Is a Schizo-Obsessive Subtype Associated With Cognitive Impairment?

Results From a Large Cross-sectional Study in Patients With Psychosis and Their Unaffected Relatives

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Abstract: The current study investigated whether candidate cognitive endophenotypes may be used to validate a schizo-obsessive subtype. Using within-subject random effect regression analyses and cross-trait cross-relative analyses, we evaluated the association between obsessive-compulsive symptoms (OCSs) and cognitive performance in 984 patients with nonaffective psychosis (22.5% with OCSs), 973 unaffected siblings (7.7% with OCSs), 851 parents (4.2% with OCSs), and 573 controls (4.5% with OCSs). No significant within-subject associations between OCSs and cognitive functioning were found for patients and siblings. Severity of OCSs was associated with worse set-shifting ability in parents and worse processing speed in controls, but effect sizes were small (0.10 and 0.05 respectively). Cross-trait cross-relative analyses yielded no significant results. Contrary to our expectations, neither within-subject analyses nor cross-relative analyses yielded a clear association between OCSs and cognitive performance. Results do not support a schizo-obsessive subtype associated with cognitive impairment.

Key Words: Schizophrenia, obsessive-compulsive symptoms, neuropsychology, siblings, endophenotype.

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Although schizophrenia and obsessive-compulsive disorder (OCD) belong to distinct diagnostic categories, there are substantial areas of overlap between the two disorders regarding affected brain areas, neurotransmitters, and pharmacotherapy (Buchsbaum et al., 1997; Cunill et al., 2009). The higher-than-expected comorbidity of obsessive-compulsive symptoms (OCSs) and psychosis suggests a special association between the two disorders, although the nature of this relation is still under debate (Bottas et al., 2005). Several explanatory hypotheses have been proposed.

First, it has been hypothesized that OCSs and psychotic symptoms could be concomitant but nevertheless unrelated pathological processes, as is the case with comorbidity (Berman et al., 1998; Patel et al., 2010). This comorbidity may be caused by shared genetic and/or environmental factors that render the brain vulnerable to both schizophrenia and other psychopathology, including OCSs. Reports that there is no typical temporal sequence of both disorders corroborate this hypothesis (Devulapalli et al., 2008). Second, OCSs and psychosis might be regarded as different expressions of the same disorder on the schizo-obsessive spectrum (Bottas et al., 2005). This hypothesis emphasizes the similarities between obsessions and delusions as being irrational thoughts, the first with insight and the latter lacking insight. Third, the emergence of OCSs in schizophrenia has been hypothesized to be induced by antipsychotics, especially clozapine (de Haan et al., 2002, 2004; van Nimwegen et al., 2008). However, observations that OCD was already present in up to 14% of first-episode, predominantly drug-naive schizophrenia patients (Poyurovsky et al., 1999) demonstrate that this cannot be the only explanation for their co-occurrence. Finally, it has been suggested that the co-expression of schizophrenia and OCSs may mark a unique subset of schizophrenia patients whose condition might be referred to as the "schizo-obsessive subtype" (Berman et al., 1998; McGlashan, 1997; Ongur and Goff, 2005; Zohar, 1997). In this view, the high co-occurrence is accounted for by a distinct diagnostic entity, with a unique pathophysiology, treatment response, and clinical course.

The study of cognitive impairments has been suggested to be a valuable method to determine whether the putative schizo-obsessive subtype represents a true diagnostic entity (Berman et al., 1998; Lysaker et al., 2009). Various researchers have investigated whether cognitive functioning may differentiate schizophrenia patients with OCSs (OCS+ patients) from schizophrenia patients without OCSs (OCS− patients). Whereas some studies reported worse cognitive functioning in OCS+ patients compared with OCS− patients on visual memory, language, and executive functioning domains (Berman et al., 1998; Hwang et al., 2000; Lysaker et al., 2002, 2000), others reported no differences in cognitive performance (Ongur and Goff, 2005; Tumkaya et al., 2009; Whitney et al., 2004). Remarkably, even better functioning in OCS+ versus OCS− patients has been reported on domains of visual reproduction, set shifting, and verbal fluency (Borkowska et al., 2003; Lysaker et al., 2002).

