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Glutamate and the Treatment of Obsessive-Compulsive Disorder

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LEARNING OBJECTIVES

After participating in this activity, the clinician should be better able to:

- To interpret new developments in our understanding of obsessive-compulsive disorder.
- To predict the translational impact of these developments on the application of novel treatments for obsessive-compulsive disorder.
- To plan for the role of glutamate in the pathophysiology and treatment of patients with obsessive-compulsive disorder.

Obsessive-compulsive disorder (OCD) is a major public health problem. Patients suffering from OCD have distressing obsessions and compulsions that impair their daily functioning. This severe and chronically debilitating disorder affects more than 3 million people in the United States. Estimates of the lifetime prevalence of OCD in pediatric and adult populations range from 1% to 3%.¹ According to the World Health Organization, OCD is among the 10 most disabling medical conditions worldwide. Among anxiety disorders, the National Comorbidity Survey Replication states that OCD has the highest percentage (50.6%) of serious cases.¹

The clinical phenomenology and nosology of pediatric OCD are well described. This makes OCD a leading candidate for innovative developmental neurobiological study. In contrast to major depression and bipolar disorder, the clinical presentation in childhood and adulthood is similar, making findings more applicable across the age span. The two reasons to focus our study and attention on pediatric OCD are:

- OCD commonly has its onset during critical stages of brain maturation; and
- Pediatric OCD is continuous with adult OCD.²

The mean age of onset for pediatric OCD is between 9 to 11 years in males and 11 to 13 years in females.³ An early age of onset in OCD is associated with a more negative outcome. Furthermore, there is a genetic component to the illness, with heritability estimates of obsessive-compulsive symptoms in children and adolescents ranging from 45% to 65%.⁴ Pediatric OCD is chronic and unremitting in up to 87% of patients who fail to receive effective treatment.⁵ Finally, children with OCD are at higher risk for other psychiatric disorders in adulthood.

The two major obstacles for people suffering from OCD are (1) getting a proper diagnosis and (2) access to effective treatment.⁶ The only FDA-approved medications for OCD are the selective serotonin reuptake inhibitors (SSRIs). While considered effective in the clinical trial literature, treatment of OCD with SSRI's is less effective in practice. Thus SSRIs are only effective in 40 to 60% of patients, leaving a considerable number still ill.⁷ Furthermore, studies often define treatment response as a 20 to 40% reduction in symptoms; and many patients classified as “responders” remain significantly symptomatic after treatment.⁷ OCD symptom severity scores, as measured by the Children's Yale-Brown Obsessive-Compulsive Scale (CYBOCS), typically range from 15 to 20 post-treatment. Such a score is indicative of significant impairment. In addition to medication, cognitive behavioral therapy (CBT) is also effective for treating OCD.⁸ Even when CBT and medication are combined, however, one-third of pediatric patients still remain markedly ill.⁸ Moreover, earlier onset of OCD may be associated with greater treatment refractoriness.⁸ Finally, OCD is one of the few psychiatric disorders for which there is a neurosurgical indication. The persistence of symptoms and limited levels of treatment response to medication indicate that the serotonin paradigm does not fully account for the neurobiology of the illness. Thus, novel evidence-based approaches are needed to advance treatment of OCD.

BASIC MODEL OF OBSESSIVE-COMPULSIVE DISORDER

In the basic neurobiological model of OCD, the *cortical-striatal-thalamic circuit* is consistently implicated (Figure 1). In the striatum, 80% of all synapses are cortical inputs. Cortical regions that project to the striatum are divided into ‘motor’ and ‘limbic associative’ projections. The motor projections include somatosensory, motor and premotor cortex. More relevant to OCD, the limbic associative projections include projections from the amygdala, hippocampus, orbital, frontal, cingulate, parietal, temporal, entorhinal, and association cortex. These cortical-striatal connections can be divided into circuit loops. There are five major loops (sensorimotor, oculomotor, dorsal cognitive, ventral cognitive, and affective and motivational) that extend from the cortex to the striatum to the thalamus and back to the cortex. The organization of the cortical-striatal circuits are reviewed in depth elsewhere.⁹ These circuits move in a self-repeating loop through distinct parts of the frontal cortex, basal ganglia, substantia nigra and thalamus.⁹ Two of the pathways regulate output from frontal cortex in an effort to ensure appropriate behavioral responses to stimuli.⁹ First, the “direct” pathway is thalamic stimulation of the cortex. Second, the “indirect” pathway acts to inhibit the thalamus (Figure 2). This permits the cortex to shift sets and respond to novel stimuli. In OCD, excessive neural tone in the direct pathway relative to the indirect pathway may subserve symptoms.

