Brain anatomy and chemistry may predict treatment response in paediatric obsessive–compulsive disorder

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Abstract

Obsessive–compulsive disorder (OCD) is a severe, highly prevalent and often chronically disabling illness with frequent onset in childhood and adolescence. This underscores the importance of studying the illness during childhood near the onset of illness to minimize potential confounds of long-term illness duration and treatment intervention as well as to examine the developmental underpinnings of the illness. In this review, the authors focus on an integrated series of brain-imaging studies in paediatric OCD suggesting a reversible glutamatergically mediated thalamo-cortical–striatal dysfunction in OCD and their relevance for improved diagnosis and treatment of the condition. Developmental neurobiological models for OCD are presented and particular attention is devoted to evaluating neuroimaging studies designed to test these models and how they may help predict treatment response in paediatric OCD.

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Introduction

Obsessive–compulsive disorder (OCD) is a severe and often chronically disabling illness that affects 1–3% of the world’s population (Rasmussen and Eisen, 1994) with at least 80% of all cases having their onset during childhood and adolescence (Pauls et al., 1995). We have argued that investigation of paediatric OCD patients near illness onset is critical to delineate the developmental neurobiological underpinnings of the disorder and minimize potentially confounding factors including long-term illness duration and treatment intervention effects (Rosenberg and Keshavan, 1998). Such an approach may also result in the development of new and improved assessment procedures and treatments for the illness. Despite the development of effective treatments for many patients suffering from OCD, at least one third of OCD patients prove refractory to standard treatment, i.e. selective serotonin reuptake inhibitors (SSRIs) and cognitive behavioural therapy (CBT), and many ‘responders’ exhibit only partial responses suffering significant residual functional impairment (Grados et al., 1999). Early-onset OCD patients may also be more likely to prove refractory to currently available treatments for the illness (Blanes and McGuire, 1997).

Although our understanding of the underlying developmental neurobiology of neuropsychiatric disorders such as OCD has lagged behind treatment development, advances in non-invasive, in-vivo brain-imaging techniques are contributing enormously to our understanding of the pathogenesis and maintenance of the illness. Therefore, treatment studies performed in conjunction with brain-imaging studies of brain anatomy, chemistry and function may identify new moderator (present at baseline) and mediator (changing with treatment) markers of illness which may have important implications for treatment development. Specifically, critical neuroanatomic, neurochemical and/or functional brain patterns may predict response to a particular treatment, i.e. SSRI or CBT (or lack, thereof) (Saxena et al., 1999). Rauch (2000) argues persuasively that these neuroimaging studies may facilitate the identification of the relevant developmental neurobiology associated with specific endophenotypes of OCD. In this paper we review a series of neuroimaging studies in treatment-naive paediatric patients with OCD and describe the changes we have observed when these patients are placed on medication.
Abnormalities in fronto-cortical–striatal–thalamic circuitry as a model for OCD

Neurobiological models for OCD have begun to consistently implicate ventral prefrontal cortical regions such as orbital prefrontal cortex and anterior cingulate cortex, the basal ganglia and thalamus in the pathophysiology of OCD (Baxter et al., 1996; Insel, 1992; Modell et al., 1989; Wise and Rapoport, 1989) (see Figure 1). This model suggests an inappropriate release of hard-wired behaviours due to abnormalities in this circuitry. Indirect support for this association is provided by observations of increased OCD behaviours in animals and humans with lesions to fronto-cortical–striatal–thalamic circuitry (Bergmann et al., 1974; Pitman et al., 1987; Sasaki et al., 1997; Swedo et al., 1989; Von Economo, 1931). Psycho-surgical lesions of the anterior cingulum and thalamus can reduce OCD symptoms in treatment-refractory OCD patients (Chiocca and Martuza, 1990; Jenike et al., 1991). More recently, neuroimaging studies in adult OCD patients have identified abnormalities in these brain regions associated with OCD symptom severity and treatment response (Baxter et al., 1992; Rauch et al., 1994; Swedo et al., 1992). Newer non-invasive and in-vivo neuroimaging techniques, particularly magnetic resonance imaging (MRI) provide an unprecedented opportunity to measure brain anatomy, chemistry and function longitudinally in paediatric patients before and after treatment intervention facilitating the generation of clinical neurodevelopmental models of illness relevant to treatment development. In the following section, we summarize a series of MRI studies that have resulted in the emergence of a new neurodevelopmental model of OCD.

