Review Paper
Examen critique

Comorbidity and pathophysiology of obsessive–compulsive disorder in schizophrenia: Is there evidence for a schizo-obsessive subtype of schizophrenia?

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Epidemiologic and neurobiologic evidence suggests that patients with comorbid obsessive–compulsive disorder (OCD) and schizophrenia may represent a special category among patients with schizophrenia. Efforts to examine the neurobiology of this group have focused on neuroimaging studies and neuropsychologic testing. Convergent evidence suggests that there may be a specific pattern of neurobiologic dysfunction in this subgroup of patients accounting for symptom co-expression. This review indicates that future studies should distinguish among (1) apparent obsessive–compulsive symptoms (OCS) that occur only in the context of psychosis and that may overlap with psychotic phenomenology, representing a forme fruste of psychosis; (2) OCS occurring only in the prodromal phase of schizophrenia; (3) neuroleptic-induced OCS or OCD; and (4) OCS or frank OCD occurring concurrently with schizophrenia. We examine the evidence for a putative schizo-obsessive disorder and outline suggestions for identifying OCS in the presence of psychosis.

Des données probantes épidémiologiques et neurobiologiques indiquent que les patients atteints à la fois d'un trouble obsessionnel compulsif (TOC) et de schizophrénie pourraient constituer une catégorie spéciale parmi les patients schizophrènes. Les efforts déployés pour examiner ce groupe sous une perspective neurobiologique se sont articulés avant tout autour d'études par neuro-imagerie et de tests neuropsychologiques. Des données probantes convergentes indiquent qu'il pourrait y avoir dans ce sous-groupe de patients un dysfonctionnement neurobiologique de tendance spécifique qui expliquerait la co-expression des symptômes. La présente étude indique que les études futures devraient faire une distinction entre : (1) les symptômes obsessionnels compulsifs (SOC) apparents qui surviennent uniquement dans le contexte de la psychose et qui pourraient chevaucher la phénoménologie psychotique, constituant une forme fruste de psychose; (2) les SOC se produisant uniquement au cours de la phase prodromique de la schizophrénie; (3) les SOC ou les TOC causés par des neuroleptiques; (4) les SOC ou les TOC francs se présentant en même temps que la schizophrénie. Nous examinons les données probantes à l'appui d'un trouble schizo-obsessif présumé et présentons des suggestions pour la détermination des

Introduction

Co-occurrence of obsessive–compulsive symptoms (OCS) and psychotic illness was first recognized over a century ago.[1] Interest in this area has been revived recently because of increased recognition of higher-than-expected comorbidity rates and observations of the emergence or exacerbation of OCS during treatment of psychosis with the atypical antipsychotics.[2–6] There is growing evidence that patients with comorbid obsessive–compulsive disorder (OCD) and schizophrenia (recently termed "schizo-obsessive"[7,8]) may represent a special category of the schizophrenia population. Contemporary investigators contend that there may be a specific pattern of neurobiologic dysfunction in this subgroup of patients that accounts for symptom co-expression.

A number of questions must be answered to determine if this putative schizo-obsessive subtype represents a true diagnostic entity: Do obsessions and delusions lie on a contin-

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uum, or are these symptoms categorically distinct? Can investigators and clinicians accurately distinguish an obsession with poor insight from a delusion? Does the observed overrepresentation of OCD in schizophrenia represent a nonrandom association (i.e., true epidemiologic comorbidity), or is this apparent relation merely a consequence of some confounding variable (i.e., artifactual comorbidity)? Do individuals who exhibit this symptom co-expression constitute a more severely ill patient population with a greater magnitude of brain involvement, or are there distinct neuroanatomic substrates unique to this subgroup? The answer to each of these questions remains nebulous to varying degrees. In this paper, we attempt to clarify current thinking and interpret existing research pertaining to these issues.

Historical perspectives

Reports of patients with both psychotic symptoms and OCS have been published since the 19th century.[1] Over the past century, there have been several systematic attempts to study the presence of OCS in schizophrenia. Studies initiated in the first half of the 20th century reported relatively low rates (1%–3.5%) of OCS in patients with schizophrenia.[9–11] Moreover, early investigators concluded that the presence of OCS might retard the "personality disintegration" associated with schizophrenia,[12] prevent the development of "malignant schizophrenia" or even herald remission of schizophrenic illness.[11] It was theorized by psychiatrists of that era that obsessions constitute a defence against psychosis and prevent the progression of schizophrenic illness. More recent studies have tended not to replicate these earlier findings, particularly in terms of long-term prognosis, probably because of the retrospective nature of the older studies and a lack of standardized diagnostic criteria for both schizophrenia and OCD during the era when those studies were performed.[13]

