

Brain Imaging in Pediatric Obsessive-Compulsive Disorder

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ABSTRACT

Objective: To review progress in understanding pediatric obsessive-compulsive disorder (OCD). The focus is on the frontal-striatal-thalamic model of OCD, neurobiological and genetic studies of the disorder, and their influence on recent advances in treatment. **Method:** Computerized literature searches were conducted with the key words "obsessive-compulsive disorder" in conjunction with "pediatric," "genetics," and "imaging." **Results:** Neuroimaging studies find evidence to support the frontal-striatal-thalamic model. Genetic and neurochemical studies also implicate glutamate in the pathological finding of OCD. This has led to the application of glutamate-modulating agents to treat OCD. **Conclusions:** Studies of pediatric OCD have led to a refined frontal-striatal-thalamic model of pathogenesis and are having an evidence-based impact on treatment. Despite this progress, fully explanatory models are still needed that would allow for accurate prognosis and the development of targeted and efficacious treatments. *J. Am. Acad. Child Adolesc. Psychiatry*, 2008; 47(11):1263–1273. **Key Words:** glutamate, gene, obsessive-compulsive disorder, pediatric, striatum.

Newer, noninvasive brain imaging approaches offer promise in enhancing understanding not only of brain development but also of the neurobiological underpinnings of childhood-onset neuropsychiatric disorders. These techniques permit unprecedented in vivo "biopsies" of brain structure, chemistry, and function. Here, we present a research aimed at generating a mechanistic understanding of the pathogenesis and treatment response of pediatric obsessive-compulsive disorder (OCD). With as many as 80% of all cases

beginning during childhood and adolescence,¹ pediatric studies are especially critical in advancing our understanding of the disorder. In this review, we discuss the neurobiology of pediatric OCD, recent genetic findings, and the novel application of glutamate-modulating agents for OCD. Special attention is focused on the glutamate hypothesis of OCD, first proffered by Rosenberg et al.²

NEUROBIOLOGY OF OCD

The cortical-striatal-thalamic circuit (Fig. 1) is most consistently implicated in OCD.³ In the following sections, we focus on neurobiological studies of this circuit in pediatric OCD (Table 1).

Frontal Cortex

Neurocognitive testing of frontal cortical functions is underexplored in pediatric OCD. Spatial-perceptual deficits similar to those of patients with a frontal lobe lesion were reported in adolescents with OCD⁴ but not replicated.^{5,6} Recently, deficits in visual attention and executive functioning were found in children with OCD.⁶ There is more evidence for prefrontal oculomotor abnormalities in pediatric OCD,^{4,7} including ability to suppress responses, volitional execution of delayed responses, and anticipation of predictable events. Patients with OCD had more response-suppression

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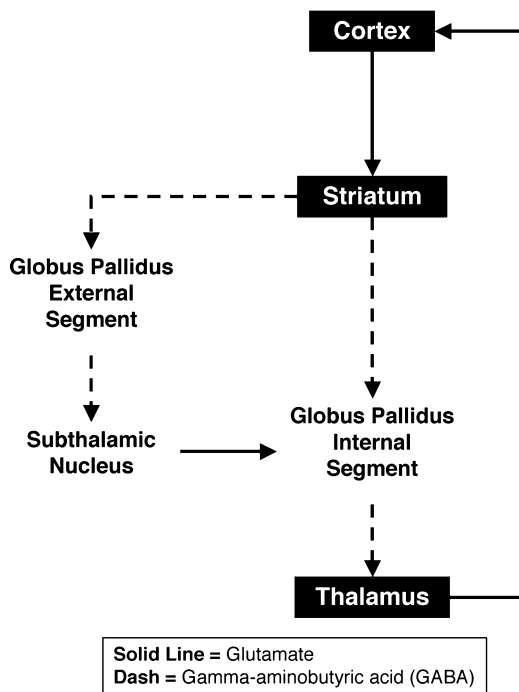


Fig. 1 Basic schematic of the frontal-striatal-thalamic circuit.