Neuroanatomic abnormalities in paediatric OCD

**Striatum**

Rauch et al. (1998) have suggested that striatal abnormalities represent the primary site of pathology in OCD. Volumetric MRI and computerized tomography (CT) studies of the striatum in adult OCD patients have yielded inconsistent findings with four MRI studies showing no significant differences between OCD patients and controls (Aylward, et al., 1991, 1996; Bartha et al., 1998; Kellner et al., 1991) and two studies reporting abnormal caudate volumes in OCD patients (Robinson et al., 1995; Scarone et al., 1992). These conflicting findings

Figure 1. Brain regions implicated in the pathophysiology of obsessive–compulsive disorder.
Figure 2. Reduced striatal volume in obsessive–compulsive disorder (OCD) patients vs. controls. Lines indicate means. (Reprinted with permission from Rosenberg et al., 1997a.)

may reflect, in part, the different neuroimaging techniques used as well as OCD being a heterogenous condition. Potential confounds also included comorbidity, long-term illness duration and most patients in these studies having been treated with CNS-active medications (Chakos et al., 1994; Keshavan et al., 1994a).

In paediatric OCD increased ventricular brain ratios (VBRs) which would be predicted with decreased striatal volume were observed in adolescent OCD patients compared to controls (Behar et al., 1984). However, the authors did not report information on striatal volumes in this report. Using quantitative CT, Luxenberg et al. (1988) noted decreased caudate volumes in adolescent and young adult male OCD patients compared to healthy controls. More recently, we reported significantly reduced striatal volumes that were correlated with OCD symptom severity but not duration of illness, or age of onset of illness, in 19 psychotropic-naive, non-depressed paediatric OCD patients, 7- to 17-yr-old as compared to 19 age- and sex-matched healthy paediatric controls (Rosenberg et al., 1997a) (Figure 2). Paediatric OCD patients also had significantly larger third ventricular volumes than controls, consistent with their reduced striatal volumes. Intracranial volume did not differ significantly between OCD patients and controls. These results suggest that reduced striatal volumes in paediatric OCD patients may represent a central neurobiological deficit in paediatric OCD associated with the clinical presentation of the illness.

It should be noted, however, that Giedd et al. (1995, 2000) observed significantly larger basal ganglia volumes in paediatric patients with OCD and tic disorders characterized by symptom exacerbations following group A β-haemolytic streptococcal (GABHS) infections. This subtype of OCD and tic disorder has been designated as paediatric autoimmune neuropsychiatric disorders associated with streptococcal GABHS infections (PANDAS) (Allen et al., 1995; Swedo et al., 1998). Recently, Peterson et al. (2000) reported that chronic or recurrent GABHS infections were associated with enlarged basal ganglia volumes in OCD patients. These enlarged basal ganglia volumes were associated with increased antibody titres of anti-streptolysin O and anti-deoxyribonuclease B. Plasmapheresis has been reported to be effective in this putative autoimmune subtype of OCD (Allen et al., 1995) and symptom resolution with plasmapheresis may be associated with reduction in basal ganglia volumes (Giedd et al., 1996).

These paradoxical findings of reduced striatal volumes in non-PANDAS OCD and increased striatal volume in PANDAS-associated OCD suggest that perturbation of the existing neural network and resulting gradient of change from the normal state may be more critical to the development of OCD symptoms than the direction of change from baseline. Different genetic subtypes of OCD in children could also impact on neuroimaging findings. Alternatively, striatal abnormalities may be an epiphenomenon of the illness. Further study delineating the developmental underpinning of potentially discrete forms of OCD is clearly indicated.

