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.
SCHIZOPHRENIA AND OCD: NEUROANATOMY

Proposed neuroanatomical circuits in OCD

Studies have shown abnormalities in the frontal cortex, the basal ganglia, the thalamus, and the cerebellum in patients with OCD. A functional circuit for OCD involving the orbitofronto-striatal-thalamic pathway had been proposed. 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. The finding that OCD improves with ablation surgery of the orbitofrontal area or the midline thalamic nuclei supports this hypothesized OCD circuit. Abnormalities of the thalamus demonstrated in patients with OCD also support the role of fronto-caudate-thalamic pathway in OCD. Now, there is a substantial evidence from neuroimaging studies that, specific cortico-striatal-thalamic-cortical circuits mediate OCD.

The OCD circuit arises in the orbital cortex and projects primarily on the ventromedial area of the caudate nucleus, then the globus pallidus, the ventral anterior and the mediodorsal thalamus, and back to the cortex. 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. 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.

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.

In addition to the fronto-striatal-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. The cerebellum has connections with the thalamus and the basal ganglia 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. In addition to the frontal cortex, brain abnormalities in schizophrenia have been demonstrated in the basal ganglia, the thalamus and the cerebellum.

Andreasen et al. 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. 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. This theory of “input overload” in schizophrenia appears very similar to that proposed for OCD.

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. 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. 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.[99]

However, not all patients respond to selective serotonin reuptake inhibitors Selective serotonin reuptake 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 assumes 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 controlled 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?

Neuromotor abnormalities 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. In addition, neurodevelopmental abnormalities have been hypothesized to explain neuromotor abnormalities in schizophrenia. Fronto-striatal disorders have been explained by neurodevelopmental etiopathogenesis. 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. 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. 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. Hence, we propose that DOCSS may indicate aberrant neurodevelopment.

NEURODEVELOPMENT, GLUTAMATE, AND DOCSS

Glutamate 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. Glutamatergic receptors play an important role in regulating neuronal migration, neurite outgrowth, synaptogenesis, and the ‘pruning’ of supernumerary neurons by apoptosis. 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. The paradox of DOCSS is that OCD is associated with hyperglutamatergic state, whereas schizophrenia is associated with glutamate deficiency. 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, to explain the paradoxical coexistence of OCD and attention-deficit hyperactivity disorder.

DIOCSS

It is still controversial whether antipsychotics ameliorate or exacerbate OC symptoms. The antipsychotics are useful as augmenting agents in treatment refractory OCD but at the same time, new-onset OC symptoms have been reported with atypical antipsychotics. For the purpose of this review, we propose to label this as DIOCSS. Many case reports involve the use of clozapine, risperidone, olanzapine, quetiapine, and clothiapine. Larger trials have shown mixed results, with more recently, a positive correlation with clozapine, as well as a negative correlation with olanzapine. Most of the cases of DIOCSS have involved schizophrenia patients on atypical antipsychotics 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-HT2A activation in improving OC symptoms. DIOCSS have mostly been reported with atypical antipsychotics. Atypical antipsychotics have an antagonistic effect at the 5-HT2 receptors. Though, antipsychotic drugs such as pimozide, haloperidol, fluphenazine, loxapine, and thioridazine, have some antagonist activity at the 5-HT2 receptors, exacerbation or induction of OC symptoms has not been reported with these drugs. Furthermore, selective 5-HT reuptake inhibitors such as fluoxetine, paroxetine, fluvoxamine and citalopram, also block the 5-HT2 receptors but they improve OC
The beneficial effect of electrophysiological study, Bergqvist et al., have demonstrated that the 5-HT response in the orbitofrontal cortex is more akin to the 5-HT subtype. They have suggested that 5-HT may play a role in the induction of OC symptoms by atypical antipsychotics in psychotic patients. Considering this, we hypothesize that 5-HT receptor may play a role in DIOCSS.

