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REVIEW ARTICLE

Schizo-obsessive spectrum disorders: an update

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The presence of obsessive-compulsive symptoms (OCS) and obsessive-compulsive disorders (OCD) in schizophrenia is frequent, and a new clinical entity has been proposed for those who show the dual diagnosis: the schizo-obsessive disorder. This review scrutinizes the literature across the main academic databases, and provides an update on different aspects of schizo-obsessive spectrum disorders, which include schizophrenia, schizotypal personality disorder (SPD) with OCD, OCD with poor insight, schizophrenia with OCS, and schizophrenia with OCD (schizo-obsessive disorder). An epidemiological discussion on the discrepancies observed in the prevalence of OCS and OCD in schizophrenia across time is provided, followed by an overview of the main clinical and phenomenological features of the disorder in comparison to the primary conditions under a spectral perspective. An updated and comparative analysis of the main genetic, neurobiological, neurocognitive, and pharmacological treatment aspects for the schizo-obsessive spectrum is provided, and a discussion on endophenotypic markers is introduced in order to better understand its substrate. There is sufficient evidence in the literature to demonstrate the clinical relevance of the schizo-obsessive spectrum, although little is known about the neurobiology, genetics, and neurocognitive aspects of these groups. The pharmacological treatment of these patients is still challenging, and efforts to search for possible specific endophenotypic markers would open new avenues in the knowledge of schizo-obsessive spectrum.

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Introduction

The prevalence rate of schizophrenia in the general population is nearly 1%,[1] whereas the corresponding rate of obsessive compulsive disorder (OCD) is as high at 2%–3%.[2] Instances of the co-occurrence of psychotic and obsessive–compulsive symptoms (OCS) have been noted since the 19th century with low prevalence rates (1%–3.5%).[3] However, more contemporary studies have documented a much higher prevalence of OCS in schizophrenia,[4] with rates reaching 25% for OCS and 12% for comorbid OCD.[5]

In fact, the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV) published in 1994 allowed for the dual diagnosis of schizophrenia and obsessive compulsive disorders, and in this same year the term "schizo-obsessiveness" was first coined by Hwang and Opler.[6] Since then, researchers have investigated this much higher-than-expected co-occurrence.[7–9] Poyurovsky and Koran[10] have examined the OCD–schizophrenia spectrum disorders, which included OCD, OCD with poor insight, OCD with schizotypal personality disorder, schizophrenia with obsessive compulsive symptoms, schizophrenia with OCD, and pure schizophrenia.

Such a spectral view of the 2 disorders was corroborated by the recent changes in the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5),[11] which excluded OCD from the anxiety disorders chapter and recognized the existence of the so-called "schizophrenia spectrum disorder."[12] Although the schizo-obsessive subgroup was not included within the recent version of the manual, the recognition of the mentioned spectrum as well as the possible existence of "obsessions without insight" integrates the schizo-obsessive subgroup into a continuum between obsessions and delusions.[13,14]

In line with this, Poyurovsky *et al*[15] recently proposed the existence of a putative new clinical entity, the so called "schizo-obsessive disorder," thus establishing a provisional set of diagnostic criteria for this representative subgroup of patients who show meaningful OCS in

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addition to positive, negative, and cognitive schizophrenia symptoms. Therefore, the purpose of this review was to provide an update on the epidemiological, clinical, phenomenological, neurobiological, genetic, neurocognitive, and pharmacological aspects of the schizo-obsessive spectrum disorders. A perspective on endophenotypic markers of schizo-obsessive spectrum is highlighted to help understand the substrate of the mentioned disorders and its relationships.

Methods

We scrutinized the literature across the main medical academic databases, such as PubMed, PsychInfo, and Google Scholar, for relevant articles on schizo-obsessive spectrum disorders until early 2016. The keywords "schizo-obsessive disorder" or "schizo-obsessive spectrum disorders"; and "schizophrenia" or "psychosis" or "psychotic disorder" linked with "OCD" or "obsessive" or "compulsive" were used. Within these results, we selected studies that addressed the clinical, epidemiological, phenomenological, neurobiological, genetics, neurocognitive, and pharmacological treatment aspects. A special survey was undertaken in search for articles that specifically addressed the endophenotypic concept for the schizo-obsessive spectrum.

Epidemiology

Schizophrenia–OCD spectrum

The prevalence of schizophrenia in the general population is nearly 1%, while for obsessive compulsive disorder (OCD) it varies from 1% to 2%.[16] Although the risk of an OCD patient developing psychotic symptoms is considerably low (1.7%), as shown by de Haan *et al*,[17] poor insight in OCD patients is fairly common ranging from 13.8% to 30.7%.[18] Similarly, schizotypal personality disorder (SPD) and OCD is a very common association, varying from 5% to 50%.[10]

A robust longitudinal study based on registers of 3 million of people who were followed for 17 years has recently shown that 30,556 people developed schizophrenia spectrum disorders, and among them, 700 individuals (2.29%) were diagnosed with OCD prior to the diagnosis of schizophrenia. Furthermore, the authors found that the parental diagnosis of OCD significantly increased the risk of developing schizophrenia spectrum disorder in their offspring.[19] Indeed, among those individuals considered at risk for developing psychosis, 12.1% exhibited OCS and 5.1% OCD, according to Fontenelle *et al*,[20,21] while Zink *et al*[22] reported similar rates of 11% for OCS and 5% for OCD in this population.