failures than controls.^{4,7} No significant differences between patients with OCD and controls were observed on other prefrontal cortical functions, such as the delayed-response task. Severity of OCD symptoms was related to response-suppression deficits.⁷ Woolley et al,⁸ using functional magnetic resonance imaging (MRI), found that during the “stop” task, patients with OCD showed reduced activation in the right orbitofrontal cortex, thalamus, and basal ganglia compared with controls. These disturbances of inhibition in OCD may underlie the repetitive behavior that characterizes the illness and indicate abnormalities in orbital prefrontal ventral striatal circuits.^{4,7} Indeed, pediatric patients with OCD had significantly greater gray matter density in the orbital frontal cortex than non-OCD patients,⁹ confirmed by manual region-of-interest measurements. Furthermore, among patients, gray matter density in the right lateral orbital frontal cortex correlated significantly with OCD symptom severity, but not with anxiety or depression.⁹ In a positron emission tomography study of adults with childhood-onset OCD, Swedo et al.¹⁰ noted greater glucose metabolism in the left orbital frontal, right sensorimotor, bilateral prefrontal, and anterior cingulate regions as compared with control patients. Glucose metabolism correlated with both state and trait measurements of OCD and anxiety in these patients. A recent

review¹¹ noted that dysfunction of the orbital frontal cortex alone is not sufficient to explain the neuronal basis of OCD and that, although the orbital frontal cortex is theoretically critical in OCD, data (functional and anatomical) from other brain regions will provide much needed context for our understanding of the disorder.

Gray matter volume of the anterior cingulate is greater in pediatric patients with OCD compared with age- and sex-matched controls.^{2,12} Anterior cingulate volume was positively correlated with age in controls but not in patients with OCD.² There was no difference between groups for anterior cingulate white matter.¹² In an independent sample, greater anterior cingulate gray matter volume was noted in patients than in controls using volumetric MRI, akin to previous findings,^{2,12} but not with voxel-based morphometry (VBM).⁹ Converse to those reports,^{2,9,12} a VBM analysis by Carmona et al.¹³ found significantly lower gray matter density in patients with OCD compared with non-OCD patients in the anterior cingulate bilaterally. This may indicate sensitivity issues with both techniques and fundamental differences in what is being measured.¹⁴ Single-voxel proton magnetic resonance spectroscopy (¹H-MRS) of the anterior cingulate found lower glutamatergic concentrations (glutamate/glutamine [Glx]) in patients with OCD than in non-OCD patients.¹⁵ Below-normal anterior cingulate Glx was also noted in adult females with OCD.¹⁶ The lower anterior cingulate glutamate correlated with symptom severity in these patients. Although no volumetric effects in dorsolateral prefrontal cortex (DLPFC) were noted,² proton magnetic resonance spectroscopic imaging did reveal above-normal concentration of the putative neuronal marker, *N*-acetyl-aspartate (NAA) in the left but not the right DLPFC in pediatric patients with OCD.¹⁷ Higher NAA in left DLPFC may indicate abnormal cortical pruning in OCD.

Subcortical

Striatum/Basal Ganglia. Patients with OCD had significantly smaller striatal volumes than age- and sex-matched non-OCD patients.¹⁸ In the patients with OCD, striatal volumes correlated inversely with symptom severity but not with illness duration.¹⁸ Consonant with that finding, in a sample of 43 patients with Tourette’s syndrome, Bloch et al³² found that caudate volume during childhood predicted early adulthood severity of tic and obsessive-compulsive symptoms. In