EVIDENCE TO SUPPORT THE ROLE OF GLUTAMATE

Brain Imaging

The excitatory neurotransmitter of the cortical-striatal-thalamic circuit is glutamate. In 1998, Rosenberg and Keshavan first hypothesized a role for glutamate in pediatric OCD.¹⁰ Using proton magnetic resonance spectroscopy (¹H-MRS), Rosenberg et al., in the first report, observed increased left caudate glutamate and glutamine (Glx) concentrations in treatment naive pediatric OCD patients compared with healthy controls (Figure 3).¹¹ By contrast, Glx concentrations in occipital gray matter, a region less implicated in the pathogenesis of OCD, did not differ between OCD patients and controls. Left caudate Glx normalized after effective treatment with an SSRI, and reduction in caudate Glx correlated robustly with reduction in OCD symptom severity. This “normalization” in striatal Glx may persist after SSRI discontinuation.¹² Interestingly, CBT did not alter caudate Glx concentrations in pediatric patients with OCD regardless of the reduction in symptoms.¹³ Converse to the striatum, a single-voxel ¹H-MRS study of the anterior cingulate, found lower Glx

concentrations in pediatric OCD patients than in healthy controls (Figure 3).¹⁴ This finding was replicated in adults with OCD.¹⁵ Whiteside et al. observed greater Glx in orbital frontal white matter in adult patients with OCD compared with controls.¹⁶ These may be regionally specific, as no effect was observed in the occipital cortex - an area not typically implicated in the pathophysiology of OCD.¹¹ The lower anterior cingulate Glx concentrations and greater caudate Glx concentrations in pediatric patients with OCD are consistent with previous reports of inverse correlations between anterior cingulate and basal ganglia volume.¹⁰

These studies are suggestive of a possible tonic-phasic dysregulation of corticostriatal Glx in OCD. Tonic Glx activity acts to inhibit phasic stress-related glutamate release from the striatum. Therefore, lower tonic Glx in the anterior cingulate cortex may predispose phasic Glx over-activity in the caudate. This is speculative; but the fact that greater caudate Glx concentrations in pediatric patients with OCD were reversible with effective SSRI treatment further supports this hypothesis.¹¹

In summary, in vivo brain-imaging studies of the cortical-striatal-thalamic circuit in OCD implicate glutamate directly.

Animal Models and Peripheral Markers

Brain-imaging findings are also supported by studies using other methods. For example, rodent models of obsessive-compulsive and stereotypic behaviors provide indirect evidence of a role for glutamate in OCD as well.¹⁷ In a human study of cerebrospinal fluid (CSF) concentration of glutamate, Chakrabarty et al. examined 21 psychotropic-naïve adults with OCD. They reported that glutamate concentration was significantly greater in patients with OCD compared with 18 healthy control subjects.¹⁸

Genetic Markers

Glutamate Transporter Polymorphisms—Three research groups independently demonstrated that the 3' region of *SCL1A1* contains a susceptibility allele for OCD, mainly in male offspring.^{19–21} The protein product of this gene is the high-affinity neuronal and epithelial transporter (EAAT3/EAAC1) for L- glutamate, L- aspartate, D-aspartate, and cysteine. EAAT3/EAAC1 can be found in cortex, basal ganglia, hippocampus and all parts of the neuron. In adults, glutamate transport acts to keep extracellular glutamate at less than neurotoxic concentrations. EAAT3/EAAC1 has a rather low expression, however, and only makes a minor contribution to the removal of synaptic glutamate compared with EAAT1 and EAAT2. In the early phases of brain development, EAAT3/EAAC1 is expressed before astrocytes are fully functional, which suggests it has a developmental role. A vital role of EAAT3/EAAC1 in brain development is consistent with the findings supporting *SLC1A1* as a primary candidate gene not only in pediatric OCD but also in autism-spectrum disorders (Autism Genome Project Consortium, 2007).^{19–22} The hormones testosterone and prolactin act to regulate the expression of EAAT3/EAAC1. The amplification of expression of EAAT3/EAAC1 by testosterone is also consistent with the finding that the association of OCD with *SLC1A1* is strongest in males.^{19,20} Although the functional importance of this polymorphism is not yet established, mice deficient in EAAC1 develop impaired self-grooming behaviors. This suggests that the function of the EAAT3/EAAC1 polymorphism in pediatric OCD is associated with greater EAAT3/EAAC1 expression. Interestingly, the rs3056 variant of *SLC1A1* is associated with increased thalamic volume (Figure 4).²³

Glutamate Receptor Polymorphisms—The 5072T/G variant of N-methyl-D-aspartate (NMDA) subunit 2B gene (*GRIN2B*) is also associated with pediatric OCD.²⁴ Specifically, the 5072G-5988T haplotype is linked with OCD. *GRIN2B*, which is on chromosome 12p,

encodes for the NR2B subunit of the ionotropic glutamate receptor. *GRIN2B* is expressed mainly in the striatum and the prefrontal cortex. These regions also demonstrate glutamatergic abnormalities in pediatric OCD patients.^{11,14} In addition, *GRIN2B* is linked to other psychiatric disorders (e.g., schizophrenia, attention deficit hyperactivity disorder and bipolar disorder). During development of the cortex, *GRIN2B* may play a role in cortical plasticity. Furthermore, neurotoxic levels of glutamate during the neonatal period cause an increase in the expression of NMDA NR2B in the striatum and cortex.