Schizo-obsessive disorder

The prevalence of OCS and OCD in schizophrenia has been shown to be considerably higher than previously expected.[23,24] While until the first half of the 20th century, obsessions were considered a defense mechanism against psychosis,[25] more contemporary studies have recorded prevalence rates of OCS in schizophrenia varying from 30% to 59%,[5] while the comorbidity with obsessive-compulsive disorder (OCD) has been estimated to be from 8% to 23%.[26,27]Accordingly, Schirmbeck and Zink[5] demonstrated a prevalence rate of 25% for OCS and 12.1% for OCD in schizophrenia patients, as well as 17.1% of OCS in the first psychotic episode.

There are many potential explanations for such discrepancies in the co-occurrence of OCS in schizophrenia across time. One such reason is that earlier studies comprised retrospective data or case reports rather than any standardized diagnostic criteria for both schizophrenia and OCD.[8] Therefore, studies performed in recent decades, particularly after the introduction of the *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition Revised (DSM-III-R) in 1987 and the Fourth Edition (DSM-IV) in 1994, have been more sensitive to comorbidities such as schizophrenia and OCD.

Another factor that could have influenced the increase in OCS prevalence in schizophrenia patients in the last few decades is the broader use of atypical antipsychotics for schizophrenia treatment. The occurrence of OCS or its *de novo* manifestation induced by clozapine is well described in the literature.[5] Further details on this issue are discussed in the section "Treatment-Related Issues."

Phenomenology

Schizophrenia–OCD spectrum

Although obsessions and delusions present distinct phenomenological features, in some cases, the clear distinction of both can become difficult. The main phenomenological characteristics that differentiate OCD from psychotic disorders include the ego-dystonicity of OCD and the presence of "insight," that is, the ability of the subject to recognize the compulsion or obsession as foreign to him or her and irrational or excessive. Oulis *et al*[28] investigated several phenomenological aspects of typical obsessions/compulsions in comparison with delusions and repetitive delusional behaviors and found that conviction, consistency with one's belief-system, awareness of its inaccuracy, awareness of its symptomatic nature, resistance, and emotional impact, features collectively known as "ego-dystonicity," are the most important tool used to differentiate delusions from obsessions.

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In line with this, a growing body of evidence shows that there is a varying spectrum from schizophrenia to OCD, which is modulated by the presence and extent of the insight.[8,28] Recent editions of the DSM corroborated such findings, as they allowed the existence of "OCD with poor insight," which has received more phenomenological attention.[18] These authors considered poor insight as an epiphenomenon of illness severity, associated with a decreased resistance and control of OCD symptoms. Furthermore, schizotypal personality disorder (SPD) was found to be associated with poor insight, even in treated patients,[29] which reinforces the idea of an OCD-schizophrenia spectrum modulated by insight.[10]

Schizo-obsessive disorder

Frías *et al*[30] compared the awareness of mental disorder, awareness of the need for treatment, and the awareness of the consequences of the disease between schizo-obsessive and non-OCD schizophrenic patients by using the Unawareness of Mental Disorder Scale (SUMD). The authors failed to find any between-group difference, with both groups manifesting a partial awareness of psychotic illness. With regard to the insight into OCD, these authors showed that schizo-obsessive subjects presented a lesser degree of insight than non-schizophrenic OCD patients, as previously described by Matsunaga *et al*.[29]

Clinics

Schizophrenia and OCD

Obsessive-compulsive symptoms may appear at different stages of psychotic illness. According to Schirmbeck and Zink,[5] OCS can manifest before and independently of psychosis, intermittently or later in the illness, or prodromally and then consistently throughout the illness. In these instances, OCS may be strongly associated with the psychotic symptoms (schizo-obsessive concept), fluctuating or induced by antipsychotics .It can also be present in those considered at risk for psychosis, such as first-degree relatives.[20]

SPD–OCD association

Schizotypal personality disorder (SPD) associated with OCD displays a more deteriorative course, poorer insight (with some patients exhibiting delusional transformation of obsessions), more negative symptoms, lower functioning, greater cognitive impairment, treatment resistance, and poorer prognosis than "pure" OCD.[10,31,32] Furthermore, these patients commonly exhibit major depression, posttraumatic stress disorder, substance use,[32,33] depression and bipolar disorder[34] as comorbid conditions, as well as increased severity of OCD and greater general psychopathology in comparison to OCD counterparts.[32–34] Interestingly, hoarding has been consistently associated with the SPD-OCD group[29,35] and has been reported as a predictor of schizotypal personality traits (SPT) in OCD.[36] Further clinical investigation is needed in order to elucidate the potential connection between hoarding symptoms and SPT, as well as its implication to the schizo-obsessive spectrum disorders.

OCD with poor insight

Similarly, OCD with poor insight has been commonly associated with schizotypal personality disorder,[15] poorer clinical outcome with greater number of obsessions and compulsions, longer duration and chronic course of illness, poorer response to treatment, earlier age-at-onset, and greater severity.[18,37,38] Poor insight also increases the risk of developing anxiety and depression,[37] and it is associated with higher rates of schizophrenia-spectrum disorders in first-degree relatives.[14,39]

Schizo-obsessive disorder

However, the literature contains conflicting results concerning the clinical profile of those who show the dual schizophrenia and OCD diagnoses (schizo-obsessive disorder).[40] Reports have attested to both greater[41,42] and fewer[43,44] numbers of positive symptoms as well as to greater[7,45] and fewer[46] negative symptoms in schizo-obsessive patients relative to subjects with schizophrenia.

