of direction errors in the antisaccade task was also evident after exclusion of relatives with psychiatric diagnoses [$F(1,36) = 5.84, p = 0.021$, $\eta_p^2 = 0.14$]. Antisaccade error rates of the OCD patients and the first-degree relatives did not significantly differ from each other [$F(1,40) = 0.99$, $p = 0.324$, $\eta_p^2 = 0.02$] (Fig. 1; Table 3).

With regard to saccade latencies, all comparisons indicated highly significant effects of condition with longer latencies in antisaccade trials as compared to reflexive saccade trials [all $p < 0.001$]. Comparing the OCD patients and the healthy control subjects showed no general group difference [$F(1,40) = 0.43$, $p = 0.514$, $\eta_p^2 = 0.01$] but an significant interaction of condition × group [$F(1,40) = 5.93$, $p = 0.019$, $\eta_p^2 = 0.13$]. However, separate one-way ANOVAs for each condition indicated no significant differences of the generally long latencies in the OCD patient group and the healthy control group [prosaccade, $F(1,40) = 0.31$; $p = 0.583$; $\eta_p^2 = 0.01$ and antisaccade, $F(1,40) = 2.29$; $p = 0.138$; $\eta_p^2 = 0.05$]. Thus, the

observed interaction effect indicated significantly larger mean differences of prosaccade and antisaccade latencies in the OCD patients (mean latency difference = 129.1 SD = 74.7) as compared to the healthy control group (mean latency difference = 81.6, SD = 49.4). Comparing saccade latencies of the unaffected relatives and the healthy controls showed no significant main effect of group or interaction of condition × group [$F(1,40) = 0.91, p = 0.347$, $\eta_p^2 = 0.02$; $F(1,40) = 2.30$, $p = 0.137$, $\eta_p^2 = 0.05$, resp.]. The saccade latencies of the unaffected relatives and of the OCD patients did not differ from each other [group: $F(1,40) = 0.01$, $p = 0.986$, $\eta_p^2 < 0.01$; condition × group: $F(1,40) = 0.37, p = 0.547, \eta_p^2 = 0.01$] (Table 3). Excluding the OCD patients and relatives with comorbid tic disorder from the analyses of antisaccade performance did not change these results (data not shown).

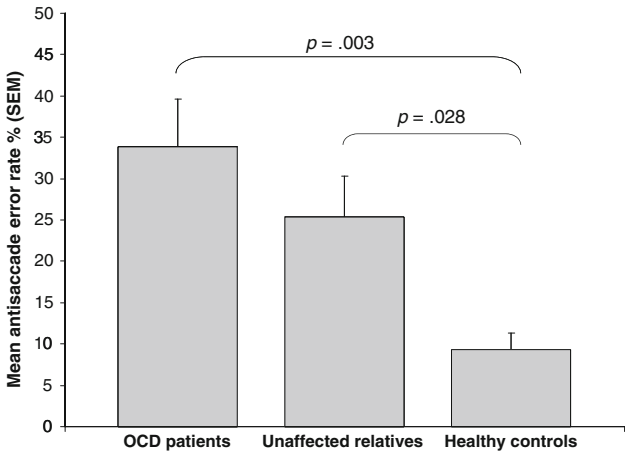

Fig. 1 Increased antisaccade error rates (%) in OCD patients and unaffected OCD relatives compared to healthy control subjects. *OCD* obsessive–compulsive disorder

Table 4 depicts the performance of the OCD patients and the unaffected relatives in the neuropsychological test battery. The OCD patients were impaired in the cognitive domains visual organisation [$F(1,58) = 6.85$, $p = 0.011$, $\eta_p^2 = 0.11$], visual memory [$F(1,58) = 8.33$, $p = 0.005$, $\eta_p^2 = 0.13$], problem-solving [$F(1,58) = 4.54$, $p = 0.037$, $\eta_p^2 = 0.07$], visual working memory [$F(1,58) = 4.3$, $p = 0.043$, $\eta_p^2 = 0.07$], and processing speed [$F(1,58) = 5.27$, $p = 0.025$, $\eta_p^2 = 0.08$]. Although the unaffected relatives showed negative z scores across all domains, no difference achieved statistical significance when contrasted against the performance of the healthy control group, thus indicating only small deficits (all $p > 0.05$). Excluding relatives with any psychiatric diagnosis did not change this finding (all $p > 0.05$). OCD patients and the unaffected relatives did not differ in any of the cognitive domains (all $p > 0.05$). When OCD patients and unaffected relatives with tic disorders were excluded from these analyses, all findings remained unchanged (data not shown) except the visual working memory deficit in OCD patients which only showed trend-level significance ($p = 0.082$).

We also tried to directly replicate significant differences in the RCFT and the TOL analysing single test scores.