The association between OCSs and cognitive functioning in schizophrenia patients needs to be considered in the context of significant heterogeneity in the etiopathology, symptomatology, and course of the disorder (Tandon et al., 2009). Likewise, interpretation of worse cognitive functioning in OCS+ patients may be confounded by the fact that these patients also express higher levels of psychotic symptoms, receive different antipsychotic treatment, and are more often hospitalized in comparison with OCS− patients (Hwang et al., 2000; Lysaker et al., 2002, 2000).

To exclude such disease-related confounding, the study of unaffected relatives may be a valuable approach. Unaffected first-degree relatives share about half of their genetic material with the proband but do not have clinical psychosis and do not receive antipsychotic treatment (Gur et al., 2007). Moreover, unaffected relatives of OCS+ patients may be more likely to display OCSs, based on the suggested familial aggregation of OCSs in the general population and in schizophrenia samples (Mataix-Cols et al., 2005; Poyurovsky et al., 2005). Likewise, in a recent review, it was noted that an important step

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toward delineation of specific subgroups within the OCS-schizophrenia axis may be the use of candidate endophenotypic markers, including cognitive functioning (Poyurovsky and Koran, 2005).

In schizophrenia, impairments in domains of executive functioning, working memory, attention/vigilance, and affect processing may provide a means to study endophenotypic traits more closely associated with specific neurobiological deficits than are psychotic symptoms (Gur et al., 2007). In addition, in OCD, cognitive deficits have been suggested as potential endophenotypic markers that may be used to clarify genetic contributions, such as nonverbal memory, executive functioning, and motor inhibitory control (Menzies et al., 2007; Rao et al., 2008). Therefore, if OCS+ patients can be distinguished from OCS− patients based on a cognitive pattern that is replicated in their unaffected relatives, this may support a shared genetic vulnerability for OCSs and psychosis as would be expected in the case of a schizo-obsessive subtype (Poyurovsky and Koran, 2005).

The first aim of the present study was therefore to investigate whether OCS+ patients can be differentiated from OCS− patients based on their cognitive performance. Second, we wanted to investigate the association between OCSs and cognitive functioning in unaffected relatives of patients with psychosis and control subjects. Because OCSs have been associated with cognitive functioning in subjects with and without psychosis, we hypothesized that a negative association between OCSs and cognitive functioning would be present in all patients, relatives, and controls. Third, as an exploratory analysis, we wanted to examine whether the level of OCSs in patients was associated with cognitive functioning in their unaffected relatives. On the basis of the assumption that both cognitive deficits and OCSs are more prevalent in genetic high-risk subjects, we expected a cross-trait cross-relative association for cognitive domains that are impaired in both OCD and schizophrenia, such as set shifting, processing speed, and sustained attention (Chamberlain et al., 2005; Kuelz et al., 2004).

METHODS

Study Design and Population

Data pertain to baseline measures of the Genetic Risk and Outcome of Psychosis (GROUP), a longitudinal study in the Netherlands and Belgium (Korver et al., 2012). In selected representative geographical areas, patients were identified through clinicians working in psychotic disorder services whose caseloads were screened for inclusion criteria. In addition, a group of patients presenting consecutively at these services as either outpatients or inpatients were recruited for the study. Controls were selected through a system of random mailings to addresses in the catchment areas of the cases.

Inclusion criteria for patients, siblings, and controls were a) age range of 16 to 50 years and b) good command of the Dutch language. Patients had to meet *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision*, criteria for a nonaffective psychotic disorder (American Psychiatric Association, 2000), which was assessed with the Comprehensive Assessment of Symptoms and History (Andreasen et al., 1992) or the Schedules for Clinical Assessment for Neuropsychiatry version 2.1 (Wing et al., 1990). Exclusion criteria for healthy controls were a history of psychotic disorder or a first-degree family member with a history of psychotic disorder. The study protocol was approved centrally by the ethical review board of the University Medical Centre Utrecht and subsequently by local review boards of each participating institute. All of the subjects gave written informed consent in accordance with the committee's guidelines.

Clinical Measures

Severity of psychotic symptoms in patients was rated with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). In relatives and controls, the Community Assessment of Psychic Experiences (CAPE) (Stefanis et al., 2002) was used to assess the prevalence of (subclinical) positive, negative, and depressive symptoms on both a frequency scale (0 = never to 3 = nearly always) and a distress scale (0 = not distressed to 3 = very distressed).

The Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) (Goodman et al., 1989) was used in all participants to measure the presence and severity of OCSs over the previous week. The Y-BOCS addresses interference, distress, and time spent on, resistance against, and control over obsessions and/or compulsions. All 10 severity items are rated on a 5-point Likert-scale, ranging from 0 (no symptoms) to 4 (extreme symptoms). The total Y-BOCS score (range, 0–40), which is the sum of all 10 severity items, was used as predictor in the analyses. The Y-BOCS has been validated for use in patients with nonaffective psychosis (Boyette et al., 2011; de Haan et al., 2006).

Cognitive Measures

Subjects were administered a neuropsychological test battery, which required 90 to 120 minutes to complete. The 10 cognitive tasks yielded 13 outcome parameters that were used as dependent variables in the analyses. Verbal learning was assessed using the Word Learning Task (Brand and Jolles, 1985), with outcome parameters of immediate recall (15-word list, three learning trials) and retention rate after 20 minutes. Set shifting ability was assessed using the Response Shifting Task (RST), a modified version of the Competing Programs Task (Nolan et al., 2004), with outcome parameters of reaction time and accuracy. Sustained visual attention and vigilance were assessed using a version of the Continuous Performance Task (Nuechterlein and Dawson, 1984), with outcome parameters of reaction time and accuracy. The following subtests of the Wechsler Adult Intelligence Scale–Third Edition (WAIS-III) (Wechsler, 1997) were assessed: Digit Symbol-Coding as a measure of processing speed, Arithmetic as a measure of working memory, Information as a measure of acquired knowledge, and Block Design as a measure of reasoning and problem solving. The Degraded Facial Affect Recognition Task (van't Wout et al., 2004) was used to assess recognition of neutral, happy, fearful, and angry emotions. The Benton Face Recognition Task (Benton et al., 1983) was used to assess visuospatial discrimination of unfamiliar faces. The Hinting Task (Versmissen et al., 2008) was used to assess theory of mind. Cognitive performance within the GROUP study on this test battery has been described previously (Meijer et al., 2012). Patients performed worse than controls did on all cognitive domains (z range, −0.18 to −1.34), whereas unaffected siblings and parents showed intermediate performance on selected tasks (z range, −0.01 to −0.43 and +0.13 to −1.17, respectively).

Statistical Analyses

Demographic and clinical characteristics were compared between OCS+ and OCS− patients using one-way analysis of variance for continuous data and chi-square tests for categorical data. Tests were two tailed, with a significance level of 0.05. The association between OCSs and cognitive functioning was assessed in three ways: by means of within-subject regression analyses, by means of cross-trait cross-relative analyses, and (within patients) by means of group comparisons.

First, we built a random effect regression model for each of 13 cognitive functioning outcomes with the Y-BOCS score (range, 0–40) as the fixed part of the model and cognitive functioning as the dependent variable. Family was used as a random factor with a random intercept to correct for intrafamily correlation because some families contributed more than one parent, sibling, or control. These models were analyzed within each status group (patient, parent, sibling, and control) separately. Covariates were added to the model in two steps. As a first step, age, sex, and educational level were entered at the same time ("enter method"). Educational level was categorized as follows: varying from lowest (1 = primary school) to highest (8 = university), with an ordinal increase in educational years. Subsequently,

TABLE 1. Level of OCSs in Patients, Relatives, and Controls

Level of OCSs (Y-BOCS score)	Patients (n = 984)	Siblings (n = 973)	Parents (n = 851)	Controls (n = 573)
No OCS (0)	77.5%	92.3%	95.8%	95.5%
Subclinical OCSs (1–7)	6.8%	3.9%	1.8%	2.6%
Mild OCSs (8–15)	10.2%	3.0%	1.9%	1.7%
Moderate-severe OCSs (≥16)	5.5%	0.8%	0.5%	0.2%

OCSs indicates obsessive-compulsive symptoms; Y-BOCS, Yale-Brown Obsessive-Compulsive Scale.

symptoms were entered as a covariate. For patients, PANSS scores were used (PANSS positive, negative, and general), whereas CAPE scores were used for the three nonclinical groups.

Second, cognitive functioning was compared between subgroups of patients based on their Y-BOCS scores. Based on the literature (Bedard and Chantal, 2011; Ongur and Goff, 2005), the following categories were created: no OCS (Y-BOCS 0), subclinical OCSs (Y-BOCS 1–7), mild OCSs (Y-BOCS 8–15), or moderate-severe OCSs (Y-BOCS ≥16). Analyses were performed by means of analysis of covariance (ANCOVA), with age, sex, educational level, and PANSS scores as covariates and family as a random factor.