Distinguishing obsessions from delusions

A long-standing challenge facing investigators and clinicians is the difficulty in differentiating an obsession from a delusion when the 2 symptoms appear to be connected. Rosen[11] proposed that psychotic symptoms and delusions are related and that obsessions could be transformed into delusions. Indeed, the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV),[14] allows for the diagnosis of OCD with the specifier "with poor insight." This raises difficulty in differentiating an obsession with poor insight from a delusion, particularly given that OCD has traditionally been distinguished from psychotic disorders on the basis of the individual recognizing the compulsions or obsessions as foreign to him or her (i.e., ego-dystonic), implying the presence of insight. Further blurring this distinction are the notions of "obsessive psychosis"[15,16] and "delusional OCD."[17]

These phenomenologic delineations remain unclear, and the concept of OCD with poor insight as distinguished from delusional thinking is receiving revived attention in the psychiatric literature.[18–20] Kozac and Foa[18] have contended that "distinctions among obsessions, delusions, and overvalued ideas are not sufficiently clear to be of diagnostic utility." Indeed, there is no universally accepted technique for identifying OCS in patients with schizophrenia (see Box 1 for the authors' suggestions.) Despite these diagnostic challenges, contemporary investigators have taken various measures to apply clearer symptom definitions, standardized diagnostic criteria and stricter protocols than did the older studies. Such measures have included (1) the administration of standardized diagnostic scales, such as the Structured Clinical Interview for DSM-IV axis I psychiatric disorders[21] and the Yale-Brown Obsessive–Compulsive Scale,[22] to more systematically and objectively evaluate symptoms; (2) the stratification of patient populations according to phase of illness; (3) the use of age-matched control groups and cross-sectional study designs; and (4) the exclusion of patients whose obsessional content is related exclusively to psychotic subject matter. These measures would be expected to reduce diagnostic and recall bias, mitigate confounding variables and consequently enhance diagnostic accuracy.

Notwithstanding these efforts to increase diagnostic clarity, the distinction between obsessionality and psychotic ideation often remains hazy. Since it is possible that at least some of the OCS occurring in schizophrenia may overlap de-

Box 1: Suggestions for identifying OCS in the presence of psychosis

1. The types of obsessions and compulsions observed in schizophrenia are phenomenologically similar to those present in pure OCD, as described in DSM-IV.
2. A repetitious act should be considered a compulsion only if it occurs in response to an obsession and not if it occurs in response to psychotic ideation (e.g., repetitive checking in response to paranoid fears does not constitute a compulsion).
3. A recurrent, intrusive, ego-dystonic thought should not be considered an obsession if it revolves exclusively around current delusional themes (e.g., violent images, which constitute a common type of obsession in OCD, may represent an entirely different phenomenological entity in the context of psychosis). In the acute psychotic phase it may be necessary to exclude questionable "obsessions" and reassess for these after the psychotic symptoms have been treated.
4. OCS may be difficult to distinguish in the presence of thought form disorder; it may therefore be necessary to reassess for OCS once thought form has normalized.
5. Primary obsessional slowness may be mistaken for prodromal schizophrenia or thought disorder; such patients may be unable to articulate any obsessions and may exhibit no compulsions.
6. At times it may not be possible to determine if apparent OCS in the presence of psychosis represent real OCS; in such cases empiric treatment with a neuroleptic and a serotonin reuptake inhibitor (the standard treatment for OCD) may be necessary.

Note: DSM-IV = *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition;[14] OCD = obsessive–compulsive disorder; OCS = obsessive–compulsive symptoms.

scriptively with psychotic phenomenology, how do we know that OCS in schizophrenia are not merely a forme fruste of psychosis? Several lines of clinical evidence support the notion that OCS in schizophrenia often represent more than just an expression of enduring psychosis. This evidence includes observations that conventional antipsychotic medications appear to be of limited utility in the treatment of OCS in schizophrenia,[23] the persistence of OCS even after successful treatment of the psychotic symptoms[24] and the effectiveness of serotonin reuptake inhibitors in the treatment of OCS in patients with schizophrenia.[25–27]

Comorbidity between OCD and schizophrenia

Recent studies have revealed much higher comorbidity rates for OCD in the schizophrenia population than previously recognized. Over the past 3 decades investigators have reported prevalence rates of clinically significant OCS in the schizophrenia population of 10%–52%[28–33] and of OCD in the schizophrenia population of 7.8%–26%.[34–40] However, recent observations of the emergence of de novo OCD with atypical antipsychotic treatment of schizophrenia[2–6] raise the possibility that some of these comorbid OCD cases were medication-induced. To date, the study least confounded by neuroleptic exposure among subjects included only patients experiencing their first episode of schizophrenia with less than 12 weeks of lifetime exposure to neuroleptics.[36] The comorbidity rate was 14%, which is close to the median reported comorbidity figure of the aforementioned studies of full-threshold OCD in schizophrenia.