Glutamate and DIOCSS
Tasceda et al., 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 and not with typical antipsychotics such as haloperidol. 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. In the majority of DIOCSS, the appearance of OC symptoms coincides with the abatement of psychotic symptoms. OCD is considered to be a hyperglutamatergic state involving prefrontal brain regions. Modulation of glutamate may play a role in the amelioration of OC symptoms by Selective serotonin 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, 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 and controlled study. 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. As per the findings of Bergqvist et al., 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 DIOCSS. Since glutamate plays a vital role in neurodevelopment, it is likely that glutamatergic abnormalities may underlie the DIOCSS 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.

REFERENCES
1. Eisen JL, Beer DA, Pato MT, Venditto TA, Rasmussen SA. Compulsive disorder in patients with schizophrenia or schizoaffective disorder. Am J Psychiatry 1997;154:271-3.
2. Poyurovsky M, Weizman A, Weizman R. Obsessive-compulsive disorder in schizophrenia: Clinical characteristics and treatment. CNS Drugs 2004;18:989-1010.
3. Bland RC, Newman SC, Orn H.: Lifetime co-morbidity in a community sample. Acta Psychiatr Scand 1987;75:383-91.
4. Karno M, Golding JM, Sorenson SB, Burnam MA. The epidemiology of obsessive-compulsive disorder in five US communities. Arch Gen Psychiatry 1988;45:1094-9.
5. Tibbo P, Warneke L. Obsessive-compulsive disorder in schizophrenia: Epidemiologic and biologic overlap. J Psychiatry Neurosci 1999;24:15-24.
6. Ganesan V, Kumar TC, Khanna S. Obsessive–compulsive disorder and psychosis. Can J Psychiatry 2001;46:750-4.
7. Khullar A, Chue P, Tibbo P. Quetiapine and obsessive-compulsive symptoms (OCS); Case report and review of atypical antipsychotic-induced OCS. J Psychiatry Neurosci 2001;26:55-9.
8. Saxena S, Rauch SL. Functional neuroimaging and the neuroanatomy of obsessive-compulsive disorder. Psychiatr Clin North Am 2000;23:563-86.
9. Khanna S. Obsessive-compulsive disorder: Is there a frontal lobe dysfunction? Biol Psychiatry 1988;24:602-13.
10. Baxter LR Jr, Schwartz JM, Bergman KS, Szuba MP, Guze BH, Mazziotta JC, et al. Caudate glucose metabolic rate changes with both drug and behavior therapy for obsessive-compulsive disorder. Arch Gen Psychiatry 1992;49:681-9.
11. Rosenberg DR, MacMaster FP, Keshavan MS, Fitzgerald KD, Stewart CM, Moore GJ. Decrease in caudate glutamatergic concentrations in pediatric obsessive-compulsive disorder patients taking paroxetine. J Am Acad Child Adolesc Psychiatry 2000;39:1096-103.
12. MacMaster FP, O’Neill J, Rosenberg DR. Brain imaging in pediatric obsessive-compulsive disorder. J Am Acad Child Adolesc Psychiatry 2008;47:1262-72.
13. Gilbert AR, Moore GJ, Keshavan MS, Paulson LA, Narula V, Mac Master FP, et al. Decrease in thalamic volumes of pediatric patients with obsessive-compulsive disorder who are taking paroxetine. Arch Gen Psychiatry 2000;57:449-56.
14. Kim JJ, Lee MC, Kim J, Kim IY, Kim SI, Han MH, et al. Grey matter abnormalities in obsessive-compulsive disorder: Statistical parametric mapping of segmented magnetic resonance images. Br J Psychiatry 2001;179:330-4.
15. Modell JG, Mountz JM, Curtis GC, Greden JF. Neurophysiologic dysfunction in basal ganglia/limbic striatal and thalamocortical circuits as a pathogenetic mechanism of obsessive-compulsive disorder. J Neuropsychiatry Clin Neurosci 1989;1:27-36.
16. Mindus P, Rasmussen SA, Lindquist C. Neurosurgical treatment for refractory obsessive-compulsive disorder: Implications for understanding frontal lobe function. J Neuropsychiatry Clin Neurosci 1994;6:467-77.
17. Stein DJ, Goodman WK, Rauch SL. The cognitive-affective neuroscience of obsessive-compulsive disorder. Curr Psychiatry Rep 2000;2:341-8.
18. Bonelli RM, Cummings JL. Frontal-subcortical circuitry and
behavior. Dialogues Clin Neurosci 2007;9:141-51.