Third, cross-trait cross-relative analyses were performed to exclude possible disease-related confounding (Toulopoulou et al., 2010). Therefore, for each cognitive outcome measure, a random effect regression model was built, with the Y-BOCS scores of the patient as the independent variable and the cognitive functioning of their relative (siblings and parents separately) as the dependent variable. Analyses were covaried for age, sex, and education and the CAPE scores of the relative.

All tests were two tailed. To correct for multiple comparisons, the alpha was set to 0.005. Significant effects were transferred into Cohen's d as a measure of effect size to differentiate between small ($d' = 0.2$), medium ($d' = 0.5$), and large ($d' = 0.8$) effects. All statistical analyses were performed with SPSS version 17.0 for Windows.

RESULTS

For the current study, we excluded subjects who did not have the Y-BOCS assessed (n = 273) as well as additional subjects who had not participated in any of the cognitive tasks (n = 30), resulting in a study sample of 3381 subjects (984 patients, 973 siblings, 851 parents, and 573 controls). Table 1 shows that subclinical, mild, and moderate-severe OCSs were more prevalent in patients compared with relatives and controls.

Table 2 demonstrates that OCS+ patients were significantly younger than OCS− patients. The sex distribution was not significantly different between the OCS groups. Moreover, OCS+ patients had significantly more positive and general symptoms on the PANSS compared with OCS− patients, whereas negative symptoms did not differ. In addition, OCS+ patients were more often currently treated with clozapine compared with OCS− patients. Observed mean cognitive test scores for OCS subgroups are also demonstrated. ANCOVA between the four OCS patient groups did not yield significant differences for any of the 13 cognitive outcome parameters.

Table 3 shows the results from random effect regression analyses. Analyses were covaried for age, sex, and education in the first step, whereas symptom scores (PANSS or CAPE) were included in the second step. Because the results for steps 1 and 2 did not differ significantly, only results for the final model are displayed. In patients, a higher Y-BOCS score (independent variable) was significantly associated with better performance on the Hinting task (dependent variable; $d' = +0.02$), but this result did not survive correction for multiple

TABLE 2. Group Comparisons of Demographic, Clinical, and Cognitive Variables Between Patients With Different Levels of OCSs

	Y-BOCS 0 (n = 763)	Y-BOCS 1–7 (n = 67)	Y-BOCS 8–15 (n = 100)	Y-BOCS ≥16 (n = 54)	F/χ^2 (df), p
Age	28.1 (8.3)	27.1 (6.4)	27.9 (8.4)	23.5 (6.6)	$F_{3,980} = 5.55$, $p < 0.001$
Sex (% male)	76.4%	73.1%	79.0%	70.4%	$\chi^2_2 = 1.80$, $p = 0.62$
Mean Y-BOCS score	0.0 (0.0)	5.0 (1.8)	11.2 (2.2)	20.8 (4.2)	–
PANSS positive	12.1 (5.1)	13.0 (6.0)	14.2 (5.1)	16.1 (5.9)	$F_{3,980} = 12.76$, $p < 0.001$
PANSS negative	13.9 (6.1)	14.0 (5.3)	14.7 (5.1)	15.6 (6.4)	$F_{3,980} = 1.68$ $p = 0.26$
PANSS general	27.0 (8.3)	28.9 (7.4)	31.1 (7.7)	33.3 (9.9)	$F_{3,980} = 15.19$, $p < 0.001$
Inpatients, %	12.7	13.4	15.0	24.1	$\chi^2_3 = 5.71$, $p = 0.13$
Clozapine use, %	8.1	13.4	14.0	18.5	$\chi^2_3 = 10.17$, $p < 0.017$
WLT-immediate recall	25.2 (6.3)	24.8 (6.5)	24.2 (6.0)	23.6 (6.9)	$F_{3,951} = 0.18$, $p = 0.91$
WLT-retention rate	0.8 (0.2)	0.8 (0.2)	0.8 (0.2)	0.8 (0.2)	$F_{3,951} = 0.34$, $p = 0.79$
Digit Symbol-Coding	73.6 (17.4)	73.9 (16.4)	67.7 (17.2)	67.2 (16.7)	$F_{3,957} = 0.63$, $p = 0.60$
Arithmetic	13.7 (4.5)	13.2 (4.7)	12.8 (4.5)	11.6 (4.7)	$F_{3,949} = 0.73$, $p = 0.54$
Block design	40.5 (16.2)	43.8 (16.2)	40.3 (16.7)	38.1 (16.6)	$F_{3,951} = 0.77$, $p = 0.51$
Information	17.4 (5.3)	17.3 (6.0)	17.0 (5.4)	15.7 (5.5)	$F_{3,952} = 0.61$, $p = 0.60$
CPT reaction time	0.4 (0.1)	0.4 (0.1)	0.4 (0.1)	0.4 (0.1)	$F_{3,891} = 0.81$, $p = 0.49$
CPT accuracy	98.9 (4.2)	99.3 (1.3)	98.8 (4.1)	98.1 (5.8)	$F_{3,891} = 0.32$, $p = 0.81$
RST reaction time	0.2 (0.2)	0.2 (0.2)	0.2 (0.2)	0.2 (0.2)	$F_{3,837} = 1.21$, $p = 0.31$
RST accuracy	0.1 (0.2)	0.1 (0.2)	0.1 (0.1)	0.1 (0.2)	$F_{3,837} = 2.09$, $p = 0.10$
DFAR	70.0 (10.0)	70.5 (10.6)	70.3 (9.9)	68.6 (11.0)	$F_{3,901} = 0.96$, $p = 0.41$
Hinting Task	18.5 (2.1)	18.6 (2.1)	18.4 (2.1)	18.2 (2.1)	$F_{3,829} = 3.03$, $p = 0.03$
BFRT	22.9 (2.3)	22.8 (2.2)	22.7 (2.4)	22.9 (2.3)	$F_{3,946} = 1.95$, $p = 0.12$