TABLE 1
Summary of Imaging Studies of Pediatric Obsessive-Compulsive Disorder

Study	Sample	Note	Findings
Rosenberg et al. ¹⁸	19 OCD, 19 non-OCD controls	Treatment-naïve, case-control matched	↓ Striatal and ↑ third ventricle volumes in OCD; no difference in prefrontal, lateral ventricle, or intracranial volumes; striatal volumes inversely correlated with symptom severity but not illness duration
Rosenberg et al. ¹⁹	21 OCD, 21 non-OCD controls	Treatment-naïve, case-control matched	↑ Corpus callosum area and all subregions (except isthmus) in OCD
MacMaster et al. ²⁰	21 OCD, 21 non-OCD controls	Treatment-naïve, case-control matched	↓ Genu signal intensity in patients with OCD; possibly indicating greater myelination of region
Rosenberg et al. ²	21 OCD, 21 non-OCD controls	Treatment-naïve, case-control matched	↑ Anterior cingulate cortex in patients with OCD; anterior cingulate volume correlated with obsessive symptoms in patients; no differences in posterior cingulate, amygdala, hippocampus, superior temporal gyrus, or whole temporal lobe
Rosenberg et al. ²¹	11 OCD, 11 post-SSRI, 11 non-OCD controls	Treatment-naïve, paroxetine (12 wk), case-control matched	↑ Caudate Glx concentrations in patients with OCD that declined after SSRI treatment; decrease in striatal Glx was associated with decrease in OCD symptom severity; occipital Glx did not differ
Benazon et al. ²²	21 OCD, 21 posttreatment	Treatment-naïve, CBT (12 wk)	No change in caudate Glx concentrations in patients with OCD after CBT, despite a decrease in symptoms
Gilbert et al. ²³	21 OCD, 10 post-SSRI, 21 non-OCD controls	Treatment-naïve, paroxetine (12 wk), case-control matched	↑ Thalamic volumes in patients with OCD that declined after SSRI treatment; decrease in thalamic volume was associated with decrease in OCD symptom severity
Rosenberg et al. ²⁴	11 OCD, 11 posttreatment	CBT (12 wk)	No significant change in thalamic volume was observed in OCD patients after CBT
Fitzgerald et al., ²⁵ Rosenberg et al. ²⁶	11 OCD, 11 non-OCD controls	Treatment-naïve, case-control matched	↓ Medial thalamic NAA/Cho and NAA/Cr in OCD; however, using a validated phantom method to achieve absolute measures, greater Cho ^{26,27} and Cr ²⁸ were found, calling into question the NAA ratio findings
Smith et al., ²⁷ Mirza et al. ²⁸	27 OCD, 18 MDD, 18 non-OCD/MDD controls	Treatment-naïve	↑ Bilateral medial thalamic Cho and Cr in OCD compared with both non-OCD and MDD; medial thalamic Cho and Cr concentrations did not differ between MDD and controls
Russell et al. ¹⁷	15 OCD, 15 non-OCD controls	Treatment-naïve, case-control matched	↑ NAA in left but not right DLPFC in patients with OCD; no significant differences in Cho or Cr were observed
Rosenberg et al. ¹⁵	20 OCD, 14 MDD, 14 non-OCD/MDD controls	Treatment-naïve	↓ Anterior cingulate Glx in both patients with OCD and patients with MDD compared with controls; Glx did not differ between patients with OCD and patients with MDD
Szeszko et al. ¹²	23 OCD, 27 non-OCD controls	Treatment-naïve	↓ Globus pallidus and ↑ gray matter in the anterior cingulate in OCD patients; no difference in caudate, putamen, superior frontal gyrus, or frontal white matter
Szeszko et al. ²⁹	11 OCD, 11 post-SSRI, 11 non-OCD controls, 11 controls time 2	Treatment-naïve, paroxetine (16 wk), no intervention	Patients demonstrated significant asymmetry of the amygdala (L > R) as compared with controls at baseline; ↓ left amygdala volume in patients with OCD after treatment; change in left amygdala correlated with higher paroxetine dosage at the time of the follow-up and total cumulative paroxetine exposure; no changes in amygdala volume were evident among non-OCD comparison subjects between scans
MacMaster et al. ³⁰	31 OCD, 31 non-OCD controls	Treatment-naïve, case-control matched	↓ Pituitary in OCD; effect more pronounced in males
Gilbert et al. ³¹	10 OCD, 10 siblings, 10 non-OCD controls	Treatment-naïve, unaffected	Using VBM, OCD showed greater gray matter density in the right putamen as compared with unaffected siblings

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TABLE 1

Continued

Study	Sample	Note	Findings
Szeszko et al. ⁹	37 OCD, 26 non-OCD controls	Treatment-naïve	Using VBM, OCD showed greater gray matter density in the putamen and orbital prefrontal cortex
Carmona et al. ¹³	18 OCD, 18 non-OCD controls	Matched by sex and handedness	Using VBM, OCD showed decreased bilateral gray matter in frontal and cingulate regions as well as decreased white matter in bilateral frontal and right parietal
Woolley et al. ⁸	10 OCD, 9 non-OCD controls	fMRI	During a "stop" task, OCD showed reduced activation in right orbitofrontal cortex, thalamus, and basal ganglia

OCD = obsessive-compulsive disorder; Glx = glutamate/glutamine; fMRI = functional magnetic resonance imaging; VBM = voxel-based morphometry; DLPFC = dorsolateral prefrontal cortex; SSRI = selective serotonin reuptake inhibitor; CBT = cognitive-behavioral therapy; Cho = choline; Cr = creatine; MDD = major depressive disorder.

