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ORIGINAL PAPER

Schizotypy and smooth pursuit eye movements as potential endophenotypes of obsessive-compulsive disorder

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Abstract

Patients with obsessive-compulsive disorder (OCD) show dysfunctions of the fronto-striatal circuitry, which imply corresponding oculomotor deficits including smooth pursuit eye movements (SPEM). However, evidence for a deficit in SPEM is inconclusive, with some studies reporting reduced velocity gain while others did not find any SPEM dysfunctions in OCD patients. Interestingly, psychosis-like traits have repeatedly been linked to both OCD and impaired SPEM. Here, we examined a large sample of $n = 168$ patients with OCD, $n = 93$ unaffected first-degree relatives and $n = 171$ healthy control subjects to investigate whether elevated levels of schizotypy and SPEM deficits represent potential endophenotypes of OCD. We applied a SPEM task with high demands on predictive pursuit that is more sensitive to assess executive dysfunctions than a standard task with continuous visual feedback, as episodes of target blanking put increased demands on basal ganglia and prefrontal involvement. Additionally, we examined the relation between schizotypy and SPEM performance in OCD patients and their relatives. Results indicate that OCD patients and unaffected relatives do not show deficient performance in either standard or predictive SPEM. Yet, both patients and relatives exhibited elevated levels of schizotypy, and schizotypy was significantly correlated with velocity gain during standard trials in unmedicated and depression-free OCD patients. These findings highlight the role of schizotypy as a candidate endophenotype of OCD and add to the growing evidence for predisposing personality traits in OCD. Furthermore, intact gain may represent a key characteristic that distinguishes the OCD and schizophrenia patient populations.

Keywords Obsessive-compulsive disorder · OCD · Smooth pursuit eye movements · SPEM · Schizotypy · Endophenotype

Introduction

Obsessive-compulsive disorder (OCD) is a debilitating and often chronic psychiatric disorder characterized by obsessions (intrusive unwanted thoughts and/or images) and/or compulsions (ritualized repetitive behaviors), which affects 1–3% of the population worldwide [87]. Symptoms of OCD

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are highly heterogeneous across patients and cover dimensions of washing/contamination, ordering/symmetry, forbidden thoughts, and hoarding [6, 37]. Converging evidence from neuroimaging studies suggests that dysfunctions of the cortico-striato-thalamo-cortical circuits (CSTC) are implicated in the pathophysiology of OCD, resulting in disturbances of executive functioning [65], e.g., performance monitoring [70], planning [8], and working memory [30, 34]. Moreover, OCD patients exhibit deficits in a variety of oculomotor functions, including antisaccades [48], volitional saccades [40], and smooth pursuit eye movements [21].

Smooth pursuit eye movements (SPEM) enable us to track a small moving target with the eyes [43], like a car driving by in the distance or a pendulum swinging back and forth. In the investigation of SPEM, different waveforms can be used to separate the distinct underlying cognitive contributions of the SPEM system [2]. A widely used approach to study predictive mechanisms and velocity memory is to briefly blank the target during a ramp of ongoing SPEM [3]. Compared to a continuously visible target, blanking leads to the recruitment of the basal ganglia and additional prefrontal sources [44, 60]. Furthermore, predictive SPEM have been assumed to be associated with working memory [13, 58; however, see 39].

OCD has a strong genetic component with first-degree relatives having a fivefold increased risk on average to also be affected with the disease [26, 61, 66] and twin studies of OCD and OCD-related traits yielding heritability estimates around 50% [62, 82]. However, the identification of the specific genetic variants underlying this heritability proved to be difficult. Two genome-wide association studies (GWAS) and a recent meta-analysis of them did not find genome-wide significant hits [32, 55, 78]. Examining potential endophenotypes may aid in the identification of risk alleles as they are supposed to depend upon variation in fewer genes than the more complex disease phenotype and are, therefore, assumed to be more tractable to genetic analysis [25]. Within families, endophenotypes and the disorder co-segregate so that unaffected relatives are expected to show abnormalities similar to those observed in patients.

SPEM are a widely studied endophenotype of the psychosis spectrum, showing deficits in patients with psychotic disorders [45], their relatives [33, 38, 46], and healthy individuals displaying high levels of schizotypal traits [41]. As schizophrenia and OCD share a high genetic overlap [1, 11], endophenotypes of schizophrenia may be fruitful targets for OCD, as well. However, studies on SPEM in patients with OCD have yielded mixed results [35, 56] including findings of impaired continuous SPEM maintenance [21, 47, 79] and others of rather intact performance [12, 16, 77]. Most notably, the validity of these studies is limited by low statistical power due to small sample sizes. Until now, there is no research on predictive SPEM in OCD.