With regard to the cognitive functioning of schizo-obsessive group, the scenario is equally conflicting. While most studies have found an association between comorbid OCS and impaired performance on tests of frontal lobe functioning, particularly abstraction and executive function,[47] some reports have failed to observe any correlation between OCS and neurocognition impairment in schizo-obsessive patients.[42,44] A more detailed discussion on this subject is provided in the section "Neurocognition."

What seems less controversial, however, is that in these patients, obsessive-compulsive symptoms are commonly severe and tend to appear during the prodromal stages of psychosis; moreover, patients' insight into their OCS varies from mild to good, as it does in OCD alone.[48–50] Compared to their schizophrenia counterparts, schizo-obsessive patients show earlier onset of psychosis, particularly in men,[50]; more depressive symptoms and suicide attempts[42,47,51]; increased rates of hospitalization; greater dysfunction; higher impairment in social behaviour[52]; smaller social networks; and poorer quality of life.[7,44,47] Furthermore, these patients tend to be more socially hostile and more anxious, as evidenced by their greater number of panic attacks and

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phobias.[52] Therefore, although still controversial, OCS seems to have a deleterious effect on schizophrenia outcome.[51]

On the other hand, Frías *et al*[30] compared schizophrenia/schizoaffective and OCD patients with a "non-OCD schizophrenic" group in relation to positive, negative, and obsessive-compulsive symptoms, as well as the assessment of the "insight" using validated scales, and did not find significant differences in any of the analyzed measures.

To further investigate the impact of OCS on schizophrenia, Faragian *et al*[50] applied an exploratory factor analysis for the Yale–Brown Obsessive-Compulsive Scale (Y-BOCS) in 110 patients diagnosed with "pure" OCD and schizophrenia with comorbid OCD. The OCS present in schizophrenia patients correlated with those in the pure OCD patients but did not correlate with the typical positive and negative dimensions of schizophrenia symptoms. These results suggest the existence of universal mechanisms in the pathogenesis of OCD regardless of the presence of schizophrenia and corroborate previous studies that showed similarities between OCS in schizo-obsessive and OCD patients.[42,51,52]

Furthermore, schizo-obsessive disorder seems to show a familial aggregation, as probands of schizo-obsessive patients had a higher risk of being diagnosed with schizo-obsessive disorder, obsessive-compulsive personality disorder, and OCD itself compared with probands of non-OCD-schizophrenia individuals.[53] In addition, first-degree relatives of psychotic patients considered to be "at-risk mental state" (ARMS) and who presented OCS showed more impairment in psychosocial functioning,[22,54,55] more severe depressive symptoms, and more suicidality.[21,48,56]

Diagnostic Criteria

Poyurovsky *et al*[15] have proposed the following provisional diagnostic criteria for the schizo-obsessive disorder as following:

- OCS symptoms are present that meet Criterion A for obsessive-compulsive disorder at some time point during the course of the schizophrenia.
- If the content of the obsessions and/or compulsions is interrelated with the content of delusions and/or hallucinations (eg, compulsive hand washing due to command auditory hallucinations), additional typical OCD symptoms that are recognized by the person as unreasonable and excessive are required.
- Symptoms of OCD are present for a substantial portion of the total duration of the prodromal, active, and/or residual period of schizophrenia.
- The obsessions and compulsions are time-consuming (more than 1 hour per day), cause distress, or significantly interfere with the person's normal routine, in addition to the functional impairment associated with schizophrenia.
- The obsessions and compulsions in the patient with schizophrenia are not due to the direct effect of antipsychotic agents, substance abuse, or organic factors.

The term "schizo-obsessive disorder" seems to be more appropriate than "OCD with psychotic features" to those who meet the above diagnostic criteria, since a large portion of schizophrenia patients develop OCD, contrasting with very few OCD patients who show psychotic symptoms.[17]

Neurobiology

Schizophrenia and OCD

The neurobiological substrates of both schizophrenia and obsessive–compulsive disorder (OCD) are thought to be related to neurodevelopment.[57] Studies in the literature have identified abnormalities in the fronto-striatal circuits as well as in the thalamus and hippocampus–amygdala complex in both conditions.[58] In fact, dissociated prefrontal cortex connections with the basal ganglia have been observed, particularly a dorsolateral prefrontal cortex (DLPFC) impairment in schizophrenia[59] and a ventromedial prefrontal cortex (VMPFC) impairment in OCD.[60] Cavallaro *et al*[61] assessed these 2 regions in both groups using the Wisconsin Card Sorting Test for DLPFC integrity and the Gambling Task, a decision-making task that examines VMPFC functions. The schizophrenic patients performed worse on the Wisconsin Card Sorting Test compared to OCD patients and controls, while OCD patients performed significantly worse on the Gambling Task relative to the schizophrenia patients and controls. These results corroborated the hypotheses of segregated "prefrontal" and "orbitofrontal" dysfunctions in both conditions.

Recent fMRI neuroimaging studies have shown diminished whole brain functional connectivity driven by some prefrontal cortical areas such as the left Inferior Frontal Gyrus (IFG) in schizophrenia patients.[62] Thus, Bleich-Cohen *et al*[63] compared the functional connectivity driven by IFG in schizophrenia and OCD patients in relation to healthy controls during an auditory verb generation task. The authors showed a diminished language asymmetry in the IFG and a reduced functional connectivity between the left and right IFG in schizophrenia patients, but not in OCD patients, relative to normal controls. Therefore, a disturbed functional brain organization during language processing seems to be a peculiar phenomenon of schizophrenia and plays an important pathogenic role in this disorder but not in OCD.