a second sample, a smaller globus pallidus was noted in pediatric patients with OCD than in non-OCD volunteers.¹² Interestingly, VBM study showed above-normal gray matter density in the bilateral putamen in pediatric patients with OCD.⁹ It should be noted that VBM and manual tracing methods for evaluating brain volume have not been well validated against each other¹⁴ and may not reflect identical aspects of brain morphology. Above-normal striatal Glx concentrations, which normalized after successful treatment with a selective serotonin reuptake inhibitor (SSRI), were noted in pediatric OCD.^{21,33} This decrease in striatal Glx may persist after SSRI discontinuation.³⁴ Interestingly, cognitive-behavioral therapy (CBT) did not change caudate Glx concentrations in pediatric patients with OCD despite a reduction in symptoms.²² Finally, subcortical hyperintensities occur more frequently in children with OCD than in controls.³⁵

Thalamus. Thalamic volume is larger in pediatric patients with OCD than in age- and sex-matched controls.²³ After 12 weeks of treatment with paroxetine, thalamic volume normalized in patients with OCD concurrent with a reduction in OCD symptoms. This decrease in thalamic volume in OCD seems specific to medication because no changes in thalamic volume were noted with CBT.²⁴ Interestingly, below-normal ratios of bilateral medial thalamic NAA/creatine (Cr) and NAA/choline (Cho) were noted in OCD.²⁵ Lower ratios could mean lower NAA. That may be inconsistent with the aforementioned above-normal overall thalamic volume in OCD,²³ insofar as lower NAA could imply lower neuron mass and thus smaller thalamic volume. However, these results need not be associated with death or decreased size of neurons. A more advanced quantification technique, in fact, using validated

phantom-replacement methodology that allowed for absolute quantification indicated greater medial thalamic Cho^{26,27} and Cr²⁸ but not lower NAA^{26–28} in patients with OCD than in non-OCD patients. This discrepancy highlights the risk inherent in using metabolite ratios to describe MRS data. The finding of altered Cho in pediatric OCD is specific to the medial thalamus as no difference was noted in the lateral thalamus.²⁶ Patients with OCD differed not only from controls with regard to medial thalamic Cho and Cr, but also from pediatric patients with major depressive disorder (MDD).^{27,28}

Other Regions

Aside from the frontal-striatal-thalamic circuit, other brain regions have been implicated in pediatric OCD. In the corpus callosum, all subregions except for the isthmus were larger in patients with OCD than in controls.¹⁹ Callosal area correlated significantly with OCD symptom severity but not with illness duration. Second, the age-related increase in callosal size observed in normal subjects was not present in patients with OCD. Magnetic resonance imaging signal intensity, related to myelination in the corpus callosum, was lower in genu of the corpus callosum in patients with OCD than in non-OCD patients.²⁰ Lower signal intensity on T₁-weighted images may indicate greater myelination of the region of the corpus callosum, leading to increased volume, as noted in the earlier study.¹⁹ The genu connects ventral prefrontal cortex with striatum, regions noted above to be critical in pediatric OCD. Dysregulation of the limbic-hypothalamic-pituitary-adrenal axis has been reported in patients with OCD.^{36–39} The pituitary gland is significantly smaller in treatment-naïve pediatric patients with OCD than in non-OCD

patients, with a more prominent difference in males.³⁰ Interestingly, the smaller gland volume found in OCD contrasts with the enlarged pituitary seen in MDD^{40,41} and bipolar disorder.⁴² It is not known if SSRI treatment changes pituitary volume in OCD as it does in MDD⁴³ or as antipsychotic medications do in schizophrenia.⁴⁴

Subtypes and Pediatric Autoimmune Neuropsychiatric Disorders Associated With *Streptococcus*

