Review Article

Neuroanatomical, Neurochemical, and Neurodevelopmental Basis of Obsessive-Compulsive Symptoms in Schizophrenia

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ABSTRACT

The prevalence of the obsessive-compulsive symptoms in schizophrenia (OCSS) appears to be higher than that expected on the basis of comorbidity rates. Review of brain abnormalities in schizophrenia and obsessive-compulsive disorder (OCD) reveals involvement of similar regions namely the frontal lobe, the basal ganglia, the thalamus, and the cerebellum, in both the disorders. Neurodevelopmental etiopathogenesis has been proposed to explain schizophrenia as well as OCD. Significant overlap in neurotransmitter dysfunction (serotonin, glutamate, and dopamine) has been documented between schizophrenia and OCD. The New-onset obsessive-compulsive (OC) symptoms have been reported with the use of atypical antipsychotics in the schizophrenia patients In this background, OCSS is an emerging area of recent interests. This article attempts to review the literature on the neurobiology of OCSS. Neuroimaging, neuropsychological, and neuromotor abnormalities in OCSS discussed in the context of neurodevelopmental etiopathogenesis suggest glutamate abnormalities in OCSS. Atypical antipsychotic induced OCSS points towards the possible roles of glutamate and serotonin. Dopamine may be responsible for the beneficial role of antipsychotics in the treatment of OCD. In summary, we propose that glutamate, serotonin, and dopamine abnormalities may be the probable basis for OCSS.

Key words: *Schizophrenia, obsessive-compulsive symptoms, neurodevelopment*

INTRODUCTION

The prevalence of obsessive-compulsive symptoms in schizophrenia (OCSS) has been reported in the range of 8%–46%.[1,2] Considering the separate lifetime prevalence rates of the two illnesses [(1%–1.5% for schizophrenia[3] and 2%–3% for obsessive-compulsive disorder (OCD)[4]], it seems that obsessive-compulsive (OC) symptoms and schizophrenia coexist more often than chance.[5]

For the purpose of this review, we have divided the OCSS into two groups: a) de-novo obsessive-compulsive symptoms in schizophrenia (DOCSS), and b) drug induced obsessive-compulsive symptoms in schizophrenia (DIOCSS). In drug-naive schizophrenia, the onset of OC symptoms can either precede or be simultaneous with the onset of psychotic symptoms.[6] We propose to label this group of schizophrenia as DOCSS. Also, new-onset OC symptoms have been reported with atypical antipsychotics.[2,7] We propose to label this group of schizophrenia as DIOCSS.

This review is divided into three sections. The first section examines the relation between schizophrenia and OCD in the context of neuroanatomical, neurochemical and neurodevelopmental abnormalities; second one reviews the neurobiological findings in OCSS; and the third attempts to explain the OCSS by proposing a hypothetical neuroanatomical, neurochemical, and neurodevelopmental basis.

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SCHIZOPHRENIA AND OCD: NEUROANATOMY

Proposed neuroanatomical circuits in OCD

Studies have shown abnormalities in the frontal cortex,[8,9] the basal ganglia,[10,11] the thalamus,[12,13] and the cerebellum in patients with OCD.[14] A functional circuit for OCD involving the orbitofronto-striatal-thalamic pathway had been proposed.[15] Of the most successful surgical operations for OCD, limbic leukotomy combines bilateral cingulate lesions with lesions in the orbital medial frontal area, which contains fibres of the fronto-caudate-thalamic pathway.[16] The finding that OCD improves with ablation surgery of the orbitofrontal area or the midline thalamic nuclei supports this hypothesized OCD circuit.[15] Abnormalities of the thalamus demonstrated in patients with OCD also support the role of fronto-caudate-thalamic pathway in OCD.[13] Now, there is a substantial evidence from neuroimaging studies that, specific cortico-striatal-thalamic-cortical circuits mediate OCD.[8,17]