Another epidemiologic approach to examining the comorbidity of these 2 disorders involves observing patients who initially receive a diagnosis of OCD. Older studies, performed from the 1950s to the 1970s, consisted of chart reviews with inconsistent diagnostic criteria, so it is not surprising that their reported comorbidity rates varied greatly.[12,41–46] More recent studies using DSM-III[47] and DSM-IV[14] criteria have yielded more consistent results. In one study of 475 OCD probands, 14% had or developed psychosis, and 4% eventually met the full criteria for schizophrenia.[48] In another study, investigators found that of 135 patients with a first psychiatric admission and a diagnosis of OCD, 5% later received a diagnosis of schizophrenia.[49] In the Epidemiologic Catchment Area Study, 12.2% of patients with OCD also met criteria for schizophrenia.[50]

It is clear from comparisons of current comorbidity figures with individual lifetime prevalence rates for each disorder (2%–3% for OCD and 1% for schizophrenia) that there exists a greater-than-chance rate of co-occurrence. However, the underlying reasons for this apparently nonrandom association remain poorly understood. One possibility is that this is a spurious association due to Berkson's bias[51] — a type of ascertainment bias resulting from the fact that people with 2 disorders are more likely to seek treatment than those with only a single disorder. Spurious or artifactual comorbidity could also arise if the treatment for one disorder causes the other (as in the case of medication-induced OCD, as previously discussed), if there is descriptive overlap among the diagnostic criteria of the 2 disorders in question or if the 2 disorders are merely different phenotypic expressions of the same disease.[52] However, as discussed above, descriptive overlap alone is unlikely to account for the significant comorbidity observed between these 2 conditions, given the clinical evidence that the 2 disorders, even when occurring together, respond to different treatments. This clinical evidence also refutes the possibility that the 2 disorders are merely different phenotypic expressions of the same disease.

This observed comorbidity could also be a reflection of high co-occurrence of schizophrenia with other psychiatric disorders in general. In fact, schizophrenia is highly comorbid with many other psychiatric disorders or symptom clusters (e.g., depression, anxiety, panic attacks, substance abuse).[53] Nonetheless, it is still relevant to examine whether there are any particular features present in this schizophrenia-and-OCD overlap group to account for symptom co-expression. There are multiple potential explanations for why OCD and schizophrenia might be integrally related. An integral relation would exist if one disorder can present as a prodrome of the other, if one disorder causes the other or if both disorders are part of a more complex syndrome.

There is evidence to suggest that OCS may represent prodromal symptoms in childhood-onset schizophrenia.[54–56] Hence, in at least some alleged comorbid cases, the OCS may simply be transient. However, this situation probably accounts for only a minority of cases, since most patients with both schizophrenia and OCS are seen beyond the prodromal phase of schizophrenic illness. The possibility that one disorder may cause the other in this comorbid group seems unlikely, since there is no evidence of a clear temporal relation or a "dose–response" relation (whereby people with more severe forms of one disorder are more likely to have the other disorder). Moreover, there are no examples in psychiatry of one psychiatric illness causing another.

The question of whether the 2 disorders are part of a more complex syndrome possibly representing a distinct diagnostic entity remains unanswered and is the core focus of the present paper. The answer could be clarified in part if neurobiologic studies were to demonstrate a distinct difference in neurobiology in this overlap group rather than just the summation or superimposition of neurobiologic lesions observed in each disorder individually.

Neurobiology of the schizophrenia–OCD subgroup

Considerable work has been done to elucidate the neurobiologic basis of both schizophrenia and OCD. This research has focused primarily on understanding key neurotransmitter systems, structural and functional neuroanatomy, and neuropsychology. However, there is very limited published research attempting to identify neurobiologic features unique to this putative schizophrenia–OCD subtype.