Indeed, these MRI studies are somewhat analogous to electroencephalogram (EEG) studies in epilepsy which help characterize distinct epileptiform conditions and guide choice of treatment. While we are not yet at the point where brain imaging can characterize the diagnostic subtype of illness and inform optimal treatment intervention, such studies may ultimately delineate several different subtypes of OCD with discrete patterns of brain abnormality requiring different treatments for particular subtypes of illness (Rosenberg and Hanna, 2000).

Ventral prefrontal cortex

Morphometric MRI measurement of ventral prefrontal cortical (VPFC) regions has demonstrated abnormalities in the operculum (Jenike et al., 1996) and orbitofrontal cortex (Szeszko et al., 1999), associated with OCD symptom severity in adult OCD patients compared to healthy controls. Grachev et al. (1998) using a topographic parcellation technique (Caviness et al., 1996) reported an increase in 6 right frontal parcellation units and 4 left parcellation units in female adult OCD patients compared to female controls.

Rosenberg et al. (1997b) reported that the genu region of the corpus callosum was significantly larger in 21 treatment-naive, non-depressed OCD patients compared
Figure 3. Schematic drawing of the regional subdivisions of the corpus callosum (a) and of commissural pathways in the corpus callosum (b). (Reprinted with permission from Rosenberg et al. 1997b, and adapted with permission from Seltzer and Pandya, 1986, and Witelson, 1989.) 1, Genu; 2, anterior body; 3, posterior body; 4, isthmus; 5, splenium.

Figure 4. Anterior cingulate volume by group. (Adapted with permission from Rosenberg and Keshavan, 1998.)

To age- and sex-matched healthy controls. The corpus callosum connects the cerebral hemispheres and each region projects to specific brain regions (deLacoste et al., 1985; Seltzer and Pandya, 1986) (Figure 3). The genu connects right and left VPFC. Increased corpus callosal area was associated with OCD symptom severity but not duration of illness. An age-related increase in corpus callosal area was noted in healthy children but absent in OCD patients. This may, in part, explain reports of no significant difference in Corpus Callosal area between adult OCD patients and controls (Breiter et al., 1994; Jenike et al., 1996). Subsequent investigation by MacMaster et al. (1999) demonstrated increased corpus callosal signal intensity in the genu region. Increased genu area in paediatric OCD patients suggestive of increased VPFC size might be related to increased myelin sheath thickness. This is particularly intriguing given the purported association between corpus callosal and cognitive development coinciding with each other into young adulthood in healthy persons (Pujol et al., 1993). An alternative explanation is delayed or reduced neuronal apoptosis in the genu region of the corpus callosum in OCD patients. Since pruning of the corpus callosum occurs much earlier in development (Rakic, 1995), this explanation may be less likely. In contrast, increased myelinization continues during the typical age of onset of OCD (Yakovlev and Lecours, 1982).

In view of the aforementioned corpus callosal abnormalities suggesting prefrontal cortical abnormalities in paediatric OCD patients, Rosenberg and Keshavan (1998) measured localized prefrontal cortical volumes including...
ventral anterior cingulate cortex, posterior cingulate cortex and dorsolateral prefrontal cortex. They observed localized increased anterior cingulate volume in OCD patients compared to controls with no abnormalities in posterior cingulate or dorsolateral prefrontal cortex (Figure 4). Increased anterior cingulate volumes were positively correlated with increased OCD symptom severity but not illness duration nor age of onset of illness. A differential maturation in anterior cingulate volume was also observed between OCD patients and controls so that the normal age-related increase in anterior cingulate volume was not seen in OCD patients (Figure 5). Increased anterior cingulate volumes also correlated with reduced striatal volumes in paediatric OCD patients.

A possible explanation for finding correlations between both increased anterior cingulate volume and decreased striatal volume with increased OCD symptom severity without any correlation with duration of illness is an aberration in postnatal pruning of these structures in OCD. The increased anterior cingulate volume may represent a delay or reduction in pruning neural brain elements. Conversely, reduced striatal volume may be consistent with increased pruning. Differential regional brain maturational abnormalities in neurodevelopmental disorders has been discussed elsewhere (Keshavan 1997; Rosenberg and Keshavan, 1998). Reduced pruning in anterior cingulate cortex is also consistent with increased size of the genu of the corpus callosum that could result from reduced axonal pruning with consequent persistence of axons.