The OCD circuit arises in the orbital cortex and projects primarily on the ventromedial area of the caudate nucleus, then the globus pallidus, the ventro-anterior and the mediodorsal thalamus, and back to the cortex [18] The present functional theory of this OCD circuit depicts that increased excitatory output from the orbitofrontal/cingulate cortex, or increased caudate activity, causes inhibition of the dorsal thalamus, which can lead to increased activation of the cortex due to loss of inhibition.[10] These findings are supported by the neuroimaging studies, which show increased activity in the orbitofrontal cortex, the caudate, and the thalamus and normalization after treatment.[19]

The thalamus is an important component of this circuit and plays an important role in filtering or "gating" sensory and motor information and, thus, in behaviour modification. The multiple nuclei that constitute the thalamus have many diffuse projections to and from various regions of the cortex. Similar to the caudate, the dorsal nucleus of the thalamus projects to the orbitofrontal region and the mediodorsal nucleus projects to the prefrontal cortex, although significant overlap exists.[20,21]

In addition to the fronto-strital-thalamic circuit, recent studies also suggest that cerebellum is involved in the pathogenesis of OCD. Also, these studies provide evidences for role of the cerebellum in OCD.[14,22] The cerebellum has connections with the thalamus[23] and the basal ganglia,[24] and could play an important role in pathogenesis of OCD.

PROPOSED NEUROANATOMICAL CIRCUITS IN SCHIZOPHRENIA

Recent concepts regarding the mechanisms of schizophrenia postulate a disruption in distributed functional circuits rather than an abnormality in a single brain region such as, the prefrontal cortex.[25] In addition to the frontal cortex, brain abnormalities in schizophrenia have been demonstrated in the basal ganglia, the thalamus and the cerebellum.[25-29]

Andreasen *et al.*,[23] have hypothesized a prefrontal-thalamic-cerebellar-prefrontal pathway to explain the symptoms of schizophrenia. This approach highlights the importance of examining cortical-subcortical circuitry in schizophrenia and examining the role of thalamus and cerebellum in more detail.[23] It is argued that the thalamus filters out unnecessary information and forwards only relevant information and the deficit of this function may lead to positive symptoms in schizophrenia.[30] This theory of "input overload" in schizophrenia appears very similar to that proposed for OCD.[5]

NEUROANATOMICAL CIRCUITS IN SCHIZOPHRENIA AND OCD: CONCLUSIONS

In summary, abnormalities of the frontal lobe, the basal ganglia, the thalamus, and the cerebellum have been demonstrated in schizophrenia and OCD. Thus, review of neuroanatomical circuits in schizophrenia and OCD reveals more similarities than differences. In fact, recent studies indicate similar abnormalities in schizophrenia and OCD.[31,32] This similarity also emerges if one considers the gating or filtering of sensory information as playing a role in either illnesses.

The fact that similar anatomical structures and parallel cortical-subcortical pathways have been independently documented for both the illnesses, raises the possibility that a common functional aberration can lead to the coexpression of what appears to be completely different symptoms. This is not to say that all patients with schizophrenia and OCD share these aberrations, but it helps to explain the subgroup of patients who share these symptoms and the relative frequency of concurrent symptoms. In fact, it seems more plausible that these symptoms can often coexist than not.[5] In conclusion, we propose probable fronto-caudate-thalamic-cerebellar abnormalities in OCSS.

SCHIZOPHRENIA AND OCD: NEUROCHEMISTRY

Serotonin

In schizophrenia, serotonergic abnormalities in the

form of elevation in the levels of 5-HT_2 receptors have been demonstrated in the frontal cortex and LSD, a 5-HT_2 agonist, is a well-known psychotomimetic.[33] Serotonergic modulation of dopaminergic function provides a viable mechanism in schizophrenia.[34]

It is suggested that serotonergic abnormalities may play an important role in OCD and this is supported by the observed differential efficacy of serotonergic reuptake inhibitors in alleviating OC symptoms.[35] Drugs which lack serotonergic mechanism (for example, desipramine) are not effective in OCD. In addition, studies have suggested association between OCD and serotonin transporter polymorphism as well as serotonin receptor.[36,37] This evidence points towards role of serotonin in pathogenesis for OCD and schizophrenia.