In accordance with the high comorbidity between schizophrenia and OCD [27, 67], patients with OCD have been found to display elevated schizotypal traits [71]. Thereby, schizotypy has been related to higher rates of symmetry/ordering obsessions, checking compulsions, aggressive obsessions, general psychopathology and overall obsessive symptom severity [7, 76, 85]. It has even been proposed that OCD patients with high levels of schizotypy represent a subtype of OCD characterized by distinct deficits and genetic contributions [67]. For example, OCD patients with high levels of schizotypy show reductions in gray matter volume [42] as well as dorsolateral and frontal lobe dysfunction [29, 75] when compared to OCD patients with low levels of schizotypy. Notably, the overlap between OCD and schizophrenia appears to also be affected by neuroleptic medication, as clozapine treatment has been shown to induce OCD symptoms in schizophrenia patients [59, 72].

The aims of the present study were threefold. First, we aimed to investigate whether OCD patients and their unaffected first-degree relatives exhibit deficits in predictive SPEM. Given the CSTC dysfunctions in OCD and the increased demand on basal ganglia and prefrontal sources during episodes of target blanking, we hypothesized that a SPEM task that comprises episodes of blanking might be more sensitive to investigate executive dysfunctions in OCD than previously applied tasks with continuos visual feedback [35]. As distinct OCD symptom dimensions are associated with differences in brain structure [81], brain response to symptom provocation [54] and neuropsychological performance [49], we also investigated whether abnormalities in SPEM vary across OCD symptom dimensions. Second, we sought to examine whether elevated levels of schizotypy represent a potential endophenotype of OCD. Third, following the widely replicated findings of impaired SPEM in psychosis [63, 80] and high schizotypy [50, 83], we assessed the relationship between schizotypy and SPEM performance in OCD patients and unaffected first-degree relatives of patients with OCD.

Methods

Participants

168 patients with OCD, 171 healthy comparison subjects and 93 unaffected first-degree relatives of OCD patients participated in the study. Patients and controls were matched for age and gender ($p > 0.05$). Relatives showed a similar gender ratio, but were significantly older than patients and controls [$F(2,429) = 40.60$, $p < 0.001$; see Table 1 for sample characteristics]. OCD patients and relatives were recruited via the outpatient clinics at the Department of Psychology of Humboldt-Universität zu Berlin and at the Department

Table 1 Sample characteristics and SPEM performance of patients with OCD, unaffected first-degree relatives and healthy control subjects

	Patients with OCD	Unaffected first-degree relatives	Healthy control subjects	Statistic	*p*
N	168	93	171		
Mean age, years (SD)	33.32 (10.77)	46.65 (13.97)	34.09 (12.71)	$F(2,429) = 40.60$	< 0.001
Gender (% male)	42.9	31.2	39.2	$\chi^2(2) = 3.44$	0.18
Mean velocity gain during non-blanking trials (SD)	87.00 (12.01)	83.96 (12.65)	85.32 (13.65)	$F(2,429) = 1.80$	0.17
Mean velocity gain during blanking trials (SD)	41.16 (15.07)	37.92 (14.48)	40.53 (15.34)	$F(2,429) = 1.45$	0.24
Schizotypy (SD)	2.20 (1.74)	1.26 (1.57)	0.64 (0.94)	$F(2,426) = 50.82$	< 0.001
Mean OCI-R score (SD)	27.76 (12.03)	6.87 (6.57)	4.51 (4.49)	$F(2,427) = 351.74$	< 0.001
Mean Y–BOCS score (SD)	22.06 (6.81)	–	–		

OCD obsessive-compulsive disorder, *OCI-R* obsessive-compulsive inventory-revised, *SD* standard deviation, *SPEM* smooth pursuit eye movements, *Y–BOCS* Yale–Brown Obsessive Compulsive Scale

of Psychiatry and Psychotherapy of the University of Bonn, Germany. Healthy volunteers were recruited from the general population via public advertisements. All participants were examined by trained clinical psychologists using the Structured Clinical Interview for DSM-IV (SCID-I) [18, 86]. To establish cross-site reliability of clinical ratings, all instructions were standardized, and raters completed assessments of four training videos. Patients and relatives were only included if they were (1) free of past or present psychotic, bipolar, or substance related disorders, (2) did not take neuroleptic medication in the past 4 weeks and (3) did not use benzodiazepines in the past 2 weeks. Additionally, healthy controls were excluded if they (1) took any psychoactive medication in the past 3 months, (2) had a current axis-I disorder, (3) lifetime diagnosis of OCD or tic disorder, or (4) a family history of OCD. All relatives were free of past or present OCD. Moreover, all participants had normal or corrected-to-normal vision and were free of any neurological disease (lifetime).