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Besides these cortices, other areas have also been implicated in both disorders. Aoyama *et al*,[64] for example, found that the left hippocampus was significantly smaller in early-onset schizophrenic subjects with OCS than in non-OCS-schizophrenic subjects. Converging findings were recorded by Kwon *et al*,[65] who used 3-dimensional magnetic resonance imaging and showed reduced hippocampal volume in both OCD and schizophrenic patients relative to normal controls. In contrast, the left amygdala volume was significantly enlarged in patients with OCD but not in those with schizophrenia or the normal controls. Therefore, a hippocampal reduction in OCD and schizophrenia would represent a neurodevelopmental abnormality of both diseases, while a left amygdala enlargement would be a specific marker of OCD. Conversely, Kim *et al*[66] recorded a reduction of the left insula in schizophrenic patients compared to the OCD group and controls, confirming the involvement of deficient insular function in the pathophysiology of schizophrenia but not OCD and its putative role as a neurodevelopmental marker for psychosis.

Similarly, Ha *et al*,[67] examining the 3-dimensional fractal dimension (FD) of the skeletonized cerebral cortical surface of schizophrenic and OCD patients compared to healthy controls, found that the schizophrenic group had a significantly smaller mean FD than the OCD group, and the latter had a smaller FD mean than normal controls. FD correctly distinguished 95.6% of the schizophrenics from the controls and 88.0% of the patients with OCD from the controls, highlighting FD as a putative biomarker of developmentally related mental illness.

With regard to neurotransmission, serotonin seems to play a central role in the underlying structural or functional changes observed in both schizophrenia and OCD. In fact, clomipramine and selective serotonin reuptake inhibitors (SSRIs) have long been used in treatment for OCD,[68] and the serotonin (5-hydroxytryptamine, 5-HT) postsynaptic receptor (5HT-1) agonist meta-chlorophenylpiperazine increases OCS in healthy volunteers, which decreases after metergoline administration, a serotonergic antagonist.[69]

Similarly, Ma *et al*[70] compared the whole blood 5-HT concentration among patients with obsessive-compulsive disorder (OCD), schizophrenic patients with and without OCS, and clozapine-treated schizophrenic patients with and without clozapine-induced OCS. They found that the whole blood 5-HT concentrations of the patients with OCS were lower than those without OCS, suggesting a relationship between OCS and low 5-HT levels. Based on the similarities between the groups with OCS in relation to the underlying serotonergic mechanisms, these authors claimed that schizophrenia associated with OCS is likely to represent a specific schizophrenia subtype.

SPD-OCD association

Similarly to schizophrenia, schizotypal personality disorder has been associated with gray matter volume reductions in different cortical areas such as the superior temporal gyrus, middle temporal gyrus, fusiform gyrus, hippocampus, frontal lobe, insula, cingulated gyrus, parietal lobe, and basal ganglia.[71] Although there are very little available data regarding neurobiological features of the SPD-OCD association, it has been suggested that this group may constitute a distinct subgroup from a neurobiological viewpoint.[29] The main neurobiological finding reported for this group refers to reductions in gray matter volume of the dorsolateral and orbito-frontal lobes in patients with OCD with higher levels of schizotypy compared to those with lower levels.[72,73] Such dual impairment observed in this group versus the orbitofrontal deficit alone seen in OCD is thought to constitute the neurobiological substrate responsible for the poorer outcome in these patients.[31,74]

OCD with poor insight

There are very limited published data regarding comparative neurobiological studies between OCD patients with poor and good insight. Aigner *et al*[75] have shown profound abnormalities in MRI scans in OCD patients with poor insight compared to those with good insight (83% versus 21%) with specific abnormalities in certain brain regions such as the basal ganglia, and parietal and frontal lobes in those with good insight. More neuroimaging studies are clearly needed to better understand the neurobiological substrate of poor insight in OCD, which seems to constitute a biologically and cognitively distinct subtype of OCD[38] within the schizo-obsessive spectrum.

Schizo-obsessive disorder

Similarly, very few structural neuroimaging studies on schizo-obsessive disorder are currently available. Aoyama *et al*,[64] using structural MRI scans, found smaller left hippocampi in childhood- and adolescent-onset schizophrenia patients with obsessive-compulsive symptoms compared to the non-OCD-schizophrenia subjects. In addition, an inverse correlation between illness duration and frontal lobe size was found in the schizo-obsessive group, but not in the group with schizophrenia alone.

The literature on functional neuroimaging in schizo-obsessive disorder is similarly scarce, but some evidence does exist of a more impaired frontal lobe function in schizophrenia patients with comorbid OC symptoms.[26] Levine *et al*[76] found a negative correlation between activation of the left dorsolateral prefrontal cortex and OCS severity in schizo-obsessive patients using functional MRI (fMRI) technique.