Although anterior cingulate abnormalities in early onset OCD coupled with the lack of association with illness duration suggest that this abnormality may have a neurodevelopmental basis in OCD, these arguments must be considered speculative. For example, the aforementioned studies were cross-sectional so that degenerative effects cannot be excluded. Longitudinal studies are clearly indicated to better examine neurodevelopmental and/or degenerative effects. Moreover, because these studies focused on early-onset, ‘first-break’ OCD, we cannot exclude the possibility that with longer-term illness duration, additional interference in normal brain developmental brain programming would occur with resultant larger differences in anatomy between OCD patients and controls. One might have expected a positive correlation between the VPFC and striatal volume given VPFC projections to the striatum (Fuster, 1989). Perhaps, in the normative state this is the case, whereas at certain points in development of OCD, this is not the case. In a study of adult OCD patients vs. controls, however, Szeszko et al. (1999) reported reduced orbital prefrontal cortical volumes in OCD patients. Thus, analysis of additional prefrontal cortical regions is necessary to better elucidate the relationship between these brain regions in OCD. These efforts are ongoing in our laboratory and will be published elsewhere.

**Thalamus**

The aforementioned findings of increased VPFC volumes correlated with reduced striatal volumes in paediatric OCD patients led us to examine the role of the thalamus in paediatric OCD. As the final subcortical input to frontal cortex, the thalamus stimulates cortical output when released from the inhibitory influence of the basal ganglia (Baxter et al., 1996). Using volumetric MRI, Jenike et al. (1996) had reported no significant differences between thalamic volumes in adult OCD patients vs. controls. However, the OCD patients studied in this sample had been treated with psychotropic medications including SSRIs and had long-term illness duration. Therefore, Gilbert et al. (2000) used volumetric MRI to compare 21 non-depressed, treatment-naive paediatric OCD patients to 21 age- and sex-matched healthy comparison subjects. Significantly increased thalamic volumes were observed in OCD patients, particularly in younger patients vs. controls (Figure 6). Thalamic volume in OCD patients decreased significantly after 12 wk of paroxetine monodrug therapy and post-paroxetine thalamic volumes did not differ significantly from those measured in healthy children. Higher pre-treatment thalamic volumes in paediatric OCD.
Figure 6. (a) Thalamic volume by diagnostic and treatment condition with groups not sharing the same letter are significantly different at \( p < 0.05 \) and (b) thalamic volume vs. age in paediatric obsessive–compulsive disorder patients and healthy comparison subjects. (Adapted with permission from Gilbert et al., 2000.)

Figure 7. Decrease in thalamic volume (–○–) associated with reduction in Obsessive–Compulsive score of the Children’s Yale–Brown Obsessive Compulsive Scales (●●●). (Reprinted with permission from Gilbert et al., 2000.)

patients predicted better response to paroxetine so that decrease in thalamic volume was associated with decrease in OCD symptom severity (Figure 7) as measured by the Children’s Yale–Brown Obsessive Compulsive Scale (CY-BOCS) (Scahill et al., 1997). Subsequent investigation revealed no significant change in thalamic volume in 11 treatment-naïve paediatric OCD patients before and after (CBT) (Rosenberg et al., 2000a). Ventral prefrontal, striatal and total brain volume did not change significantly with either SSRI or CBT, suggesting that localized abnormalities in the thalamus may serve as a primary site of anti-OCD drug effect (Gilbert et al., 2000).

Serotonin plays a crucial role in thalamocortical development and resultant activity (Bennett-Clarke et al., 1995). Reduction in thalamic volume may, therefore, be specific to paroxetine treatment as opposed to the non-specific drug effects on basal ganglia volume observed after treatment of schizophrenic patients with antipsychotic medication (Chakos et al., 1994; Keshavan et al., 1994a). Recent investigation to examine the role of the thalamus in OCD more closely with proton magnetic resonance spectroscopy (\(^{1}H\)-MRS) provided new evidence of localized medial but not lateral thalamic functional neurochemical marker abnormalities in paediatric OCD patients associated with increased thalamic volumes (Fitzgerald et al., 2000). This is an area of current active investigation in our laboratory.