Obsessive-compulsive disorder cannot be considered an etiologically homogeneous disorder. Indeed, childhood-onset OCD may be a phenomenologically and etiologically distinct subtype of OCD.⁴⁵ Family loading, presence of tics, sex distribution, and patterns of comorbidity may differ between adult and pediatric OCD.⁴⁵ To date, there has been little research on the neurobiology of the subtypes of pediatric OCD. The best-studied possible subtype of pediatric OCD using imaging, pediatric autoimmune neuropsychiatric disorders associated with *Streptococcus*, noted distinct differences from published reports of smaller basal ganglia structures in pediatric OCD.^{12,18} Enlarged basal ganglia volume was reported in a case study of a patient with a pediatric autoimmune neuropsychiatric disorder associated with *Streptococcus* that resolved with plasmapheresis.⁴⁶ In a larger study, Giedd et al⁴⁷ examined basal ganglia volumes in 34 children with presumed *Streptococcus*-associated OCD and/or tics and 82 control comparison children who were matched for age and sex. Larger caudate, putamen, and globus pallidus, but not thalamus or total cerebrum, were noted in the group of children with *Streptococcus*-associated OCD and/or tics as compared with the non-OCD patients. The authors hypothesized that the enlarged basal ganglia was a consequence of an autoimmune response to streptococcal infection.

GENETICS OF OBSESSIVE-COMPULSIVE DISORDER

Estimates of the heritability of obsessive-compulsive symptoms in children and adolescents range from 45% to 65%,⁴⁸ indicating a strong genetic component to the illness. To date, two glutamate-related genes (transporter and receptor) have shown promise in explaining the above-described neurobiology of the illness.

Glutamate Transporter Genes: SLC1A1

Three independent groups found that the 3' region of SCL1A1 may contain a susceptibility allele for OCD,

primarily in male offspring.⁴⁹⁻⁵¹ The protein product of this gene is the high-affinity neuronal and epithelial transporter (EAAT3, EAAC1) for L-glutamate, L- and D-aspartate, and cysteine.^{52,53} EAAT3/EAAC1 is present in the cortex, basal ganglia, and hippocampus and is detected in all parts of the neuron.⁵⁴ EAAT3/EAAC1 binds and transports cysteine more effectively than astrocyte glutamate transporters.⁵⁵ Furthermore, EAAT3 is localized to some GABAergic (γ -aminobutyric acid [GABA]) neurons, where it may play a role in regulating GABA synthesis.⁵⁶ In the adult brain, glutamate transport keeps extracellular glutamate below neurotoxic concentrations.⁵⁷ However, in adults, EAAT3/EAAC1 exhibits rather low expression and is thought to make a minor contribution to the removal of synaptic glutamate compared with EAAT1 and EAAT2.⁵⁸ It is expressed during early brain development, before astrocytes are functional. This suggests that EAAT3/EAAC1 is involved in the developmental role of glutamate and, possibly, GABA, which is also excitatory in certain brain regions during early brain development.⁵⁸ This role of EAAT3/EAAC1 in brain development is consistent with the linkage and association findings supporting SLC1A1 as a primary candidate gene in pediatric OCD⁴⁹⁻⁵¹ and in autistic spectrum disorders (Autism Genome Project Consortium, 2007). Expression of EAAT3/EAAC1 is regulated by testosterone and prolactin.⁵³ Increased expression of EAAT3/EAAC1 by testosterone is consistent with association of OCD, with SLC1A1 being strongest in males.^{49,50} Mice deficient in EAAC1 develop dicarboxylic aminoaciduria,⁵⁹ reduced neuronal glutathione, and, with aging, brain atrophy, increased aggressiveness, and impaired self-grooming.⁵² These results in EAAT3/EAAC1 knockouts suggest that pediatric OCD may be associated with increased rather than with decreased EAAT3 expression. Pharmacogenetically, increased SLC1A1 expression may be a compensatory response of the brain that tends to suppress OCD symptoms and that could be supported by glutamate receptor antagonists or EAAT3 agonists if these can be identified. Underexpression of SLC1A1, glutamate receptor agonists, and EAAT3 antagonists, in contrast, could aggravate OCD symptoms. Underexpression of SLC1A2 and SLC1A3 could produce OCD symptoms that would be aggravated by EAAT1 and EAAT2 antagonists, whereas enhanced expression of these genes or EAAT1 and EAAT2 agonism could have therapeutic effects. In

adult OCD, CBT has multiple effects on MRS metabolites,⁶⁰⁻⁶² including reduction of above-normal baseline glutamate levels in the anterior cingulate.⁶³ Although different physiological conditions may prevail in adult versus pediatric OCD, the relative expression of neuronal and astrocytic glutamate transporters may again be instrumental in the production of symptoms in OCD and their remediation with CBT.