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Also, Bleich-Cohen *et al*[77] compared shifts in brain activation patterns and functional connectivity (FC) using fMRI during the N-back working memory task in schizo-obsessive subjects, schizophrenia subjects, and healthy volunteers. They found that schizo-obsessive patients exhibited functional brain activation patterns quite similar to their non-OCS schizophrenia counterparts during this task. Independent of the presence of OCS, schizophrenia patients had reduced activation of the right DLPFC and right caudate relative to healthy controls. Moreover, the functional connectivity in the right DLPFC with the right intra-parietal (IP) and right caudate as well as between the right caudate with right IP and right DLPFC was shown to be lower in both schizophrenia groups compared to healthy controls. Such results suggest that schizophrenia and schizo-obsessive patients failed to properly recruit their brains' working memory networks.

Indeed, working memory deficits have long been described in schizophrenia[78]; however, their presence has been much less pronounced in OCD.[79] This is possibly due to the greater involvement of the dorsolateral prefrontal cortex in schizophrenia and of the orbitofrontal prefrontal cortex in OCD. Conversely, Bleich-Cohen *et al*[80] performed a search for activation in schizophrenia and schizo-obsessive groups during a working memory task using a fMRI-based method called searchlight-based feature extraction (SBFE), which is able to assess both the regions of interest (ROI) and the whole-brain activities. This method was able to properly distinguish these groups with 91% accuracy based on activations in the right intraparietal sulcus (r-IPS), which was correlated with milder negative symptoms in schizo-obsessive patients. This finding speaks in favor of a possible protective effect of OCD in schizophrenia in relation to working memory performance.

Abnormalities in the inferior frontal gyrus (IFG) related to impaired language control and processing have been described in schizophrenia but not in OCD.[63] This team also compared the activation and language lateralization in the IFG and inter-hemispheric functional connectivity (FC) in schizo-obsessive patients, schizophrenia, OCD, and healthy individuals. However, while OCD patients showed a lateralization and FC similar to the healthy controls, both schizophrenia groups presented a diminished lateralization in the IFG and reduced inter-hemispheric FC, providing evidence that the OCD in schizophrenia does not alter the abnormal processing of language peculiar to this disorder.[81]

Genetics

Because both schizophrenia and OCD have a considerable genetic substrate, we might expect to find some specific genetic risk factor that predisposes patients with schizophrenia to develop OCS.[5] However, a pioneer study performed by Poyurovsky *et al*[53] failed to identify any evidence that the specific COMT Val158Met polymorphism was associated with susceptibility to schizo-obsessive disorder. More recently, a Val66Met polymorphism in the brain-derived neurotrophic factor (BDNF) gene was associated with OCS in schizophrenia,[82] but that result requires further replication.

With regard to OCS induced by second-generation antipsychotics, Kwon *et al*[83] found a strong association with specific single nucleotide polymorphisms (SNPs) of the candidate gene SLC1A1 in an Asian population, which is involved in the glutamatergic neurotransmission and known to be implicated in OCD.[84] However, Deng *et al*[85] did not find any association between this gene and a vulnerability to schizophrenia spectrum disorders. Similarly, Cai *et al*[86] have described an association between the SNPs in SLC1A1 gene as well as in the N-methyl-D-aspartate receptor gene (GRIN2B) and OCS severity in a Chinese clozapine-induced OCS-schizophrenia population. These findings suggest that polymorphism in these genes may confer susceptibility to OCS in schizophrenia patients treated with clozapine.

Therefore, more genetic studies in this subgroup are necessary, particularly like those using new techniques such as genome-wide association studies (GWAS), which would open new avenues for neurobiological studies in this group.

Neurocognition

Schizophrenia and OCD

The most consistent deficits in neuropsychological functioning found in schizophrenia refer to attention, executive function, and memory domains,[87] in particular to deficits in attentional set-shifting, working memory, strategic ability, and verbal fluency, resulting in impairments in temporal and sensory integration, planning, and maintenance of goal-directed behavior as well as behavioral flexibility and problem solving.[87]

Event-related potentials (ERPs) in EEG evoked by sensory stimuli have long been considered a neurophysiological correlate of cognitive functioning,[88] particularly the P300, which is one of the ERP components observed approximately 300 ms after stimulus onset and is associated with information processing in the human brain.[89] Reduced P300 amplitude is probably the most consistent and robust neurophysiological abnormality observed in schizophrenia.[90–98]

In a recent meta-analysis on neurocognitive impairments in OCD, Abramovitch *et al*[99] have shown reduced performance across several cognitive domains (attention, executive function, memory, visuospatial abilities,

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processing speed, and working memory) and subdomains (sustained attention, planning, response inhibition, set-shifting/cognitive flexibility, verbal memory, nonverbal memory, visuospatial abilities, processing speed, working memory, and spatial working memory) compared to healthy controls. Such neurocognitive deficits observed in OCD have been associated with dorsolateral and especially orbitofrontal cortical dysfunctions, as shown by Chamberlain *et al.*[79]

Therefore, in general, a failure in integrating neurocognitive abilities, a tendency to perseverate and to improperly notice details, attributed to impairments in DLPC, have been reported in schizophrenia,[99] while problems related to impulse control, regulation of behavior, and ability to maintain cognitive set, attributed to orbitofrontal dysfunction, have been observed in OCD.[79]