19. Saxena S, Brody AL, Ho ML, Alborzian S, Maidment KM, Zohrabi N, et al. Differential cerebral metabolic changes with paroxetine treatment of obsessive-compulsive disorder vs major depression. Arch Gen Psychiatry 2002;59:250-61.

20. Alexander GE, Crutcher MD. Functional architecture of basal ganglia circuits: Neural substrates of parallel processing. Trends Neurosci 1990;13:266-71.

21. Alexander GE, DeLong MR, Strick PL. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu Rev Neurosci 1986;9:357-81.

22. Pujol J, Soroiano-Mas C, Alonso P, Cardoner N, Menchon JM, Deus J, et al. Mapping structural brain alterations in obsessive-compulsive disorder. Arch Gen Psychiatry 2004;61:720-30.

23. Andreasen NC, Paradiso S, O’Leary DS. Cognitive dysmetria as an integrative theory of schizophrenia: A dysfunction in cortical-subcortical-cerebellar circuitry? Schizophr Bull 1998;24:203-18.

24. Middleton FA, Strick PL. Basal ganglia and cerebellar loops: Motor and cognitive circuits. Brain Res Brain Res Rev 2000;31:236-50.

25. Keshavan MS, Tandon R, Boutros NN, Nasrallah HA. Schizophrenia, “just the facts”: what we know in 2008 Part 3: Neurobiology. Schizophr Res 2008;106:89-107.

26. Schultz SK, Andreasen NC. Schizophrenia. Lancet 1999;353:1425-30.

27. Konick LC, Friedman L. Meta-analysis of thalamic size in schizophrenia. Biol Psychiatry 2001;49:28-38.

28. Heckers S. Neuropathology of schizophrenia: Cortex, thalamus, basal ganglia, and neurotransmitter-specific projection systems. Schizophr Bull 1997;23:403-21.

29. Andreasen NC, Pierson R. The role of the cerebellum in schizophrenia. Biol Psychiatry 2008;64:81-8.

30. Andreasen NC. The role of the thalamus in schizophrenia. Can J Psychiatry 1997;42:27-33.

31. Kang DH, Kim SH, Kim CW, Choi JS, Jang JH, Jung MH, et al. Thalamic surface shape deformity in obsessive-compulsive disorder and schizophrenia. Neuroreport 2008;19:609-13.

32. Kwon JS, Shin YW, Kim CW, Kim YI, Yoon T, Han MH, et al. Similarity and disparity of obsessive-compulsive disorder and schizophrenia in MR volumetric abnormalities of the hippocampus-amygda] complex. J Neurol Neurosurg Psychiatry 2003;74:962-4.

33. Busatto GF, Kerwin RW. Perspectives on the role of serotonergic mechanisms in the pharmacology of schizophrenia. J Psychopharmacol 1997;11:3-12.

34. Agid O, Kapur S, Remington G. Emerging drugs for schizophrenia. Expert Opin Emerg Drugs 2008;13:479-95.

35. Murphy DL, Zohar J, Benkelfat C, Pato MT, Pigott TA, Insel TR. Peripheral markers of serotonin and dopamine function in obsessive-compulsive disorder. Psychiatri Res 1992;42:41-51.

36. Bloch MH, Landeros-Weisenberger A, Kelmendi B, Coric V, Bracken MB, Leckman JF A systematic review: Antipsychotic augmentation with treatment refractory obsessive-compulsive disorder. Mol Psychiatry 2006;11:622-32.

37. Rapeo JL, Addington AM, Frangou S, Psych MR. The neurodevelopmental model of schizophrenia: Update 2005. Mol Psychiatry 2005;10:434-49.

38. Venkatasubramanian G, Jayakumar PN, Gangadhar BN, Keshavan MS. Neuroanatomical correlates of neurological soft signs in antipsychotic-naive schizophrenia. Psychiatry Res 2008;164:215-22.