It should also be noted that Giedd et al. (1995, 2000) reported no differences in thalamic volume between patients with the PANDAS subtype of OCD tic disorders and healthy children. This autoimmune subtype of illness may, however, have distinct neurobiological abnormalities with increased rather than decreased basal ganglia volumes. Moreover, many of the PANDAS patients studied by Giedd et al. (1995, 2000) had been treated with CNS-active medications including the SSRIs and also had longer-term illness duration than the treatment-naïve, first clinical presentation paediatric OCD patients we have reported on.
A new clinical neurodevelopmental model of OCD

At this juncture of our studies, in an effort to put together findings of reduced striatal volumes and increased ventral prefrontal and thalamic volumes in paediatric OCD, we hypothesized a 'neural network dysplasia of OCD (Rosenberg and Keshavan, 1998) involving an aberration in synaptic pruning that occurs during normal development (Keshavan et al., 1994b). Specifically developmental abnormalities in ventral–prefrontal–striatal circuitry might involve aberrations in postnatal pruning so that an exaggeration of pruning is seen in the striatum resulting in reduced volumes, while a delay in pruning occurs in VPFC and the thalamus leading to increased volumes in these regions.

Are there alterations in glutamatergic–serotonin interactions in ventral prefrontal–striatal–thalamic circuitry in paediatric OCD?

This question was suggested by a variety of reports in the literature which will be briefly reviewed here. The caudate nucleus, a primary site of metabolic abnormality in OCD (Baxter et al., 1992), receives a massive glutamatergic innervation from the VPFC (Becquet et al., 1990) with the majority of axon terminals in the striatum being comprised of glutamatergic afferents (Parent et al., 1995; Parent and Hazrati, 1995). In fact, a marked decrease in striatal glutamate concentrations is observed after ablation of the frontal cortex (Calabresi et al., 1996; Kim et al., 1977). Converging lines of evidence have also demonstrated in vivo evidence for glutamatergic control of presynaptic serotonin release in the caudate nucleus (Becquet et al., 1990; Reisine et al., 1982). The caudate nucleus receives a dense serotonergic innervation from cell bodies in the dorsal raphe nucleus (Greybiel and Ragsdale, 1983; Smith and Parent, 1986) so that serotonergic neurons also influence striatal glutamate (Edwards et al., 1996).

Using another MRI technique, proton magnetic resonance spectroscopy (1H-MRS) which allows for the non-invasive measurement of glutamatergic concentrations, Rosenberg et al. (2000b) reported significantly increased caudate glutamatergic concentrations in paediatric OCD patients compared to healthy children (Figures 8 and 9). A striking decrease in caudate glutamatergic concentrations

![Figure 8. Illustration of voxel placement in left caudate nucleus. 1H-MRS of a 0.7 ml volume of interest centred in the left caudate in a 10-yr-old healthy control and a 9-yr-old treatment-naive patient with obsessive–compulsive disorder as shown on the T1-weighted MR images. ml, myo-inositol; Cho, choline compounds; Cr, creatine/phosphocreatine; Glx, glutamate/glutamine/GABA; NA, N-acetylaspartate. (Adapted with permission from Rosenberg et al., 2000b and Rosenberg and Hanna, 2000.)](image)
Figure 9. Left caudate glutamatergic concentrations in treatment-naive paediatric obsessive–compulsive disorder patients and age- and sex-matched healthy comparison subjects. Glx, glutamate/glutamine/GABA. (Adapted with permission from Rosenberg et al., 2000b.)

Figure 10. Caudate glutamatergic concentration by diagnostic and treatment condition. Groups not sharing the same letter are significantly different at \( p < 0.05 \). (Adapted with permission from Rosenberg et al., 2000b.)

was observed in OCD patients after paroxetine monodrug therapy so that levels comparable to those observed in controls were achieved (Figure 10). Higher baseline caudate glutamatergic concentrations predicted better response to paroxetine in paediatric OCD patients. A positive correlation was observed between reduction in caudate glutamatergic concentrations and reduction in OCD symptom severity as measured by the CY-BOCS (Figure 11). No glutamatergic abnormalities were observed in occipital cortex in paediatric OCD patients nor did occipital glutamatergic concentrations change after treatment with paroxetine.