SPD–OCD association

In contrast to schizophrenia and OCD, few studies have addressed the neurocognitive performance in schizoptypical patients and, particularly, in SPD-OCD association. As observed in schizophrenia, cognitive processes mediated by the prefrontal cortex, such as working memory and context processing, have been shown to be impaired in SPD compared to healthy controls.[100] Indeed, patients with comorbid schizophrenia and SPD have demonstrated consistent deficits in tests sensitive to dorsolateral prefrontal cortex.[101] Accordingly, the literature demonstrates that patients with SPD associated with OCD show greater cognitive impairment than their OCD counterparts.[31] Such neuropsychological impairment has been found especially in tasks that assess dorsolateral and orbitofrontal cortices compared to those with OCD alone.[72,73] Therefore the dual impairment in dorsolateral and orbitofrontal prefrontal cognitive functions in the OCD-SPD population has been pointed as a predictor of poorer clinical and treatment outcomes in this group.[72,73]

OCD with poor insight

Similarly, little is known about the neurocognitive profile in OCD with poor insight. Tumkaya *et al*[13] found that patients with poor insight performed worse in executive function tasks compared to those with good insight, but they performed similarly to those with schizophrenia. Accordingly, Kitis *et al*[102] reported poorer performance in tasks on verbal learning and memory in relation to those with good insight. More recently, Kashyap *et al*[37] also found a worse performance in several cognitive abilities related to conflict resolution, response inhibition, verbal learning, and memory in OCD subjects with poor insight in comparison to good insight. These authors suggest that such impairments may lead to problems related to conflict solution between an existing irrational belief and incoming corrective information that fails to properly neutralize the former. These results collectively support the idea of an OCD–schizophrenia spectrum modulated by insight.

Schizo-obsessive disorder

Contradictory findings have been found regarding the neuropsychological performance in schizo-obsessive groups compared to schizophrenia groups without OCS. For instance, several authors have reported no between-group differences.[23,30,44,103] However, some have reported better cognitive performance in the schizo-obsessive group,[104,105] while the majority have reported poorer performance in these patients.[27,45,106–111] Such deficits have been especially pronounced in the domains of executive functioning,[7,45] cognitive flexibility,[108,110] attentional set-shifting,[108] delayed visual memory,[106,109] processing speed,[111] and social cognition.[112]

However, cognitive deficits in schizo-obsessive patients were shown to be stable and correlated with OCS severity in a 12-month longitudinal study performed by Schirmbeck *et al*,[109] particularly in relation to visuospatial perception, visual memory, executive functioning, and cognitive flexibility cognitive domains. In this study, schizo-obsessive subgroups did not show differences in the performance of tasks known to be impaired in schizophrenia, but did in those that assess the orbitofrontal cortex function.[113] These results speak in favor of an addictive cognitive impairment in schizo-obsessive patients.

Similarly, Kim *et al*[114] found reduced P300 amplitude in both schizophrenia and OCD patients compared to controls, with no significant difference between them. Pallanti *et al*[88] examined ERPs evoked during a response inhibition task and compared schizo-obsessive patients with OCD, schizophrenic patients, and control subjects. They found that schizo-obsessive patients showed a distinct ERP pattern compared with both OCD and schizophrenic patient groups. The schizo-obsessive patients presented increased target activation similar to OCD patients and dissimilar to schizophrenia patients but a reduced P300 amplitude similar to schizophrenia patients and dissimilar to OCD patients. The existence of such a specific ERP profile in schizo-obsessive patients that is distinguishable from schizophrenia and OCD suggests that this might constitute a specific subgroup, at least from a neurocognitive point of view.

Endophenotypic Markers

Frangou[115] has recently updated the concept of the endophenotypes as "quantifiable, state-independent traits that are genetically correlated with disease liability and can

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be expressed in unaffected family members" (p. 1223). This concept is particularly useful to identify and stratify psychiatric patients, not from a categorical viewpoint but rather from a pathophysiological continuum or spectral perspective. In fact, Gottesman and Gould[116] have established several endophenotype candidates for psychiatric syndromes, such as neurophysiological, biochemical, endocrinological, neuroanatomical, cognitive, and neuropsychological traits. Within the schizo-obsessive spectrum, intermediate phenotype studies may help to identify its underlying pathophysiology, and eventually, they may have an impact over nosological classifications and treatment outcome.[117]

Schizophrenia and OCD

Although Meijer *et al*,[103] examining the cognitive performance of 984 patients with non-affective psychosis, 973 unaffected siblings, 851 parents, and 573 controls, failed to find any associations between OCS and cognitive functioning, several neurocognitive endophenotypes have been proposed for schizophrenia and OCD.

In a review article, Allen *et al*[118] scrutinized the literature in search of endophenotypes for schizophrenia, and the strongest markers included the following: ventricular volume; planum temporale volume; superior temporal gyrus volume; fMRI activation during a 2-back task; prepulse inhibition; P50, P300, and P400 alterations in ERPs; smooth pursuit and saccadic eye movement; neuromotor deviations; and performance on the Wisconsin Card Sorting Task (which assesses the cognitive flexibility domain).