70 OCD patients were medicated with selective serotonin reuptake inhibitors (SSRIs) or other antidepressants. Furthermore, the majority of patients had one or more current comorbid axis-I disorder, with major depression being the most common comorbidity ($n = 36$ current episode, $n = 66$ remitted). The severity of obsessions and compulsions was assessed using the German version of the Yale–Brown Obsessive-Compulsive Scale (Y–BOCS) [24, 28]. OCD symptom dimensions, i.e., washing, checking, ordering, obsessing, hoarding, and neutralizing, were measured via the Obsessive-Compulsive Inventory-Revised (OCI-R) [20, 23]. The self-report questionnaire of the Structured Clinical Interview for DSM-III-R Personality Disorders (SCID-II) [19] was used to assess schizotypal personality traits. Importantly, this measure of schizotypy does not include any items addressing pseudo-obsessive symptoms. Each of the questionnaire scales showed acceptable to high internal consistencies ($0.76 < \alpha < 0.93$).

Written informed consent was obtained and participants were compensated for their time with 10 € per hour. The study was in accordance with the revised Declaration of Helsinki, and approved by the local ethics committees of the Charité Universitätsmedizin Berlin and the University Clinic Bonn.

Eye movement recordings

Testing took place in a quiet, dimly lit room. Participants were seated comfortably in front of a 22-inch LCD monitor (Viewsonic; height 29.5 cm; width 47.5 cm; resolution 1680 × 1050 pixels; 60 Hz refresh rate) with a distance from eyes to screen of 70 cm. A chin rest was used to minimize head movements. At the Bonn assessment site, movements of the right eye were recorded using the EyeLink 1000

system (SR Research, Mississauga, Ontario, Canada) at a sampling frequency of 1000 Hz, whereas in Berlin, eye movements were recorded using the EyeLink II system (SR Research, Mississauga, Ontario, Canada) at a sampling rate of 250 Hz. Before the task started, the eye-tracker was calibrated with a five-point calibration task (0°, horizontal ± 13.3°, vertical ± 9.3°). Additionally, five practice trials were conducted immediately before the experimental sessions.

SPEM task and analysis

The SPEM task was implemented using ExperimentBuilder (SR Research, version 1.10.1241) and data analysis was performed with purpose-written routines in Matlab R2014a (The MathWorks, Natick, MA). Saccades were identified using the velocity (≥ 30°/s) and acceleration (≥ 8000°/s^2) criteria of the SR research algorithm. Additionally, saccades were required to exhibit a minimum amplitude of ≥ 1°. SPEM were part of a larger oculomotor battery with additional tasks, of which the results were already [4] and will be reported elsewhere. Completion of the whole battery took approximately 15 min.

In the SPEM task, the target moved horizontally in a triangular waveform (± 9.86° from the center) at a constant target velocity of 13°/s. During 44 of 89 half-cycles, the target was pseudo-randomly blanked off in the middle of the half-cycle for 500 ms. The duration of one half-cycle was 1500 ms. The main dependent variables were mean velocity gain scores at 900–1100 ms analogously in blanking and non-blanking half cycles. Thus, for blanking half-cycles, we received a mean residual gain score of 400–600 ms after target blanking [80]. Velocity gain was calculated using mean time-weighted and averaged scores for segments of pursuit with a minimum length of 50 ms (excluding blinks or saccades).

Statistical analysis

Statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS) Release 23.0 (SPSS Inc., Chicago, IL, USA). First, main effects of blanking and age on velocity gain were investigated by analysis of covariance (ANCOVA) with blanking (blanking/non-blanking) as within-subject factor and age as covariate. To test the hypothesis of impaired SPEM in OCD patients and relatives, we conducted a 3 × 2 analysis of variance (ANOVA) with group as between-subject factor (OCD patients/unaffected first-degree relatives/healthy comparison subjects) and blanking (blanking/non-blanking) as within-subject factor. Group differences regarding schizotypal traits and OCD symptom dimensions as assessed by OCI-R were computed using one-way ANOVAs (OCD patients/unaffected first-degree relatives/healthy comparison subjects) and post hoc *t* tests. Furthermore, Pearson correlation coefficients were computed to explore relationships between oculomotor performance, OCD symptom dimensions and schizotypal traits in OCD patients and unaffected relatives. In these analyses, the significance threshold was set at $\alpha = 0.005$ to account for multiple comparisons while also considering inter-correlations between the different variables. All analyses were rerun excluding medicated patients and patients with depressive comorbidity ($n = 82$).