Data are presented as mean (SD), unless otherwise stated.

OCSs indicates obsessive-compulsive symptoms; Y-BOCS, Yale-Brown Obsessive-Compulsive Scale; PANSS, Positive and Negative Syndrome Scale; WLT, Word Learning Task; CPT, Continuous Performance Task; RST, Response Shifting Task; DFAR, Degraded Facial Affect Recognition; BFRT, Benton Face Recognition Task.

TABLE 3. Test Statistics and Effect Sizes of Significant Random Effect Regression Results With Y-BOCS Score as Independent Variable and Cognitive Functioning as Dependent Variable

	F(*df*)	*p* Value	*d′*
Patients			
Hinting task	$F_{1,947} = 4.47$	<0.04	+0.03
Parents			
RST accuracy	$F_{1,658} = 14.63$	<0.01[a]	−0.10
Controls			
Information	$F_{1,529} = 3.99$	<0.05	+0.03
Digit Symbol-Coding	$F_{1,525} = 7.04$	<0.01[a]	−0.05

Y-BOCS indicates Yale-Brown Obsessive-Compulsive Scale; RST, Response Shifting Task.
[a]Significant after correction for multiple comparisons ($p < 0.005$).

comparisons. In siblings, the Y-BOCS score was not significantly associated with any of the cognitive parameters. In parents, a higher Y-BOCS score was significantly associated with worse performance on the RST accuracy ($d' = -0.10$). In controls, a higher Y-BOCS score was significantly associated with better performance on the WAIS-Information task ($d' = +0.03$) and worse performance on the Digit Symbol-Coding task ($d' = -0.05$), of which only the latter result survived correction for multiple comparisons.

Finally, cross-trait cross-relative analyses did not yield significant associations between Y-BOCS scores in probands and any of the cognitive parameters in their siblings or parents (results not shown).

DISCUSSION

To the best of our knowledge, our study was the first to assess the association between OCSs and cognitive functioning in patients with nonaffective psychosis, their unaffected siblings and parents, and control subjects. Contrary to our hypothesis, neither within-subject analyses nor cross-relative analyses yielded a clear association between OCSs and cognitive performance. Although OCSs were significantly associated with worse set shifting accuracy in parents and worse processing speed in controls, the effect sizes were too small to be clinically relevant. Cross-trait cross-relative analyses were performed to exclude possible disease-related confounding but failed to demonstrate an association between level of OCSs in patients and their relatives' cognitive performance. Our results therefore do not support the existence of a schizo-obsessive subtype from a neurocognitive perspective. Possible implications of the findings, together with suggestions for future research, are provided here.