There is no published research investigating unique neurotransmitter involvement in this overlap group. However, serotonin and dopamine have most consistently emerged as the principal neurotransmitters of interest in both disorders. In schizophrenia, the dopamine hypothesis has long been re-

garded as the fundamental neurochemical premise; this is most strongly supported by successful treatment of the disorder with dopamine receptor antagonists. However, the superior efficacy of the serotonin–dopamine receptor antagonists in the treatment of schizophrenia additionally supports the importance of the serotonergic system in the pathophysiology of this disorder and may reflect the modulation of dopaminergic systems by serotonin.[57] (For in-depth reviews of this topic, see Kapur and Remington[57] or Tibbo and Warneke.[58])

Conversely, in OCD a somewhat opposing picture has emerged with respect to neurotransmitter involvement. The serotonin hypothesis of OCD is supported by successful treatment of the disorder with serotonin reuptake inhibitors. Pharmacologic challenge studies with serotonin agonists and cerebrospinal fluid neurotransmitter metabolite studies have provided further evidence for the involvement of the serotonergic system in OCD.[59] However, these studies have not yielded consistent results, and not all studies support a singular role for serotonin in OCD.[59] Typically only 40%–60% of patients with OCD exhibit response to monotherapy with selective serotonin reuptake inhibitors, and the magnitude of response is often modest.[60] This observation suggests the involvement of other neurotransmitter systems in the pathophysiology of OCD, and evidence supporting the role of the dopaminergic system in this disorder[61] has led to a proposed dopamine–serotonin hypothesis of OCD.[59] Several lines of evidence implicate the dopaminergic system in the pathophysiology of OCD, including the role of dopamine in stereotypic behaviours in animal models,[61] the etiologic role of dopamine in Tourette's disorder (which is frequently comorbid with and shares neuroanatomic substrates with OCD),[62] preclinical evidence of dopamine's reciprocal modulatory effects on the serotonin system[57] and successful treatment of refractory OCD with dopamine receptor antagonists and serotonin–dopamine receptor antagonists.[63,64]

The latter observation (of the therapeutic utility of antipsychotic medications in OCD) is difficult to interpret, given numerous reports of the emergence of de novo OCD or exacerbation of pre-existing OCD in patients with schizophrenia who have been treated with atypical antipsychotics.[2–6] Such paradoxical findings are a testimony to the extreme complexity of the neurotransmitter systems involved in each disorder.

Neuroanatomy and neurocircuitry

Several investigators have hypothesized that similarities in the neurocircuitry and specific anatomic structures implicated in each disorder may account for symptom co-expression in a subgroup of patients.[58,65,66] The functional circuitry implicated in the pathophysiology of OCD is generally believed to involve a cortico-striatal-thalamic-cortical circuit.[67] Specific structures implicated in this pathway include the basal ganglia, orbitofrontal cortex and anterior cingulate cortex.[68] In schizophrenia, the dorsolateral prefrontal cortex circuit contains anatomic substrates similar to those of the OCD orbitofrontal circuit.[58] Thus, the specific neuroanatomic sites identified by structural and functional neuroimaging studies performed in each of these disorders independently show considerable overlap in implicated structures,[65] including the basal ganglia, thalamus, anterior cingulum, orbitofrontal cortex and regions of the temporal cortex, although some of these findings are controversial.[66]

In contrast to the plethora of neuroimaging studies investigating structural brain abnormalities in OCD and schizophrenia separately, there is a paucity of such studies specifically in the comorbid subgroup. Attempts to study the pathophysiology of this subgroup have focused on 2 main approaches: neuroimaging studies and neuropsychologic testing.

Neuroimaging studies

Neuroimaging studies suggest that there may be a specific pattern of neuroanatomic dysfunction in the comorbid subgroup. Aoyama et al[69] performed MRI in subjects with juvenile-onset schizophrenia and OCS and found significantly smaller left hippocampi in this group than in subjects who had schizophrenia without OCS and in control groups. These researchers also found an inverse correlation between illness duration and frontal lobe size in the group with both schizophrenia and OCS, but not in the group with schizophrenia only. In another MRI study of patients with juvenile-onset schizophrenia, investigators demonstrated significant enlargement of the anterior horn of the lateral ventricle and the third ventricle in patients with OCS relative to those without OCS.[70] In the only published study of functional MRI performed on patients with schizophrenia and various degrees of OCS, one subgroup exhibited a negative correlation between activation of the left dorsolateral prefrontal cortex and OCS severity.[71] Taken together, these findings suggest specific neuroanatomic abnormalities in the overlap group that differ from what is observed in each disorder individually.