Glutamate

Glutamate is increasingly implicated in pathophysiology of schizophrenia, and glutamate deficiency is one of the hypotheses, proposed to explain the pathophysiology of schizophrenia.[38] Glutamate receptor expression was upregulated in the frontal cortex after chronic exposure to clozapine, and to a lesser extent to olanzapine, but not with haloperidol.[39] The adaptive mechanisms taking place in glutamatergic transmission due to atypical antipsychotics might prove useful in ameliorating some of the dysfunction observed in the brain of schizophrenia.[39]

However, not all patients respond to selective serotonin reuptake inhibitors Selecive seretonergic uptake inhibitors, and that indicates the involvement of other neurotransmitters. Thus, the studies have examined various other neurotransmitters, dopamine and glutamate being the important. Reports from neuroimaging, genetic, and course structure file (CSF) studies support the involvement of glutamate in the pathogenesis of OCD.[40] Consistent use of neuroimaging studies using MRS has demonstrated increased glutamate in caudate and frontal cortex.[11,12] The glutamatergic genes involved in glutamate transmission (SLC1A1) implicated in association studies.[41] It is important to note that, till date none of the genes implicated in serotonergic or dopaminergic transmission have attained significant value in genetic studies such as glutamatergic genes. The CSF studies examining the glutamate levels has reported increased glutamate in patients compared to the normal controls.[42] Recent open-label study using the glutamate, antagonist Riluzole has shown efficacy of this agent in treatment of refractory OCD. [43] Overall, data from different studies support the hyperglutamatergic state in pathogenesis of OCD. This is in accord with proposed anatomical substrates as glutamate is the primary excitatory neurotransmitter in fronto-striato-thalamic circuit.

Dopamine

The dopaminergic hypothesis of schizophrenia postulates that an aberration of the brain's dopamine transmitter systems is key to the pathophysiology of schizophrenia.[25] In its current form, it assumess that overactivity in the neurotransmission from dopamine cell bodies, located in the ventral tegmental area of the midbrain, results in the development of psychotic symptoms. In addition, a hypodopaminergic state in the frontal cortical terminal fields of the mesocortical dopamine neurons has been hypothesized to be the basis of the 'negative symptoms' of schizophrenia.[44] Several lines of evidence from preclinical and clinical investigations implicate dopamine in the mediation of certain types of repetitive behavior.[45] Dopamine and serotonin abnormalities have been demonstrated in patients with OCD.[46] Recent trials of combined SSRI and typical and atypical antipsychotic treatment suggest that dopamine receptor antagonism may further reduce OC symptom severity in SSRI-refractory OCD patients, particularly for those with comorbid tic disorders.[47] It may be also that some forms of OCD are associated with dysregulated dopaminergic function. In summary, studies show abnormalities of serotonin, glutamate, and dopamine in schizophrenia as well as in OCD.

SCHIZOPHRENIA AND OCD: NEURODEVELOPMENTAL ABNORMALITIES

Schizophrenia and neurodevelopmental abnormalities

Several reasons have been advanced to support the view that schizophrenia is a neurodevelopmental disorder.[48] The primary reason is that the onset of schizophrenia has a cumulative age incidence distribution, or developmental function, that is nonlinear with a peak change in slope or acceleration that usually takes to occur during young adulthood. Given the plausibility of the existence of brain abnormalities in schizophrenia at the onset of the illness,[49] it further seems reasonable to conceive the onset of schizophrenia as a neurodevelopmental disorder.[50] Further support has been provided by epidemiological studies showing premorbid intellectual deficits dating back to early development[51,52] and neuropathological studies showing altered cerebral cytoarchitecture indicative of a developmental rather than an acquired encephalopathy.[53]