In relation to OCD, Menzies *et al*,[119] studying brain fMRI and behavioral performance on a response inhibition task, proposed the existence of neurocognitive endophenotypes for OCD, such as cognitive flexibility, decision-making, and motor inhibition.[120,121] In this line and among several cognitive domains examined, Rajender *et al*[122] found delayed verbal recall, set-shifting, inhibitory control, and visuo-constructive ability to be relatively easily measured endophenotypic markers for OCD, which can distinguish these patients and unaffected relatives from healthy controls. Furthermore, repetitive behaviors and poor conflict resolution/response inhibition deficits commonly seen in OCD were also reported in their unaffected first-degree relatives, thus constituting an endophenotypic candidate for OCD.[79,121,123]

Therefore, neurocognition impairment, in particular changes in the P300 wave amplitude and latency in the ERP, has proven to be one of the most replicated neurophysiological correlates of cognitive function and thus remains an endophenotypic indicator candidate for both schizophrenia[93,98] and OCD.[114]

SPD–OCD association

Schizotypy has been proposed as an endophenotype for the schizophrenia spectrum disorders, since it is commonly observed at a different degree and extent in schizophrenic patients, clinically unaffected relatives of schizophrenic patients, schizotypal patients, and their first-degree relatives.[124] These authors have demonstrated the following endophenotype candidates associated to schizotypy: P50 and P300 ERP suppressions, prepulse inhibition, smooth-pursuit eye movement, antisaccade, executive functioning, working memory, thought disorder index, ego impairment index, continuous performance test, span of apprehension, visual backward masking, and reaction time. Similarly, Saperstein *et al*[125] found visuospatial working memory impairment as a cognitive endophenotype for schizophrenia and associated personality disorders. Considering that one-third of OCD-SPD patients have family members diagnosed with schizophrenia-spectrum disorders,[31] these endophenotype candidates found for the schizophrenia-spectrum are likely to co-transmit across the SPD-OCD spectrum. Therefore, it does lack well-designed and controlled trials evaluating neurobiological and neurocognitive endophenopytic markers for the SPD-OCD association, which would better clarify the substrate and position of this group within the schizo-obsessive spectrum.

OCD with poor insight

Similarly, very few studies have addressed endophenotypic candidates for OCD with good and poor insight. Since conflict resolution/response inhibition and memory impairments have been described as endophenotypic candidates for OCD,[78,121,123] Kashyap *et al*[37] compared these traits between OCD patients with varying degrees of insight and found that poor insight is strongly associated with poorer conflict resolution/response inhibition, verbal memory, and fluency. Therefore, these traits might be considered as putative endophenotypic markers for the OCD with poor insight group. Neurological soft signs have also been reported by Tumkaya *et al*[126] as a possible endophenotypic candidate for this group. They found that OCD patients with poor insight performed worse and similarly to schizo-obsessive patients in tasks assessing neurological soft signs compared to OCD with good insight counterparts. Therefore, a better understanding of the neurobiology of insight would contribute greatly to our current knowledge of the schizo-obsessive spectrum.

Schizo-obsessive disorder

Neurocognitive performance appeared to be an attractive endophenotypic marker capable of distinguishing the

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putative schizo-obsessive disorder from the parental diseases.[10] In line with this, ERP was proposed as an endophenotype candidate for the schizo-obsessive disorder, as these patients showed a distinct ERP profile in relation to schizophrenia and OCD.[88] Further studies comparing schizo-obsessive patients with OCD and schizophrenia patients with varying degrees of insight as well as first-degree relatives might confirm such findings.

Neurological soft signs (NSSs), generally grouped as sensory integration, motor coordination, and complex motor acts, might also be potential intermediate phenotypes. Tumkaya *et al*[128] found that schizo-obsessive patients performed worse on graphesthesia tasks (one item from a sensory integration subscale) when compared to schizophrenia and OCD patients. Such pronounced somatosensory deficit in schizo-obsessives was attributed to a jeopardizing neurodevelopmental dysfunction in somatosensory, dorsolateral prefrontal, and orbitofrontal cortices in the comorbid group. However, studies that also include first-degree relatives might clarify the role of graphesthesia deficits as putative endophenotypic markers for schizo-obsessive disorder.

Eye tracking dysfunction is another endophenotype candidate for schizo-obsessive disorder. In a robust sample of schizo-obsessive patients, eye tracking dysfunction was found to be elevated compared to schizophrenia and OCD patients in contrast to other traits such as craniofacial dysmorphology and thought disorder, which were not shown to be altered.[117] This study, however, did not include unaffected relatives; thus, any conclusions about intermediate phenotypes are limited.

Therefore, neurocognitive performance associated with brain functional connectivity, which can help assess the dynamic neural networks engaged by neurocognitive tasks,[115] constitutes a promising tool for investigating endophenotypes not yet applied to patients on the schizo-obsessive spectrum and their first-degree relatives. Such an effort would open new avenues in the research on schizo-obsessive spectrum.

Treatment-related issues

Schizophrenia and OCD

Schizophrenia is commonly treated with both typical and atypical antipsychotics, which show different affinities for D2 and 5HT receptors as well as distinct side effects. Although these drugs are known to modulate schizophrenia symptoms, the molecular and biochemical mechanisms involved in this improvement are poorly understood.[127]

Cognitive behavioral therapy (CBT) with exposure and subsequent response prevention associated with serotonin reuptake inhibitors (SRIs) or clomipramine are the most effective and well-established treatment strategy for adult OCD, although 40%–60% of patients show resistance.[2] However, SRIs have been preferred because clomipramine, although it presents clinically relevant serotonin and noradrenaline reuptake inhibition,[128] is commonly associated with anticholinergic and other adverse effects which limit its use at high doses commonly needed for OCD.[129]

The addition of anti-psychotics has proved to be an efficient augmentation strategy for refractory OCD.[130,131] In fact, a recent review including double-blind, randomized, placebo-controlled trials on the efficacy of antipsychotic augmentation in treatment of SRI-resistant OCD patients demonstrated that about one-third benefited from this strategy. Based on the risk–benefit ratio, risperidone was suggested as the agent of first choice over quetiapine and olanzapine.[132] No conclusions regarding aripiprazole and haloperidol could be made due to methodological issues.