Neuropsychologic testing

Numerous studies have compared the profiles of neurocognitive deficits in patients with schizophrenia only and in patients with both schizophrenia and OCD or OCS. Most, but not all, of these studies have revealed more severe neuropsychologic impairments in the patients with both conditions. Berman et al[24] found that patients with schizophrenia and OCS demonstrated delayed nonverbal memory and cognitive shifting abilities, and performed worse in the areas of visuospatial skills than their counterparts with schizophrenia only. On the other hand, a neuropsychologic study investigating orbitofrontal cortex function in OCD and schizophrenia with OCD showed no difference between the 2 groups in the performance of an alternation learning task; the investigators concluded that the functioning of the orbitofrontal cortex in OCD is unrelated to comorbid schizophrenia.[72] However, this result is consistent with the convergent evidence that schizophrenia involves primarily the dorsolateral prefrontal cortex,[73–78] whereas OCD implicates predominantly the orbitofrontal cortex.[77–84]

Several studies have reported greater impairment of executive function (a frontal lobe function), as measured by performance on the Wisconsin Card Sorting Test, in patients with

schizophrenia and OCS than in those with schizophrenia only.[85–87] A recent study comparing executive function in patients with both schizophrenia and OCD with that in patients with schizophrenia only or OCD only suggested that rather than having a unique pattern of neuropsychologic deficits, the group with both conditions was more impaired than the other 2 groups across several neuropsychologic domains.[88] The investigators concluded that this finding supports a "pathophysiological double jeopardy" in the overlap group.[88]

Conversely, Borkowska et al[89] recently compared the performance of matched patients with schizophrenia with or without OCS and patients who had OCD but not schizophrenia on selected frontal lobe tests and found that those with schizophrenia only were the most impaired and those with OCD the least impaired, whereas the patients with both conditions scored between these 2 groups. In an attempt to reconcile these differences in study results, Borkowska's group hypothesized that the effect of OCS in schizophrenia may depend upon the stage of schizophrenic illness, with OCS conferring greater impairment in chronic schizophrenia but possibly a protective effect early in schizophrenic illness. This hypothesis is supported by the Poyurovsky et al[36] study of OCD in first-episode schizophrenia, which found that the patients with schizophrenia and OCD had less severe symptoms of schizophrenia across several domains, although a subsequent study (performed by the same investigators) comparing patients with both schizophrenia and OCD matched for age and number of hospital admissions with a schizophrenia-only comparison group did not identify stage of illness as a predictor of symptom severity.[90]

Several investigators have examined the prevalence and severity of negative symptoms in schizophrenia comorbid with OCD and in schizophrenia alone, but these studies have yielded contradictory results. Some investigators have reported that the presence of OCS in schizophrenia is associated with higher levels of negative symptoms,[85–87] whereas others have found either an absence of such an association[24] or lower levels of negative symptoms in groups with both schizophrenia and OCS.[36,37] There have also been reports that compared with patients who have schizophrenia only, those with both schizophrenia and OCD have more motor symptoms including catatonia[40] and extrapyramidal symptoms.[37]

Conclusions

Despite the growing body of evidence supporting the existence of an epidemiologic and biologic relation between OCD and schizophrenia, the association remains poorly understood. Although the distinction between obsessions and delusions is often unclear, clinical evidence suggests that OCS in schizophrenia represent more than just an expression of enduring psychosis. The epidemiologic data strongly suggest a unique relation between these 2 disorders, given the marked degree of comorbidity that has been consistently and historically observed and that appears to represent more than just an artifactual or spurious association. Furthermore, the neurobiologic data on each disorder suggest the involvement of common brain regions and neurotransmitter systems, although there is very limited neurobiologic research focusing specifically on the putative schizophrenia-and-OCD subtype.

The paucity of neuroimaging data for the overlap group does not help in efforts to distinguish specific structural abnormalities unique to this putative subtype. Although neuropsychologic testing has not identified a unique pattern of impairment in this overlap group, it has generally revealed more severe impairment than among patients who have schizophrenia and not OCD (and patients who have OCD and not schizophrenia), which suggests a specific and active interaction between these 2 disease processes. The apparently contradictory nature of this interaction has led to the hypothesis that the effect of OCS in schizophrenia may depend upon the stage of schizophrenic illness.

On the basis of this review it appears key that future studies distinguish among apparent (1) OCS that occur only in the context of psychosis and that may overlap with psychotic phenomenology, representing a forme fruste of psychosis; (2) OCS that occur only in the prodromal phase of schizophrenia; (3) neuroleptic-induced OCS or OCD; and (4) OCS or frank OCD occurring concurrently with schizophrenia. Clearly, further neurobiologic research focusing specifically on this overlap group is essential and should clarify the nature of this putative entity in the years to come.

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