OCD AND NEURODEVELOPMENTAL ABNORMALITIES

Although OCD at times is episodic, with stress related exacerbations followed by partial remissions, there is a substantial group of patients whose illness follows a chronic deteriorating course. These patients are more likely to be men, with an early age of illness onset, and comparatively severe symptoms. This is consistent with the predominance of males among childhood onset OCD, and the lower age of first admission and poorer outcome in males who develop OCD as adults.[54] Children with OCD are also more likely to show neurological signs than adults, with 80% exhibiting tics, and one-third displaying choreiform movements.[55] Neurological soft signs such as involuntary movements, mirror movements, and disturbed fine motor coordination have been demonstrated in OCD.[56,57] OCD patients with high soft sign scores have significantly increased ventricular volumes compared to OCD patients with low soft sign scores and controled subjects.[58] These data suggest the existence of a subgroup of patients, characterized by male sex, early onset, severe symptoms, neurological signs, and a chronic course. Thus, this putative form of OCD, to a certain extent, resembles to neurodevelopmental disorders such as autism, dyslexia, and attention deficit disorder which has been termed as 'neurodevelopmental OCD'.[54]

NEUROBIOLOGY OF DOCSS: IS THERE A NEURODEVELOPMENTAL BASIS FOR DOCSS?

Neuroimaging findings in DOCSS

In a Magnetic Resonance Imaging (MRI) study performed on childhood- and adolescent-onset schizophrenia patients with OC symptoms, significant enlargement of the anterior horn of the lateral ventricle, and the third ventricle had been demonstrated.[59] The ventricle-brain ratios (VBR) in male patients with schizophrenia or schizotypal personality disorder (SPD) who had prodromal symptoms of OCD, were compared to male patients with nonpsychotic OCD and normal male comparison subjects using three-dimensional magnetic resonance imaging.[60] The VBR of the SPD group was significantly larger, compared to nonpsychotic OCD group or the comparison subjects. The patients with childhood- and adolescent-onset schizophrenia associated with OC symptoms had significantly smaller left hippocampus compared to schizophrenia patients without associated OC symptoms as well as healthy controls suggesting neurodevelopmental etiology in the former group.[61] Childhood- and adolescent-onset schizophrenia patients with prodromal OC symptoms were characterized by higher proportion of males, poor response of treatment with typical neuroleptics, a longer prodromal phase, and a predominance of negative symptoms.[59,61] Neurodevelopmental etiology has been proposed in schizophrenia with associated OC symptoms.[61]

Neuroimaging studies have demonstrated brain abnormalities in patients with schizophrenia and OCD. Neurodevelopmental abnormalities have been hypothesized to explain these brain abnormalities, especially in patients with early-onset psychiatric illness![62] Patients with DOCSS have had their first professional contact at a younger age compared to OCD patients.[63] In this context, the brain abnormalities in DOCSS suggest probable neurodevelopmental etiopathogenesis.

Neuropsychology of DOCSS

Berman *et al.*, compared the neuropsychological profile of schizophrenia patients with and without OC symptoms.[64] Compared to non-OC schizophrenia patients, those with OC symptoms performed worse on visual-spatial skills, delayed nonverbal memory, and cognitive shifting abilities. In addition, the severity of OC scores correlated with poor performance in these areas of cognition. Similarly, Lysaker *et al.,*[65] and Hwang *et al.*,[66] have demonstrated poorer executive function in schizophrenia patients with OC symptoms than those without OC symptoms. However, other studies have not replicated these findings.[67] In an explorative functional MRI study of schizophrenia patients with varying degrees of OCD symptomatology, Levine *et al.*,[68] have demonstrated negative relationship between OCD symptomatology and activation of the left dorsolateral prefrontal cortex, for a subgroup of patients.

Together these findings suggest that patients with DOCSS may have poorer executive function, thus indicating poorer frontal lobe functioning compared to patients with schizophrenia without OC symptoms. Frontal lobe dysfunction in schizophrenia could be secondary to neurodevelopmental etiopathogenesis. Hence, we hypothesize that the poorer frontal lobe functioning in patients with DOCSS may be secondary to neurodevelopmental etiology.