In case of negative findings, as in our study, it is important to evaluate differences with other study designs in the field to reflect on whether we might have missed an association between OCSs and cognition in schizophrenia that is actually present. In contrast to our study, seven studies reported a negative association between OCSs and cognitive functioning in schizophrenia (Berman et al., 1998; Hwang et al., 2000; Kumbhani et al., 2010; Lysaker et al., 2002, 2000, 2009; Patel et al., 2010). Alternatively, seven studies corroborated our results, with OCS+ patients demonstrating similar or even slightly better cognitive functioning compared with OCS− patients (Borkowska et al., 2003; Hermesh et al., 2003; Lee et al., 2009; Ongur and Goff, 2005; Tiryaki and Ozkorumak, 2010; Tumkaya et al., 2009; Whitney et al., 2004).

It may be argued that an association between OCSs and cognitive functioning in schizophrenia is to be detected only if the level of OCSs is considerably high and the sample size is large enough. The mean Y-BOCS score of 11.6 in our OCS+ sample was relatively low because of the fact that patients with subclinical OCSs were also included. In comparison, studies that did report an association between OCSs and worse cognitive functioning included OCS+ patients with a higher Y-BOCS score (weighted mean, 21.6) (Berman et al., 1998; Hwang et al., 2000; Lysaker et al., 2002; Patel et al., 2010). However, apart from patients with subclinical (Y-BOCS 1–7) and mild (Y-BOCS 8–15) OCSs, we also included a group with moderate to severe OCSs (Y-BOCS ≥16; mean, 20.8). Although this group represented only 5.5% of the patients, because of our large sample size, the number of OCS+ patients was still considerable ($n = 54$). In comparison, studies that did demonstrate an association between OCSs and worse cognitive functioning were performed in a weighted mean number of 18.2 OCS+ patients (Berman et al., 1998; Hwang et al., 2000; Lysaker et al., 2002, 2000, 2009; Patel et al., 2010). Consequently, our negative results cannot be merely attributed to relatively mild OCSs or to insufficient numbers of OCS+ patients.

Moreover, it has been suggested that the association between OCSs and cognition in schizophrenia is age dependent (Borkowska et al., 2003). Although our patients were younger (mean age, 27.8 years) compared with those of studies that demonstrated worse cognitive functioning in OCS+ patients (weighted mean age, 42.6 years) (Berman et al., 1998; Hwang et al., 2000; Kumbhani et al., 2010; Lysaker et al., 2002, 2000, 2009; Patel et al., 2010), they were also considerably younger compared with patients in studies that failed to demonstrate such an association (weighted mean age, 38.1 years) (Borkowska et al., 2003; Hermesh et al., 2003; Lee et al., 2009; Ongur and Goff, 2005; Tiryaki and Ozkorumak, 2010; Tumkaya et al., 2009; Whitney et al., 2004). Together with the fact that age differences were controlled for in our analyses, it is unlikely that our negative findings are the result of the inclusion of younger patients.

Another possibility is that we did not assess the right cognitive domains. In the case of a schizo-obsessive subtype, OCS+ patients would be expected to differ from OCS− patients on cognitive domains that show impairments in nonschizophrenic OCD patients (Berman et al., 1998; Whitney et al., 2004). The neurobiology of OCD is believed to be characterized by structural and functional abnormalities in the orbitofrontal cortex, anterior cingulate gyrus, and basal ganglia. Accordingly, OCD patients have shown impaired performance on neurocognitive tasks subserved by these brain regions, including verbal memory, processing speed, set shifting, and sustained attention (Chamberlain et al., 2005; Kuelz et al., 2004). We did not find an association between performance on these domains and OCSs in our study sample.

On the other hand, three cognitive domains that are known to be associated with OCD were not assessed in our study: decision making, response inhibition, and visual memory (Chamberlain et al., 2005; Kuelz et al., 2004). Only 2 of 14 previously mentioned studies used a gambling task to assess decision-making performance and failed to report an association with OCSs (Patel et al., 2010; Whitney et al., 2004). Response inhibition was also assessed in two studies, with one reporting a negative association with OCSs (Lysaker et al., 2009) that could not be replicated in the second study (Patel et al., 2010). Visual memory was assessed in five studies, with mixed results of worse, equal, and even better performance in OCS+ patients (Berman et al., 1998; Lee et al., 2009; Lysaker et al., 2002; Tumkaya et al., 2009; Whitney et al., 2004). Results demonstrate that, so far, it has not been possible to identify a unique pattern of cognitive impairment that distinguishes OCS+ from OCS− patients.