39. Keshavan MS, Anderson S, Petegrew JW. Is schizophrenia due to excessive synaptic pruning in the prefrontal cortex? The Feinberg hypothesis revisited. J Psychiatr Res 1994;28:239-65.

40. Jones EF, Rodgers B, Murray R, Marmot M. Child development risk factors for adult schizophrenia in the British 1946 birth cohort. Lancet 1994;344:1398-402.

41. Done DJ, Crow TJ, Johnstone EC, Sacker A. Childhood antecedents of schizophrenia and affective illness: Social adjustment at ages 7 and 11. BMJ 1994;309:699-703.

42. Akbarian S, Bunney WE Jr, Potkin SG, Wigal SB, Hagman JO, Sandman CA, et al. Altered distribution of nicotinamide-adenine dinucleotide phosphate-diaphorase cells in frontal lobe of schizophrenics implies disturbances of cortical development. Arch Gen Psychiatry 1993;50:169-77.

43. Geller D, Biederman J, Jones J, Park K, Schwartz S, Shapiro S, et al. Is juvenile obsessive-compulsive disorder a developmental subtype of the disorder? A review of the pediatric literature. J Am Acad Child Adolesc Psychiatry 1998;37:420-7.

44. Geller DA, Biederman J, Griffin S, Jones J, Lefkowitz TR. Comorbidity of juvenile obsessive-compulsive disorder with disruptive behavior disorders. J Am Acad Child Adolesc Psychiatry 1996;35:1637-46.

45. Sevincok L, Akoglu A, Topaloglu B, Aslantas H. Neurological soft signs in schizophrenic patients with obsessive-compulsive disorder. Psychiatry Clin Neurosci 2004;58:274-9.
Venkatasubramanian, et al.: Obsessive-compulsive symptoms in schizophrenia

57. Bolton D, Raven P, Madronal-Luque R, Marks IM. Neurological and neuropsychological signs in obsessive compulsive disorder: Interaction with behavioural treatment. Behav Res Ther 2000;38:695-708.

58. Stein DJ, Hollander E, Chan S, DeCaria CM, Hilal S, Liebowitz MR, et al. Computed tomography and neurological soft signs in obsessive-compulsive disorder. Psychiatry Res 1993;50:143-50.

59. Iida J, Iwasa H, Hirao F, Hashino K, Matsumura K, Tahara K, et al. Clinical features of childhood-onset schizophrenia with obsessive-compulsive symptoms during the prodromal phase. Psychiatry Clin Neurosci 1995;49:201-7.

60. Kurokawa K, Nakamura K, Sumiyoshi T, Hagino H, Yotsutsuji T, Yamashita I, et al. Ventricular enlargement in schizophrenia spectrum patients with prodromal symptoms of obsessive-compulsive disorder. Psychiatry Res 2000;99:83-91.

61. Aoyama F, Iida J, Inoue M, Iwasa H, Sakiyama S, Hata K, et al. Brain imaging in childhood- and adolescence-onset schizophrenia associated with obsessive-compulsive symptoms. Acta Psychiatr Scand 2000;102:32-7.

62. Keshavan MS, Diwadkar V, Rosenberg DR. Developmental biomarkers in schizophrenia and other psychiatric disorders: Common origins, different trajectories? Epidemiol Psychiatr Soc 2005;14:188-93.

63. Eisen JL, Rasmussen SA. Obsessive compulsive disorder with psychotic features. J Clin Psychiatry 1993;54:373-9.

64. Berman I, Kalinowski A, Berman SM, Lengua J, Grandin AI. Obsessive and compulsive symptoms in chronic schizophrenia. Compr Psychiatry 1996;36:6-10.

65. Lysaker PH, Marks KA, Ficone JB, Rollins AL, Fastenau PS, Bond GH. Obsessive and compulsive symptoms in schizophrenia: Clinical and neurocognitive correlates. J Nerv Ment Dis 2000;188:73-83.

66. Hwang MY, Morgan JE, Lesconczy MF. Clinical and neuropsychological profiles of obsessive-compulsive schizophrenia: A pilot study. J Neuropsychiatry Clin Neurosci 2000;12:91-4.