Neuromotor abnormalities in DOCSS

In a study by Kruger *et al*,[69] schizophrenia patients with OCD had more motor symptoms than non-OCD schizophrenic subjects. Tibbo *et al*,[70] have shown a trend in increased parkinsonian symptoms in schizophrenic patients with OCD than those without OCD. The high prevalence of motor symptoms in these subjects supports the hypothesis of a basal ganglia-frontal lobe connection linking OCD with schizophrenia.[70]

Basal ganglia dysfunction in schizophrenia has been hypothesized to be secondary to neurodevelopmental

abnormalities.[71] In addition, neurodevelopmental abnormalities have been hypothesized to explain neuromotor abnormalities in schizophrenia.[72] Fronto-striatal disorders have been explained by neurodevelopmental etiopathogenesis.[73] Hence, we hypothesize that the fronto-striatal dysfunction demonstrated in patients with DOCSS could be secondary to neurodevelopmental etiopathogenesis.

In summary, review of the neurobiological findings points toward significantly increased, brain abnormalities, frontal lobe dysfunction, and basal ganglia dysfunction (and thus fronto-striatal dysfunction) in DOCSS compared to schizophrenia patients without OC symptoms. Neurodevelopmental abnormalities have been proposed to explain brain abnormalities, frontal lobe, and basal ganglia dysfunction in schizophrenia (as reviewed above). In addition, fronto-striatal disorders have been explained by neurodevelopmental etiopathogenesis.[73] Given this context, we hypothesize that the significantly excessive brain abnormalities and fronto-striatal dysfunction in patients with DOCSS may be secondary to neurodevelopmental etiopathogenesis.

It is possible that these neurodevelopmental abnormalities demonstrated in the patients with DOCSS may simply be reflective of the same in schizophrenia. However, schizophrenia patients with OC symptoms have significantly more brain abnormalities than those without OC symptoms.[61] Also, frontal lobe and basal ganglia dysfunction (and thus fronto-striatal dysfunction) is more in schizophrenia patients with OC symptoms than in schizophrenia patients without OC symptoms.[65,66] Hence, we propose that DOCSS may indicate aberrant neurodevelopment.

NEURODEVELOPMENT, GLUTAMATE, AND DOCSS

Glutamatergic signaling is more than simply the critical step in excitatory neurotransmission. The spatial and temporal distribution of electrical activity is a key modulator of the constructive and destructive processes that determine neuronal form and sculpt the pattern of neural circuitry during ontogeny.[74] Glutamatergic receptors play an important role in regulating neuronal migration, neurite outgrowth, synaptogenesis, and the 'pruning' of supernumerary neurons by apoptosis.[75] Thus, glutamate plays a vital role in neurodevelopment.

The onset of DOCSS can precede the onset of psychotic symptoms or be simultaneous with onset of psychotic symptoms.[6] The paradox of DOCSS is that OCD is associated with hyperglutamatergic state,[76] whereas schizophrenia is associated with glutamate deficiency.[75,77] As we have reviewed above, neurodevelopmental abnormalities may underlie DOCSS. Since aberrant neurodevelopment is associated with glutamate dysfunction, the paradoxical coexistence (of OC symptoms and schizophrenia) could perhaps be due to unstable prefrontal glutamate systems fluctuating between hyperactivity, producing OC symptoms, and hypoactivity producing psychotic symptoms. Another possibility is that selected prefrontal glutamate neurons are hyperactive while others are hypoactive simultaneously. A third possibility is that prefronto-striatal glutamate neurons may be hyperactive initially producing OC symptoms and may become intermittently hypoactive due to exhaustion following periods of intense hyperactivity. The first and the second possibilities may explain the simultaneous onset of DOCSS along with psychotic symptoms. The third possibility may explain the onset of DOCSS preceding psychotic symptoms. This hypothesized model proposed to explain the paradox of DOCSS is somewhat similar to the one proposed by Carlsson,[76] to explain the paradoxical coexistence of OCD and attention-deficit hyperactivity disorder.