Reduction in caudate but not occipital glutamatergic concentrations in paediatric OCD patients treated with paroxetine suggests localized rather than global effects of SSRI treatment on glutamatergic concentrations. It should be noted that these pilot studies must be considered preliminary in view of the small sample sizes studied and require replication before definitive conclusions can be drawn. Nonetheless, localized changes in brain metabolism have been reported in adult OCD patients after SSRI treatment (Baxter et al., 1992). Gilbert et al. (2000) also reported a localized reduction in thalamic volume without change in total brain volume in paediatric patients treated for 12 wk with paroxetine. Findings of reductions in caudate but not occipital glutamatergic concentrations after 12 wk of paroxetine therapy may, in fact, be consistent with El Mansari et al.’s (1995) observation that sustained administration of SSRIs increased serotonin release in the VPFC, a region that sends dense efferent projections to the striatum and thalamus (Modell et al., 1989). Thus, additional study of other areas within the ventral prefrontal–striatal–thalamic circuit as well as other regions less implicated in the pathogenesis of OCD is necessary. This is currently an area of active investigation in our laboratory. Ongoing studies in our laboratory are focusing on measuring glutamatergic concentrations in other relevant brain regions including the VPFC and
thalamus as well as comparing the impact of CBT vs. pharmacotherapy on brain glutamatergic concentrations in paediatric OCD patients.

Conclusions and future directions

Taken together, the data suggest dysfunction in ventral prefrontal–striatal–thamic circuitry may be involved in the pathogenesis of childhood-onset OCD and may be mediated by abnormalities in glutamatergic-serotonergic neurotransmission. These abnormalities may be reversible with effective SSRI treatment. Sustained administration of SSRIs has been shown to markedly increase serotonin release in the VPFC (El Mansari et al., 1995) which sends dense efferent projections to the caudate nucleus and thalamus (Modell et al., 1989). GABAergic interneurons inhibit glutamatergic projections from ventral prefrontal cortex to the caudate nucleus and thalamus (Parent et al., 1995; Parent and Hazrati, 1995). Stimulatory 5-HT-2a receptors are located on these GABAergic interneurons. Since the majority of axon terminals in the caudate nucleus are glutamatergic, stimulating 5-HT-2a receptors would be expected to decrease glutamatergic efferents from the VPFC to the caudate nucleus with resultant decreased caudate glutamatergic concentrations.

Increased caudate glutamatergic concentrations in paediatric OCD patients that decreased after effective SSRI therapy are also consistent with prior functional neuroimaging studies in adult OCD patients demonstrating increased metabolic rates associated with OCD symptom severity that decreased after SSRI treatment (Baxter et al., 1992). Brain glucose metabolism is influenced by energy demands of glutamatergic afferent terminals (Baxter et al., 2000). Glutamatergic activity parallels brain glucose metabolism (Sibson et al., 1997). Serotonin agonists can also decrease brain glucose metabolism (Grome and Harper, 1986). El Mansari et al. (1995) found that SSRI administration increases serotonin release by desensitizing ventral prefrontal cortical seroton autorceptors suggesting that SSRI treatment alters serotonergic neurotransmission in the VPFC which, in turn, alters ventral prefrontal–striatal glutamatergic efferent projections with resultant changes in caudate glutamatergic concentrations (Rosenberg et al., 2000b).

These findings illustrate the promise of integrating treatment studies with neurobiological studies designed to elucidate markers of illness and treatment response. Hyman (2000) has emphasized the importance of translating neuroscientific advances into the development of better assessment procedures and treatments. An active area of investigation in our laboratory involves the study of medications which inhibit glutamate release. This is critical as at least one third of OCD patients prove refractory to currently available treatments (Grados et al., 1999; Hollander et al., 1992). Early-onset OCD is also more commonly associated with non-response to traditional treatment (Blanes and McGuire, 1997). Truly exciting times lay ahead in our efforts to translate advances in neuroimaging into treatment development.

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