Glutamate Receptor Genes: GRIN2B

The 5072T/G variant of GRIN2B is significantly associated with OCD in pediatric patients.⁶⁴ In addition, the 5072G-5988T haplotype was associated with OCD. The NMDA subunit 2B gene (GRIN2B [MIM 138252]) on chromosome 12p encodes for the NR2B subunit of the ionotropic glutamate receptor. GRIN2B is expressed in the striatum and the prefrontal cortex,⁶⁵ consistent with regions demonstrating glutamatergic abnormalities in pediatric patients with OCD.^{15,21} GRIN2B has also been linked to schizophrenia,⁶⁶ attention-deficit/hyperactivity disorder⁶⁷ and bipolar disorder.⁶⁸ GRIN2B is thought to play a role in plasticity during cortical development.⁶⁹ In addition, neurotoxic levels of glutamate during the neonatal period increase the expression of NMDA NR2B in the striatum and cortex.⁷⁰ The increased expression of GRIN2B in response to excess glutamate⁷¹ suggests that pediatric OCD is associated with increased GRIN2B expression in the striatum.

NOVEL PHARMACOTHERAPY FOR OCD

Selective serotonin reuptake inhibitors are the only Food and Drug Administration approved medications for OCD. However, SSRIs are typically effective only in 40% to 60% of patients, leaving a substantial number still ill.⁷² Indeed, because treatment response is defined by a 20% to 40% decrease in symptoms, many “responders” are still markedly symptomatic.⁷² Given the persistence of symptoms and levels of treatment response, it is clear that the serotonin paradigm of understanding OCD does not fully account for the neurobiology of the disorder.

As discussed in the previous sections, evidence of glutamate abnormalities in OCD is mounting.^{15,16,21,49,50,64,73-76} Indeed, all of the ¹H-MRS and CSF measures of glutamate concentration in OCD demonstrated large effect sizes (*d* > 1.00), indicating robust differences in regional glutamate concentrations in OCD patients as compared with controls (Fig. 2; note that this includes both pediatric and adult studies). This neurobiological evidence has led to the search for agents that modulate glutamate.⁷⁷ Indeed, the glutamate-modulating agent riluzole (1-amino-6-trifluoromethoxybenzothiazole) has shown promise in neuropsychiatric disorders.⁷⁸⁻⁸³ Riluzole is well tolerated and is Food and Drug Administration approved for treatment of amyotrophic lateral sclerosis.⁸⁴⁻⁸⁶ Riluzole is primarily an inhibitor of glutamate release but also inactivates

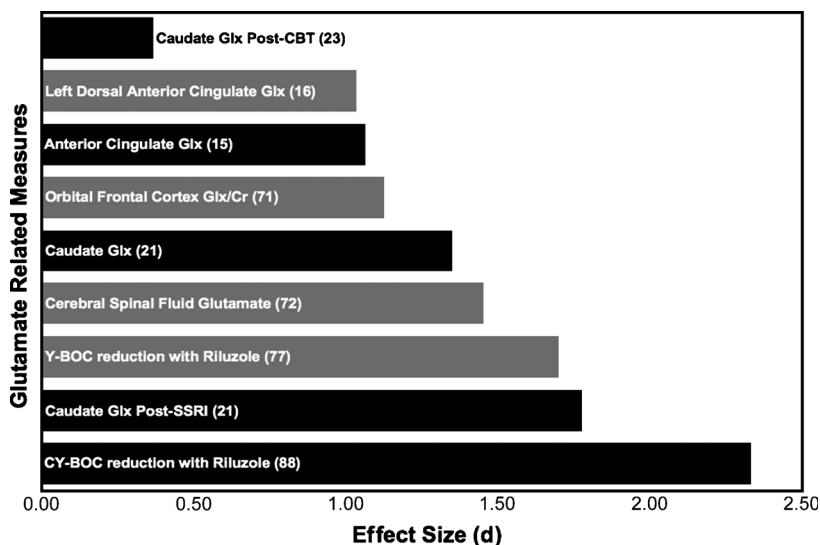


Fig. 2 Graph of the effect sizes (x-axis) for glutamate-related measures (y-axis) in obsessive-compulsive disorder. *Note:* This includes pediatric (black) and adult (gray) studies. Glx = glutamate/glutamine; CBT = cognitive-behavioral therapy; SSRI = selective serotonin reuptake inhibitor.

voltage-dependent sodium channels in cortical neurons and blocks GABA reuptake.⁸⁷⁻⁸⁹ In a case report⁷⁶ and an open-label trial in adults,⁷⁹ riluzole has shown promise for ameliorating the symptoms of OCD. More recently, an open-label trial in children (8-16 years) with OCD found riluzole to be beneficial and well tolerated.⁹⁰ A larger placebo-controlled trial at NIMH is under way.