DIOCSS

It is still controversial whether antipsychotics ameliorate or exacerbate OC symptoms.[78] The antipsychotics are useful as augmenting agents in treatment refractory OCD,[47] but at the same time, new-onset OC symptoms have been reported with atypical antipsychotics.[2,7] For the purpose of this review, we propose to label this as DIOCSS. Many case reports involve the use of clozapine, risperidone, olanzapine,[2,7] quetiapine,[7] and clothiapine.[79] Larger trials have shown mixed results,[80] with more recently, a positive correlations with clozapine,[81] as well as a negative correlation with olanzapine.[82] Most of the cases of DIOCSS have involved schizophrenia patients on atypical antipsychotics[7] and most commonly on clozapine.

Serotonin and DIOCSS

The reports describing the beneficial effects of LSD, mescaline, psilocin, psilocybin, and peyote cactus in OCD, point to the beneficial role of 5-HT_{2A} activation in improving OC symptoms.[83] DIOCSS have mostly been reported with atypical antipsychotics.[7] Atypical antipsychotics have an antagonistic effect at the 5-HT_2 receptors.[84] Though, antipsychotic drugs such as pimozide, haloperidol, fluphenazine, loxapine, and thioridazine, have some antagonist activity at the 5-HT_{2A} receptors,[85] exacerbation or induction of OC symptoms has not been reported with these drugs.[86] Furthermore, selective 5-HT reuptake inhibitors such as fluoxetine, paroxetine, fluvoxamine and citalopram, also block the 5-HT_{2A} receptors but they improve OC

symptoms. 5-HT_{2c} receptors have been implicated in OCD.[87] Clozapine has the highest affinity for 5-HT_{2c} receptors among antipsychotic drugs.[88] In an *in vivo* electrophysiological study, Bergqvist *et al.*,[89] have demonstrated that the 5-HT_2 response in the orbitofrontal cortex is more akin to the 5-HT_{2c} subtype. They have suggested that 5-HT_{2c} may play a role in the induction of OC symptoms by atypical antipsychotics in psychotic patients.[89] Considering this, we hypothesize that 5-HT_{2c} receptor may play a role in DIOCSS.

Glutamate and DIOCSS

Tascedda *et al.*,[39] have shown that glutamate receptor expression was upregulated in the frontal cortex after chronic exposure to clozapine, and to a lesser extent to olanzapine, but not in case of haloperidol. DIOCSS have been reported mostly with atypical antipsychotics[7] and not with typical antipsychotics such as haloperidol.[86] As we have reviewed above, adaptive mechanisms taking place in glutamatergic transmission by atypical antipsychotics might prove useful in ameliorating some of the glutamate hypofunction observed in the brain of schizophrenia.[39] In the majority of DIOCSS, the appearance of OC symptoms coincides with the abatement of psychotic symptoms.[76] OCD is considered to be a hyperglutamatergic state involving prefrontal brain regions.[76] Modulation of glutamate may play a role in the amelioration of OC symptoms by Selecive seretonergic uptake inhibitors and clomipramine. Considering all these findings, we hypothesize that glutamate may also play a role in DIOCSS. Given the interaction between glutamate and serotonergic systems,[76] the putative role of glutamate becomes especially important in DIOCSS.

Dopamine and DIOCSS

Although, risperidone causes DIOCSS, it is observed beneficial in OCD patients in open-labelled trials[90] and controlled study.[91,92] The beneficial effect of risperidone was obtained with lower doses (1–4 mg/day), whereas higher doses have been associated with either exacerbation of OCD symptoms or DIOCSS.[2,89] As per the findings of Bergqvist *et al.*,[89] we hypothesize that the beneficial effect of low doses of risperidone may be due, in part, to the antagonism of dopamine receptors.

CONCLUSION

In this article, we have hypothesized a neurodevelopmental etiopathogenesis for DOCSS. Since glutamate plays a vital role in neurodevelopment, it is likely that glutamatergic abnormalities may underlie the DOCSS and glutamatergic and serotonergic abnormalities may explain the DIOCSS. Also dopaminergic antagonism can thoroughly explain the beneficial role of antipsychotics in the treatment of OCD. Hence, in summary, we propose that glutamate, serotonin, and dopamine abnormalities may underlie the pathogenesis of OCSS.

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