Likewise, the only cognitive test domain that has shown impairments in OCS+ patients more than once is cognitive flexibility, assessed with the Wisconsin Card Sorting Test (WCST) (Hwang et al., 2000; Lysaker et al., 2002, 2000). Impairment in the WCST has been described to be typical for dorsolateral prefrontal cortex dysfunction in schizophrenia (Abbruzzese et al., 1995). On the other hand, Goldberg and Weinberger (1994) have cautioned against an overinterpretation of the WCST as a specific measure of focal (schizophrenia-related) prefrontal dysfunction because, due to task complexity, it addresses many cognitive domains and may therefore merely represent a final common cognitive pathway. This is in line with the statement that the cognitive profile of OCS+ patients is more likely to represent a "pathophysiological double jeopardy" (*i.e.*, having two conditions instead of one) rather than a unique pattern of cognitive deficits (Whitney et al., 2004).

In addition to this lack of consistency in the cognitive domain, some methodological issues of previous studies should be taken into consideration. Despite the argument that cognitive impairment on a single domain is regarded as insufficient ground to label a patient (or a group of patients) as cognitively impaired (Palmer et al., 1997), four of seven studies concluded OCS+ patients to be "impaired" in comparison with OCS− patients based on deficits in one domain (Kumbhani et al., 2010; Lysaker et al., 2000, 2009; Patel et al., 2010). Moreover, most of the studies did not adequately minimize the risk of a type I error by maintaining an alpha level of less than 0.05 despite multiple statistical comparisons (Berman et al., 1998; Kumbhani et al., 2010; Lysaker et al., 2000; Patel et al., 2010). Third, although cognitive performance in schizophrenia is known to be affected by the level of psychotic symptoms, some studies did not correct their analyses for the fact that positive (Lysaker et al., 2002, 2000) and negative (Hwang et al., 2000; Lysaker et al., 2002) symptoms were significantly higher in the OCS+ patients compared with the OCS− patients. Hence, in those studies, worse cognitive functioning may have been erroneously attributed to OCSs.

Our study extended upon previous research by the inclusion of subjects at increased genetic risk for psychosis. Unaffected relatives have been used in the search for cognitive endophenotypes in schizophrenia (Gur et al., 2007) and OCD (Menzies et al., 2007) but not for the combination of both disorders. In case of an association between OCSs and cognitive functioning in patients, replication of this result in their unaffected relatives would indicate a) that this association is not merely state related and b) that there may be a shared genetic vulnerability for both schizophrenia and OCD (Poyurovsky and Koran, 2005). In our case, no distinct cognitive pattern in the patients emerged, and thus, the analysis of relatives was not necessary to exclude any psychosis-related confounding. However, the inclusion of unaffected relatives was still valuable to investigate whether subjects at increased genetic risk for both psychosis and OCSs display an additional cognitive vulnerability compared with relatives of OCS− patients, which could not be confirmed. Moreover, unaffected relatives did not display higher levels of OCSs compared with controls. These results do not corroborate the previous results of a strong familial-genetic component in OCD (Mataix-Cols et al., 2005), at least not in families with genetic loading for psychosis.

The results of this study should be viewed in the light of some limitations. Because the same researchers administered both the PANSS and the Y-BOCS, rater bias cannot be excluded. What makes rater bias less likely though is that the cognitive and OCS assessments were part of a large test battery in a group of patients and relatives that were unselected for the presence of OCSs. Second, although the heterogeneity of our sample in age, illness duration, and psychotic severity enhanced generalizability, it may have equaled out cognitive differences in specific subgroups of patients. Third, we did not include all cognitive measures that were found to be associated with OCS comorbidity in former studies.

CONCLUSIONS

Despite the large sample size and the inclusion of unaffected relatives, this study could not confirm the existing premise that OCS+ patients may be differentiated from OCS− patients based on their cognitive performance. Although OCS+ patients displayed a more severe clinical profile, our results do not validate a schizo-obsessive subtype from a cognitive perspective. Although OCS+ patients in previous studies demonstrated a rather nonspecific cognitive profile, the majority of results was either marginally significant, present in a single cognitive domain, or possibly confounded by higher levels of psychotic symptomatology. Hence, future research including patients and their unaffected relatives is warranted to clarify the nature of genetic and environmental factors that predispose individuals with psychosis to OCS comorbidity.

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