Table 3 Antisaccade performance in OCD patients and unaffected OCD relatives as compared to healthy control subjects

	OCD	REL	CON	Significant pairwise contrasts
Mean antisaccade error rate (SD)	33.8 % (26.6)	25.4 % (22.5)	13.1 % (9.3)	OCD > CON ($d = 1.01$)
				REL > CON ($d = 0.72$)
Mean prosaccade latencies (SD)	324.5 (75.4)	331.7 (29.7)	335.3 (48.2)	Group: ns
Mean antisaccades latencies (SD)	453.7 (99.0)	445.8 (80.2)	416.9 (51.2)	Group × condition: OCD > CON ($d = 0.77$)

Latencies are given in ms. Cohen's d is given as a measure of effect size

OCD OCD patients, *REL* unaffected OCD relatives, *CON* healthy control group

Table 4 Performance in neuropsychological domains in OCD patients and unaffected OCD relatives as compared to healthy control subjects

	OCD	REL	CON	Significant pairwise contrasts
Verbal fluency	−0.31 (0.82)	−0.37 (0.90)	0 (1.0)	ns
Visual organization	−0.92 (1.66)	−0.45 (1.53)	0 (1.0)	OCD < CON
Visual memory	−0.76 (1.04)	−0.28 (1.27)	0 (1.0)	OCD < CON
Problem-solving	−0.73 (1.60)	−0.30 (1.15)	0 (1.0)	OCD < CON
Spatial working memory	−1.05 (2.58)	−0.15 (1.10)	0 (1.0)	OCD < CON
Processing speed	−0.78 (1.56)	−0.24 (0.64)	0 (1.0)	OCD < CON
Verbal memory	−0.40 (1.14)	−0.18 (0.91)	0 (1.0)	ns

Mean z scores (standardized according to mean and SD of the control group) are given with SD in parenthesis. Negative scores indicate impairment. *OCD* OCD patients, *REL* unaffected OCD relatives, *CON* healthy control group

Significant impairments were obtained for the OCD patients when contrasted against the healthy control subjects in the TMT A [$F(1,58) = 4.89$, $p = 0.031$, $\eta_p^2 = 0.08$], and TMT B [$F(1,58) = 4.06$, $p = 0.049$, $\eta_p^2 = 0.07$], the 5-s delay condition of the spatial working memory task [$F(1,58) = 5.75$, $p = 0.020$, $\eta_p^2 = 0.09$], the AVLT recall after interference [$F(1,58) = 4.28$, $p = 0.043$, $\eta_p^2 = 0.07$], the RCFT copy [$F(1,58) = 7.27$, $p = 0.009$, $\eta_p^2 = 0.11$] and the RCFT delayed recall [$F(1,58) = 8.33$, $p = 0.005$, $\eta_p^2 = 0.13$], the VOT [$F(1,58) = 4.56, p = 0.037, \eta_p^2 = 0.07$], and the TOL score [$F(1,58) = 4.06$, $p = 0.049$, $\eta_p^2 = 0.07$]. Again, no significant difference between the unaffected relatives and the healthy control subjects or the OCD patients was found ($p > 0.05$). All single test z scores of the OCD patients and unaffected relatives are given in Table 5 (supplemental material).

Discussion

In the present study, we sought to examine oculomotor function as a candidate endophenotype of obsessive–compulsive disorder (OCD). Increased error rates during an antisaccade task were evident not only in OCD patients, but also in unaffected relatives of OCD patients. Moreover, correlation analyses indicated that antisaccade errors were unrelated to OCD and depression severity, supporting the notion that the antisaccade error rate is state independent. Only the OCD patients but not the unaffected relatives showed significantly prolonged antisaccade latencies as compared to prosaccade latencies when contrasted against latencies of the healthy control group. In contrast to impaired oculomotor function, deficits in visuospatial abilities in OCD patients were not confirmed in the unaffected relatives.

It has been hypothesized that impaired response inhibition constitutes a neurobiological substrate of OCD reflecting the inability to stop prepotent motor actions or impulses [8]. To our best knowledge, the present study is the first to show aberrant response inhibition in unaffected OCD relatives as measured by an antisaccade task. Previous studies using different measures also found impaired response inhibition in OCD patients [2, 9, 43] and in their unaffected relatives as well [10, 35]. Thus, poor response inhibition appears to be a familial marker of OCD across different tasks. Antisaccade performance is clearly heritable (h2–57 %) as indicated by a study in female twins conducted by Malone et al. [28]. Temporal stability of oculomotor functions has been demonstrated in several studies in healthy volunteers and psychiatric populations [16, 61]. Moreover, with regard to OCD, impaired antisaccade performance has been previously described in medication-naïve OCD patients [53, 63], in non-depressed OCD patients [53, 54, 60], and in OCD patients without any comorbid diagnoses [63]. These findings suggest that impaired antisaccade performance is associated with OCD independently from depressive mood and medication status and thus cannot be regarded as a pure epiphenomenon of the disorder. Similarly, parameters of the antisaccade task were not related to OCD severity or OCD symptom dimensions in our study, suggesting that deficient oculomotor function is a broad and state independent feature of OCD. In sum, the present study, in concert with previous investigations, clearly underlines the suitability of response inhibition and oculomotor functions as an endophenotype of OCD.