Functionally, increased expression of *GRIN2B* in reaction to excess glutamate suggests an association with greater expression in the striatum in pediatric patients with OCD. More recently, an imaging genetics study of pediatric patients with OCD found a significant association between the rs1019385 polymorphism of *GRIN2B* and lower anterior cingulate cortex Glx but not with left caudate or occipital Glx.²⁵ The association with this specific polymorphism indicates that lower anterior cingulate Glx is a trait rather than state abnormality. Furthermore, the rs1805476 variant of *GRIN2B* is associated with right but not left anterior cingulate cortex volume and left but not right orbital frontal cortex (Figure 4).²³

TREATMENT STUDIES

The glutamate hypothesis and supportive evidence translates to the application of glutamate-modulating agents for the treatment of pediatric OCD.¹⁰ Given the limitations of SSRI treatment for OCD, as discussed, novel medications/applications and drug combinations are necessary. The glutamate-modulating agent *riluzole* shows particular promise in treating psychiatric disorders.^{26–28} Riluzole is FDA-approved for the treatment of amyotrophic lateral sclerosis and is typically well tolerated by patients. The mechanism of action of riluzole is not fully elucidated but it can act in three ways:

- As an inhibitor of *glutamate release*;
- To inactivate voltage dependant *sodium channels* in cortical neurons; and
- To block γ -*aminobutyric acid (GABA) reuptake*.

In a case report and small open-label trial in adults with OCD, riluzole decreased symptoms.^{26,27} This work was extended to children and adolescents (8–16 years) with OCD in an open-label trial, which demonstrated riluzole was effective at reducing symptoms and was well tolerated.²⁸ These data led to a National Institutes of Mental Health-sponsored double-blind, clinical trial, which is ongoing.

Additional glutamate and GABA-modulating medications also show promise. For example, *topiramate* is used to treat OCD symptoms in adults. There have been case reports, however, indicating that some glutamate-modulating medications (e.g., lamotrigine, topiramate) can also induce OCD-like behaviors. In addition, the possible occurrence of serious skin rash with *lamotrigine* is a concern. Aside from safety issues, the mechanism of action is also important in considering which glutamatergic agent to test. Although topiramate enhances GABA activity and lamotrigine is a sodium channel blocker, riluzole acts primarily to inhibit glutamate.

N-acetylcysteine, which attenuates glutamate transmission, also showed initial promise in treatment refractory OCD.²⁹ *D-cycloserine*, a partial agonist at the NMDA glutamatergic receptor, may augment behavior therapy.³⁰ Finally, adjunctive *memantine*, a NMDA receptor antagonist, shows promise for treating OCD.³¹

Given the above neurobiological findings and clinical reports, glutamate modulating agents offer particular promise as anti-OCD therapies. It is important to note that the use of glutamate modulating agents is considered off-label and investigational.

PITFALLS AND PROMISE

Limitations to the Glutamate Hypothesis of Obsessive-Compulsive Disorder

Clearly, a hypothesis that focuses on a single neurotransmitter is insufficient. As discussed, the preferential response of OCD patients to SSRIs spawned the “serotonin hypothesis” of OCD, and some neurobiological evidence followed to substantiate that assertion. Nevertheless, the persistence of symptoms despite focused pharmacologic targeting of this system indicates its limits.^{7,32}

Of note, glutamate and serotonin interact on a number of levels in the critical frontal striatal circuit and change over the course of development. For example, a preclinical study by Becquet et al. demonstrated that glutamate exerts a robust inhibitory effect on serotonin release in the caudate, an area showing elevated Glx concentration in pediatric OCD.^{11,33} Furthermore, the orbitofrontal cortex projects to the dorsal raphe nuclei, which in turn sends serotonergic input to the striatum. The orbitofrontal cortex also has direct glutamate projections to the striatum, which play a role in the release and turnover of serotonin, as well as the regulation of serotonin receptor number in the striatum.