DISCUSSION

Glutamate Hypothesis of Obsessive-Compulsive Disorder

In 1998, Rosenberg et al.² first hypothesized a role for glutamate in pediatric OCD. The first reports of in vivo differences in Glx between pediatric patients with OCD and non-OCD patients were published shortly thereafter.^{21,33} Since these initial articles in patients with OCD, a lower concentration of glutamate has been noted in the anterior cingulate,^{15,16} although greater Glx/Cr levels have been seen in orbital frontal white matter.⁷³ These neuroimaging articles found additional support in genetic studies that noted an increased susceptibility to OCD in those expressing alterations in the neuronal glutamate transporter gene^{49,50} and certain glutamate receptor genes.^{64,75} Furthermore, peripheral markers⁷⁴ and animal models⁷⁶ have provided additional support for glutamate dysfunction in OCD. Clinically, glutamate-modulating agents are showing promise for OCD.^{78,79,90} Hence, ¹H-MRS, CSF, genetic, animal and clinical studies have implicated glutamate in OCD.

Research Strategies for OCD

The traditional strategy of going from pharmacology to pathophysiology has failed to demonstrate substantive progress in our ability to understand psychiatric illnesses.⁹¹ It is becoming clear that investigators need to combine strategies (genetic, neuroimaging, pharmacological, animal models, etc.) to allow for the most advancement.^{91,92} Research into diabetes, heart disease, and oncology is focused on cure and prevention. In psychiatry, the bar is typically set lower, with an eye only on incremental advances.⁹¹ A road map of how to achieve these advances is coming into focus only now. The progress described in pediatric OCD in this review is a rare occurrence in psychiatry, an example in which neurobiological studies of a disorder have di-

rectly informed its treatment. Indeed, if what is known regarding diabetes is compared with what we are starting to see in pediatric OCD, it can be seen how the disorder is coming into greater focus using multiple methods (Table 2). Brain imaging has demonstrated great potential for aiding in the diagnosis, treatment, prevention, and cure of neuropsychiatric disorders.⁹³ When coupled with advances in assessment, genetics, pharmacology, and animal models, the potential to have meaningful clinical impact becomes profound.

Issues That Need Further Study

Separation of Glutamate-Glutamine. To date, ¹H-MRS studies of OCD have reported the combined Glx measure (glutamate and glutamine).^{15,16,21,33,73} Given

TABLE 2
Model of Obsessive Compulsive Disorder as Compared to Diabetes^{91,92}

Item	Diabetes	Obsessive-Compulsive Disorder
Trigger	Genetics—IDDM1 to IDDM18 (type I) ⁹⁴ and CAPN10 ⁹⁵ and HNF4A ⁹⁶ (type II) environment—viruses, early diet, obesity	Genetics—evidence for GRIN2B ⁶⁴ and SLC1A1, ⁴⁹⁻⁵¹ more may follow; environment—stress, unknown
Primary pathological findings	Attack on the β cells in pancreas	Changes in glutamate function/activity in the cortical-striatal-thalamic-cortical loop ²
Physiological expression	Less insulin Changes in blood sugar Sugar ketones in urine	\uparrow Striatal ²¹ and orbital frontal glutamate ⁷³ \downarrow Anterior cingulate glutamate ¹⁵
Behavioral ramifications	Increased thirst, urination Hunger Weight changes Fatigue Blurred vision	Core DSM criteria ⁹⁷ Recurrent/persistent thoughts, impulses, or images Intrusive and inappropriate causing anxiety/stress Repetitive behaviors, driven to perform by obsession

CAPN10 = calpain 10; GRIN2B = *N*-methyl-D-aspartate receptor 2B; HNF4A = hepatocyte nuclear factor 4 α ; IDDM1 = insulin-dependent diabetes mellitus 1; IDDM18 = insulin-dependent diabetes mellitus 18; SLC1A1 = solute carrier family 1 (neuronal/epithelial high-affinity glutamate transporter), member 1.