SPD–OCD association

Patients with treatment-resistant obsessive-compulsive disorder have been shown to present high rates of personality disorders, in particular schizotypal personality features.[14,133,134] Furthermore, SPD predicts a poorer response to both SSRIs and behavioral intervention,[10,133] as well as an earlier treatment-seeking age in OCD.[34] Therefore, the combination of SSRIs and low-dose antipsychotics such as olanzapine has been shown to be an effective therapeutic strategy for the SPD-OCD group.[135]

OCD with poor insight

Although greater insight into OCD has been associated with a better response to cognitive-behavioral therapy,[136] the current knowledge regarding its relationship with pharmacological treatment is still inconclusive. While most authors have considered poor insight as a predictor of decreased pharmacological treatment response[14,137,138] and responsible for a lower engagement[139] or delayed treatment-seeking,[140] some studies have failed to find any correlation between the insight degree and response to SSRI treatment.[141] Therefore, the pharmacological treatment of this group seems to be particularly challenging, and more conclusive studies are clearly needed.[18,38]

Schizo-obsessive disorder

The combination of antipsychotics with anti-obsessive drugs is presumably the best treatment of choice for the comorbid schizo-obsessive group,[10,26,40] although very few studies have addressed pharmacological strategies for the comordid group.[15] Among the available anti-obsessive drugs for OCD, SSRIs and clomipramine show

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comparable efficacy, but the former is commonly preferred due to its more favorable risk profile,[142] as opposed to the previously mentioned side effects presented by clomipramine.[129] Among the several SSRIs tested for OCD in randomized controlled trials (RCTs), including citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline, no differences among them were noticed regarding efficacy.[143]

However, little information is currently available on SSRIs for the schizo-obsessive group. Stryjer *et al*,[102] in a prospective 12-week study, demonstrated a positive effect of escitalopram on obsessive symptoms as well as improvement in positive, negative, anxiety, tension, and depression symptoms in patients with schizophrenia and OCD taking antipsychotic medication.

Second-generation antipsychotics are commonly the first choice in the treatment of OCD-refractory patients[132] and for the schizo-obsessive group[15] due to their affinity to both dopaminergic and serotoninergic systems.[144] However, SSRIs show pharmacokinetic interactions with second-generation antipsychotics, particularly clozapine, increasing the risk of inducing seizures and other toxic side effects.[145]

Furthermore, several authors have reported that second-generation antipsychotics, especially clozapine, induce obsessive compulsive symptoms (OCS), which limits their use for schizo-obsessive patients.[5,146–149] Additionally, these antipsychotics may provoke a *de novo* emergence of such symptoms.[146,147,150] In fact, while Poyurovski *et al*[10] estimated that 70% of schizophrenic patients on SGAs may develop secondary OCS, Lykouras *et al*[148] confirmed rates similarly high (77%) in clozapine-treated patients, and Fonseka *et al*[150] estimated a risk of 20%–28% of *de novo* occurrence of OCS in schizophrenic clozapine-treated patients.

Second-generation antipsychotic-induced OCS is likely to be attributed to the antidopaminergic and antiserotonergic properties of second-generation antipsychotics that markedly exceed the 5HT-receptor blockade presented by the first-generation drugs.[151] Indeed, Schirmbeck *et al*[146] compared 70 schizophrenic patients under 2 different antipsychotic treatments, clozapine/olanzapine (group I) and aripiprazole/amisulpride (group II), and found that more than 70% of patients from group I showed OCS compared to less than 10% of group II. Importantly, the severity of OCS was correlated with the dosage of clozapine and treatment duration, and there was a persistence of OCS in group I but not in group II after 12 months of treatment.[83] Recently, this team was also able to show in a fMRI study that group I showed an increased activation in the orbitofrontal cortex (OFC) during a response inhibition task in comparison to group II.[152]

Interestingly, Juven-Wetzler *et al*[153] has recently found a bimodal response of schizo-obsessive patients to ziprazidone regarding OCD symptoms improvement. Nearly half of patients under this medication showed a significant improvement in OCS, while the other half showed no response or worsening of symptoms. Curiously, negative and general schizophrenia symptoms followed the same tendency in both groups. Therefore, these authors suggest ziprazidone as an option for the schizo-obsessive group and make a claim for a personalized treatment for the complex OCD-schizophrenia spectrum disorders.

Therefore, further longitudinal studies are needed that compare the effects of different antipsychotics and serotonin reuptake inhibitors on schizo-obsessive disorder. A better understanding of the pharmacological and biological mechanisms, as well as the clinical effects of the combined drugs on the symptoms of schizo-obsessive disorder, would provide some insights into the pathological mechanism of this comorbid group, improve its management, and avoid inconvenient effects of polypharmacy.

Conclusions

There is sufficient evidence in the literature demonstrating the clinical relevance of the schizo-obsessive spectrum disorders, particularly the schizo-obsessive disorder, which seems to show epidemiological, clinical, and phenomenological differences from the parental conditions. However, little is known about the neurobiology, genetics, and neurocognitive aspects of all the schizo-obsessive spectrum disorders, as well as the pharmacological treatment strategies. Efforts in search for possible specific endophenotypic markers would constitute a promising tool to better understand the schizo-obsessive spectrum substrate and, eventually, validate the existence of the putative schizo-obsessive disorder.

Disclosures

The authors do not have anything to disclose.

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