67. Ongur D, Goff DC. Obsessive-compulsive symptoms in schizophrenia: Associated clinical features, cognitive function and medication status. Schizophr Res 2005;75:349-62.

68. Levine JB, Gruber SA, Baird AA, Yurgelun-Todd D. Obsessive-compulsive disorder among schizophrenic patients: An exploratory study using functional magnetic resonance imaging data. Compr Psychiatry 1998;39:308-11.

69. Kruger S, Braunig P, Hoffler J, Shugar G, Borner I, Shugar S, et al. Obsessive-compulsive symptoms during treatment with clozapine. J Am Acad Child Adolesc Psychiatry 1995;34:1469-72.

70. Goff DC, Coyle JT. The emerging role of glutamate in the pathophysiology and treatment of schizophrenia. Am J Psychiatry 2001;158:1367-77.

71. Carlson ML. On the role of cortical glutamate in obsessive-compulsive disorder and attention-deficit hyperactivity disorder, two phenomenologically antibithetical conditions. Acta Psychiatr Scand 2000;102:401-13.

72. Tamminga CA, Frost DO. Changing concepts in the neurochemistry of schizophrenia. Am J Psychiatry 2001;158:1365-6.

73. Sareen J, Kirshner A, Lander M, Kjernisted KD, Eleff MK, Reiss JP. Do antipsychotics ameliorate or exacerbate Obsessive Compulsive Disorder symptoms? A systematic review. J Affect Disord 2004;82:167-74.

74. Toren P, Samuel E, Weizman R, Golomb A, Ender S, Laor N. Case study: Emergence of transient compulsive symptoms during treatment with clozapine. J Am Acad Child Adolesc Psychiatry 1995;36:267-70.

75. Haan L, Linsens DH, Gonsira R. Clozapine and obsessions in patients with recent-onset schizophrenia and other psychotic disorders. J Clin Psychiatry 1998;60:364-5.

76. Baker RW, Ames D, Umbricht DS, Chengappa KN, Schooler NR. Obsessive-compulsive symptoms in schizophrenia: A comparison of olanzapine and placebo. Psychopharmacology Bull 1996;32:89-93.

77. Moreno FA, Delgado PL. Hallucinogen-induced relief of obsessions and compulsions. J Am Acad Child Adolesc Psychiatry 1997;154:1037-8.

78. Kinon BJ, Lieberman JA. Mechanisms of action of atypical antipsychotic drugs: A critical analysis. Psychopharmacology (Berl) 1996;124:2-34.

79. Roth BL, Ciaramello RD, Meltzer HY. Binding of typical and atypical antipsychotic agents to transiently expressed 5-HT1A receptors. J Pharmacol Exp Ther 1992;260:1361-5.

80. Dursun SM, Revely MA. Obsessive-compulsive symptoms and clozapine. Br J Psychiatry 1994;165:267-8.

81. Aouizerate B, Guehl D, Cuny E, Rougier A, Burbaud P, Tignol J, et al. Updated overview of the putative role of the serotoninergic system in obsessive-compulsive disorder. Neuropsychiatr Dis Treat 2005;1:231-43.

82. Dursun SM, Revely MA. Clozapine in the management of schizophrenia. Clozapine has unique pharmacological profile. BMJ 1993;307:200.

83. Bergqvist PB, Dong J, Blier P. Effect of atypical antipsychotic drugs on 5-HT1A receptors in the rat orbito-frontal cortex: An in vivo electrophysiological study. Psychopharmacology (Berl) 1999;143:89-96.

84. Stein DJ, Bowers CH, Hawkr ridge S, Emsley RA. Risperidone augmentation of serotonin reuptake inhibitors in obsessive-compulsive and related disorders. J Clin Psychiatry 1997;58:119-22.

85. McDougle CJ, Epperson CN, Pelton GH, Waslynck S, Price LH. A double-blind, placebo-controlled study of risperidone addition in serotonin reuptake inhibitor-refractory obsessive-compulsive disorder. Arch Gen Psychiatry 2000;57:794-801.

86. Denys D. Pharmacotherapy of obsessive-compulsive disorder and obsessive-compulsive spectrum disorders. Psychiatr Clin North Am 2006;29:553-84.