Dependent variables were screened for violation of normal distribution in both conditions and each of the three groups by Shapiro–Wilk tests [74], skewness scores and outliers. Homogeneity of variances was tested using Levene's test [22]. All post hoc tests were conducted using Bonferroni–Holm correction [31]. Effect sizes were estimated using partial eta-squared [9] for ANOVAs and Cohen's *d* [10] for post hoc *t* tests.

Results

Across subjects, there was a strong effect of blanking [$F(1,430) = 736.60$, $p < 0.001$, $\eta^2 = 0.63$] indicating that velocity gain was smaller in blanking than in non-blanking trials. Age did not have a significant impact in terms of a main or an interaction effect [$F(1,430) = 0.17$, $p = 0.68$, $\eta^2 = 0.00$ and $F(1,430) = 0.11$, $p = 0.74$, $\eta^2 = 0.00$, respectively] and was hence not included in further analyses.

Analyzing SPEM in OCD patients, controls and unaffected relatives did not yield a significant effect of group or the group by blanking interaction [$F(2,429) = 1.86$,

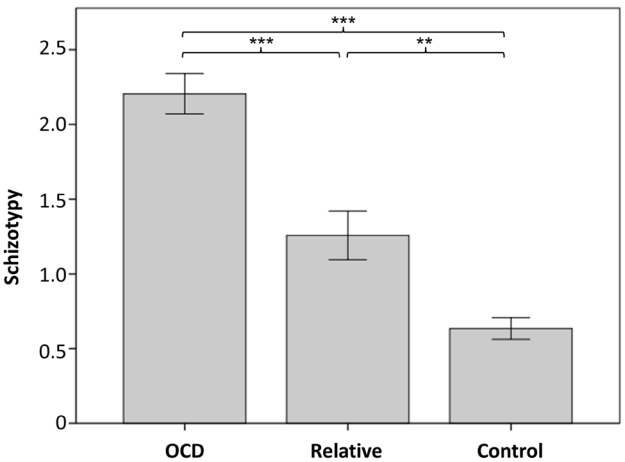

Fig. 1 Schizotypy as assessed by the SCID-II questionnaire in patients with obsessive-compulsive disorder (OCD), unaffected first-degree relatives and healthy controls. Error bars indicate standard errors. $^{**}p < 0.01$; $^{***}p < 0.001$

$p = 0.16$, $\eta^2 = 0.009$ and $F(2,429) = 0.45$, $p = 0.64$, $\eta^2 = 0.002$, respectively].

However, groups differed significantly regarding schizotypy [$F(2,426) = 50.82$, $p < 0.001$, $\eta^2 = 0.19$; Fig. 1] with patients exhibiting higher scores than relatives and controls (both $p < 0.001$; $d = 0.56$ and $d = 1.13$ respectively). Strikingly, unaffected relatives also showed elevated schizotypy compared to controls ($p = 0.002$, $d = 0.52$). OCD patients had significantly higher OCI-R scores than control subjects regarding the global scale and all symptom dimensions (all $p < 0.001$, $0.58 < d < 2.58$), while there were no significant differences between relatives and healthy controls in Bonferroni-corrected post hoc tests (all $p > 0.05$, $d < 0.41$).

In patients, schizotypy was nominally significantly associated with velocity gain during non-blanking ($r = -0.17$, $p = 0.034$), but not during blanking trials ($r = -0.07$, $p = 0.37$). Washing symptoms showed a negative correlation with gain during non-blanking trials ($r = -0.22$, $p = 0.005$), i.e., a higher severity of washing symptoms was related to poorer SPEM performance, whereas the other correlations between symptom dimensions and velocity gain did not remain significant after controlling for multiple comparisons ($p > 0.005$). Correlations between SPEM and symptom severity as assessed by Y–BOCS did not reach significance, either ($p > 0.005$).

Excluding medicated patients and patients with major depression did not change the results substantially. Notably, however, the correlations between velocity gain during non-blanking and schizotypal traits were more strongly pronounced when these patients were excluded ($r = -0.33$, $p = 0.003$).

Discussion

This is the first study to investigate predictive SPEM and schizotypy in OCD patients and their unaffected first-degree relatives. We did not observe any impairment in SPEM, but our findings provide novel evidence that schizotypy may represent a potential endophenotype of OCD, as both patients and unaffected relatives exhibited elevated scores compared to controls.