tamine, techniques that allow for the separation of the two similar resonances need to be applied in OCD. Techniques include improved spectral editing^{98–100} or the use of higher field MRI scanners.¹⁰¹

Relation of Glutamate Concentration and Activity of Glutamate-Related Genes. The combination of genetics and imaging methods offers tremendous potential for advancing our understanding of psychiatric illnesses.¹⁰² First-order studies combining genetic and imaging findings in pediatric OCD are needed. The initial studies linking genetic markers with neuroimaging findings in pediatric OCD are currently under way by our group. Second-order studies are also needed to look at what cellular mechanisms linked to gene polymorphisms may be responsible for the changes noted in the imaging studies.

Additional studies of glutamate-related genes are required. The two candidate genes (SLC1A1 and GRIN2B) mentioned in this review represent only the start of tying genetic studies into glutamate-related findings with pediatric OCD because there are many glutamate-related genes that have not yet been explored. Indeed, there are at least 25 genes for glutamate receptors and 5 genes for neuronal and glial glutamate transporters.¹⁰³ We are unaware of investigations of potential associations between OCD and expression of the SLC1A2 gene (encoding for EAAT2 at 11p13-p12) or the SLC1A3 gene (encoding for EAAT1 at 5p13), although unpublished negative findings may exist. These two astrocyte glutamate transporters may influence the pathophysiology of OCD and its pharmacological regulation by regulating regional glutamate levels. Glutamate enters astrocytes through these transporters⁵⁸ and is rapidly converted to nontoxic glutamine,¹⁰⁴ which then is exported to neurons (through monocarboxylate transporters^{105,106}) for reconversion to glutamate.¹⁰⁷ Enhanced expression of SLC1A2 and SLC1A3 would therefore increase the local residence time of glutamate and glutamine through this neuron-astrocyte cycling, resulting in higher Glx, as observed in the caudate in pediatric OCD.^{21,33} Underexpression of SLC1A2 and SLC1A3, in contrast, would result in diversion of incoming synaptic glutamate to neurons, causing faster neuron firing, greater remote synaptic export of glutamate, and/or consumption in the Krebs cycle¹⁰⁸ to sustain the higher metabolic rate and lower overall levels of tissue Glx, as observed in the anterior cingulate in pediatric OCD.¹⁵ Increased expression of SLC1A1 and

the glutamate receptor gene GRIN2B (see above) may therefore be secondary responses, that is, the generation of more EAAT3 transporters and glutamate receptors to handle higher extracellular glutamate concentrations, to a primary astrocyte defect in OCD. SLC1A1 accounts for 59% of cases of OCD.⁴⁹ It may be possible to account for additional OCD cases by considering the combinations of relative expression of SLC1A1, SLC1A2, and SLC1A3 that lead to suboptimal synaptic glutamate distribution between astrocytes and neurons.

There are limitations to the published work on the neurobiology of pediatric OCD. Most studies have small samples. More attention and research are needed regarding the neurobiology of possible subtypes of OCD. Many of the studies come from one group. Hence, there is a pressing need to involve more investigators, including new investigators, in this research. As with much research in psychiatry, replication studies are warranted. That said, the evidence supporting glutamate dysfunction in OCD is derived from a number of angles (imaging, genetics, CSF, animal studies). Studies that combine methods (i.e., linking MRS measures glutamate directly with genetic findings) are also required. However, the articles discussed here have provided evidence needed to guide larger, more robust studies.

Given that the clinical phenomenology and nosology of OCD are, for the most part, well worked out, applying techniques developed in the emerging field of imaging genetics can further explicate the underlying developmental neurobiology of pediatric OCD. Studies using advanced spectroscopy techniques (i.e., special editing, multivoxel, functional MRS), larger samples (including multisite), and developmental and longitudinal designs (to track course and outcome) are needed. Most critically, studies that combine methodology (imaging, genetic, neuropsychology) will push the field forward. Such studies may provide additional support for the glutamate hypothesis of OCD. The combined study of biological, genetic, and behavioral/symptom variables also responds to the call for translational approaches to mental illness made by the National Institute of Mental Health. Such approaches may lead to better understanding of pediatric OCD and, in turn, to new diagnostic and treatment approaches.

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