Previous findings of impaired visuospatial abilities and planning in unaffected relatives were not replicated in the present study. One study has demonstrated visual memory deficits as assessed with the RCFT in unaffected OCD relatives [57]; another study found visuoconstructive impairments during the copy trial of this task [49]. Others found impairments with regard to planning as assessed with the TOL and the Tower of Hanoi in first-degree relatives of OCD patients [7, 13]. However, in the studies conducted by Viswanath et al. [65] and Rajender et al. [49], neither RCFT visual memory score nor TOL performance indicated impairments in the groups of unaffected relatives of OCD patients. The negative z scores in the unaffected relatives in our study ranging from -0.15 to -0.45 indicate small (but statistically not significant) deficits as compared to the healthy control group. Thus, our sample size may have been too small to statistically confirm such deficits. More replication in larger samples and meta-analytical integration is needed to corroborate that visuospatial deficits and planning abnormalities heritable neurobiological features of OCD.

The exact neural mechanisms underlying inhibition of the reflexive saccades (quantified by antisaccade errors) during antisaccade tasks are not yet fully understood. Several studies found specifically increased activation of parietal regions, the frontal eye field (FEF), the dorsolateral prefrontal cortex (DLPFC), the anterior cingulate cortex (ACC), and in striatal and thalamic regions during antisaccade compared to prosaccade trials [22, 33]. Increased DLPFC activity was found to precede correctly performed antisaccades but not antisaccade errors, thus suggesting an inhibitory role of this region [14, 17, 34]. Recent fMRI studies also indicated a region in the parietal lobule, the supramarginal gyrus (SMG, BA 40) to be specifically activated during inhibitory processes of antisaccade performance [4, 15, 51]. Raemaekers and colleagues showed that schizophrenia patients and unaffected siblings both failed to recruit the caudate nucleus during antisaccade performance [47, 48]. To date, no study has used an antisaccade paradigm to relate oculomotor inhibition to brain

structure and activity in OCD patients versus healthy controls. However, there are several OCD studies linking neural regions involved in antisaccade performance with the disorder and investigating brain activity during other measures of response inhibition [36]. For instance, reduced fractional anisotropy indicating altered white matter in the ACC and the SMG was found in a group of OCD patients compared to healthy control subjects, and volume of the parietal lobe (including the SMG, BA 40) was negatively related to OCD severity [59]. A recent meta-analysis of voxel-based morphometry studies in OCD also indicated reduced grey matter density in several regions including the SMG, the DLPFC, and the FEF as well as increased grey matter density in the striatum [55]. The DLPFC has also been related to OCD in an fMRI study demonstrating increased activation of this region during impaired planning (Tower of London) in OCD patients [62]. Interestingly, abnormal activation of the orbitofrontal cortex, the DLPFC, and the SMG was observed in OCD patients and their unaffected relatives performing an attentional switch task [11]. Moreover, prolonged stop-signal reaction times (indicating an inhibitory deficit) of OCD patients and first-degree relatives were significantly related to alterations of grey matter volume in several brain regions including the SMG and the orbitofrontal cortex [35]. Some of these regions (SMG, DLPFC) probably take a key position in inhibitory phase of antisaccade tasks [4, 15, 33]. Thus, the present study suggests the inheritance of abnormal inhibitory processes in OCD by reporting increased antisaccade errors in OCD patients and in unaffected OCD relatives.

Preliminary findings regarding the genetic background of antisaccade performance have been published. For instance, the met158 allele of the COMT val158met polymorphism, which was found to be more frequent in male OCD patients [44], was also associated with increased antisaccade latencies and tended to elicit more antisaccade errors in one study [21]. Moreover, a variant located in the promoter region of the dopamine D4 receptor (DRD4) gene affected antisaccade error rate [23], and this gene has also been related to OCD [5].

One limitation of the present study may be that the OCD patients were largely medicated and not free of psychiatric comorbidity. However, impaired antisaccade performance has also been reported in medication-naïve OCD patients and in patients free of psychiatric comorbidity [53, 63]. Another limitation of our study regards the identification of the exact underlying oculomotor deficit in OCD. Our antisaccade task was not designed to disentangle inhibitory and volitional saccade generation processes which both are assumed to be involved in antisaccade completion [24]. Therefore, future studies should directly manipulate these functions to further delineate the exact underlying deficit of impaired oculomotor function in OCD.

In conclusion, we assume oculomotor function as assessed by the antisaccade task to present a valid endophenotype of OCD. We would expect that impaired oculomotor control and other measures of response inhibition may facilitate the search for genes which confer a risk for the development of OCD.

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Conflict of interest The authors report no biomedical financial interests or potential conflicts of interest.

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