To the best of our knowledge, this is the largest study so far to assess SPEM in OCD, including up to nine times as many subjects as previous investigations, which have yielded inconsistent results. The missing association between OCD and velocity gain is hence very unlikely to be explained by a lack of statistical power. In accordance with the widely replicated SPEM deficits in schizophrenia patients [63] and the findings of Spengler et al. [77] and Damilou et al. [12], who observed impaired gain only in schizophrenia but not in OCD, our results support the assumption that intact gain may represent a key characteristic that distinguishes the two patient populations. Additionally, the correlations between schizotypal personality and SPEM gain in OCD patients (at least in the medication and major depression-free subsample) are in accordance with low SPEM performance in high schizotypes [41] and further support the close relationship between psychosis and SPEM performance. This finding also indicates that levels of schizotypy may represent a moderator contributing to mixed results across studies.

While schizotypy has only been discussed as an endophenotype of schizophrenia so far, the present results highlight its significance as a candidate endophenotype for OCD. The observation of elevated levels of schizotypy in OCD is in accordance with previously discussed overlaps between the diagnostic categories of OCD and schizophrenia, e.g., OCD symptoms in patients with schizophrenia [68, 84] and OCD symptoms induced or aggravated by second-generation antipsychotic drugs [17]. Schizotypal personality traits have a substantial genetic component, with twin studies yielding heritability estimates around 50% [15, 51]. Schizotypy is associated with OCD [71; present results] and elevated in unaffected relatives, which are key characteristics of an endophenotype. Moreover, schizotypy is easily and reliably measurable, making it a low-hanging fruit for future studies. As a potential endophenotype that is presumably less genetically complex and thus more tractable to genetic analysis [25], it may aid in the identification of genes predisposing an individual to develop OCD.

Our findings are in line with the growing evidence for shared genetic variation in OCD, schizophrenia, and common predisposing personality traits [1]. It has been shown that the presence of prior diagnosis of OCD is associated with an increased risk of developing schizophrenia later in life, and that offspring of parents diagnosed as having OCD have an increased risk of schizophrenia [57]. In addition to the strong genetic correlation between the two diseases, a substantial genetic overlap has been observed between schizotypy and neuroticism [52], which may partially mediate the genetic risk for both OCD and schizophrenia. Neuroticism has previously been discussed as an endophenotype of OCD, as levels of neuroticism and the related trait harm avoidance are increased in both OCD patients and relatives [5, 14, 73]. Considering the genetic overlap between neuroticism and schizotypy, it appears plausible that unaffected relatives of OCD patients also display elevated scores of schizotypy. The identification of multiple risk factors may eventually facilitate the identification of the genetic variants underlying OCD. Specifically, multivariate genetic approaches combining the analysis of disease phenotypes and endophenotypes may provide greater statistical power for detecting genetic variants than a univariate approach based on either phenotype alone [64].

A relevant factor that might play an important role in the explanation of inconsistent findings across studies is

variability in OCD symptom dimensions. We found that washing symptoms were negatively associated with gain during non-blanking trials. Though SPEM performance has not been investigated in relation to OCD symptom dimensions so far, a variety of studies has assessed the impact of symptom dimensions on neuropsychological performance measures associated with SPEM, e.g., working memory [13, 58]. While for the majority of cognitive functions, patients with checking compulsions showed larger impairments than patients with washing symptoms in a recent meta-analysis, no significant differences between these groups were found with regard to working memory [49]. In a large study that used a dimensional rather than a categorical approach, washing symptoms were associated with worse working memory performance [36], which is in line with our findings of impaired SPEM. However, further research is clearly warranted to investigate the association between washing symptoms and predictive SPEM in more detail.

The present study is not without limitations. Notably, relatives were significantly older than OCD patients and controls. However, there were no main or interaction effects of age on SPEM performance, making this issue unlikely to account for the absent group difference. While we observed a significant association between schizotypy and SPEM dysfunction in OCD patients, this correlation did not reach significance in relatives, presumably due to low variance in schizotypy. Though the SCID-II questionnaire for personality disorders is a valid measure, other inventories that comprise more items like the Schizotypal Personality Questionnaire (SPQ) [69] or the Oxford–Liverpool Inventory of Feelings and Experiences [53] may have been more sensitive to differences between relatives and controls, and would have allowed for subscale analyses of positive and negative symptoms of schizotypy. Future studies may thus want to employ more elaborate questionnaires. Strengths of our study are the large sample size, the detailed characterization of subjects and the consideration of medication and comorbidity effects.

In conclusion, OCD patients and unaffected relatives did not show deficient performance in either sustained or predictive SPEM. However, both patients and relatives exhibited elevated levels of schizotypy, providing first evidence for a candidate endophenotype of OCD.

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Compliance with ethical standards

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

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