An important caveat is that we do not know for certain where the glutamate signal is derived from the cellular level (i.e., metabolic pool, active transmitter, etc. as measured by ¹H-MRS) or the functional import of changes in concentration. There is also a regional effect, with the anterior cingulate showing a lower glutamate concentration in pediatric patients with OCD, whereas the striatum shows an increase. This means that glutamate-modulating agents would have to act in a regionally specific manner and not globally, which would exacerbate symptoms (i.e., lowering anterior cingulate glutamate further). Given the evidence thus far, however, **glutamate is a logical biomarker choice and translational focus given its role in the pathophysiology of OCD and its interplay with serotonin, the target of currently approved OCD medications.

Translational Impact

The traditional strategy in psychiatry is to move from pharmacotherapy of a disorder to theories on its pathophysiology. The development of the serotonin hypothesis of OCD is an example of this approach. Thus, medications were applied initially and a physiological explanation of the illness shaped around response. This approach, unfortunately, fails to spur real progress in our understanding of psychiatric disorders. Elucidating the underlying pathophysiology of psychiatric disorders is challenging. The development of advanced brain imaging methodologies allows in vivo examination of the structure, function, and chemistry of the living brain. Postmortem studies are also revealing but provide limited information. In addition, in pediatric populations with psychiatric disorders, samples are very rare. In the 20 years since the application of brain imaging to the study of OCD, much progress has been made in our understanding of the disorder. Bringing these advances from the “bench” to the clinic, however, is more difficult.

Translational research faces two major hurdles.³⁴ First, it is difficult to transfer discoveries of the mechanisms of the disorder into novel treatments, diagnostic tools and prevention. Second, it is difficult to bring these novel therapies, diagnostic tools and preventative methods into the clinic. Still, significant progress is occurring in our understanding of the neurobiology of pediatric OCD. These discoveries are leading to the novel application of agents to treat pediatric OCD. This is a rare instance where knowledge moved from the

`bench' and closer to the bedside. Indeed, work on the glutamate hypothesis in pediatric OCD fits well with Dr. Insel's call for "rational therapeutics" for psychiatric illness (Keynote address, Society for Biological Psychiatry, 2008).

CONCLUSIONS

Converging biological evidence indicates a role for glutamate in the symptoms of OCD. Furthermore, modulating glutamate with targeted medications appears to benefit OCD symptoms.^{26–28} There is a clear conceptual link between glutamate and OCD symptoms, in which ¹H-MRS, CSF, genetic, animal, and clinical studies all provide supportive evidence. Considering the substantial number of OCD nonresponders and partial responders to SSRI treatment, there is an urgent need for novel treatments to close the existing gap in positive outcomes. The work described herein has the potential for high clinical impact; may stimulate the wider application of glutamate modulating agents for pediatric OCD; and could push this area of translational research forward. After reading this review, psychiatrists should have a better understanding of the role of glutamate in the pathophysiology and, potentially, the treatment of OCD.

CME QUIZ

1. Evidence suggesting problems with the serotonin hypothesis of obsessive-compulsive disorder (OCD) arises from the limited number of responders to selective serotonin reuptake inhibitors and substantial residual symptoms in many responders.
 - A. True
 - B. False
2. Evidence supporting the role of glutamate in OCD is derived from
 - A. proton magnetic resonance spectroscopy studies
 - B. studies of cerebrospinal fluid
 - C. animal models
 - D. all of the above
3. Problems with some glutamate-modulating agents include
 - A. serious skin rash
 - B. induction of OCD-like behaviors
 - C. neither of the above
 - D. both of the above
4. If mice deficient in *EAAC1*, the product of *SLC1A1*, demonstrate impaired self-grooming behaviors, this suggests that *SLC1A1* as associated with OCD indicates an increase in expression rather than a decrease.
 - A. True
 - B. False
5. Which one of the following agents currently used in the treatment of amyotrophic lateral sclerosis also showed promise in treating pediatric OCD in a small, open-label trial?
 - A. Lamotrigine

- B.** Riluzole
- C.** Topiramate
- D.** D-cycloserine

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Figure 1.
The cortical-striatal-thalamic circuit.

Figure 2.
Direct and indirect pathways.

Figure 3.

Summary figure of key proton spectroscopy studies of pediatric obsessive-compulsive disorder (OCD). Left caudate glutamate and glutamine (Glx) in healthy controls and patients with OCD (A) before and after selective serotonin reuptake inhibitor (SSRI) treatment; and in patients with OCD (B) before and after cognitive behavioral therapy (CBT). (C) Anterior cingulate Glx in healthy controls and patients with OCD.^{11,13,14}

Figure 4.

Summary figure of imaging studies of pediatric patients with OCD. (A) *SLC1A1* and thalamic volume. (B) *GRIN2B* and anterior cingulate glutamate and Glx. (C) *GRIN2B* and anterior cingulate volume. (D) *GRIN2B* and orbital frontal cortex volume.^{22,24}