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J Am Acad Child Adolesc Psychiatry. Author manuscript; available in PMC 2009 June 15.

Published in final edited form as:
J Am Acad Child Adolesc Psychiatry. 2008 November ; 47(11): 1262–1272. doi:10.1097/CHI.0b013e318185d2be.

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 keywords "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 pathology of OCD. This has led to 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.

Newer, non-invasive brain imaging approaches offer promise in enhancing understanding not only of brain development but also of the neurobiologic underpinnings of childhood-onset neuropsychiatric disorders. These techniques permit unprecedented *in vivo* 'biopsies' of brain structure, chemistry and function. Here, we present 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 and Keshavan [2].

NEUROBIOLOGY OF OCD

The cortical-striatal-thalamic circuit (figure 1) is most consistently implicated in OCD [3]. Below we focus on neurobiological studies of this circuit in pediatric OCD (table 1).

Frontal Cortex

Neurocognitive testing of frontal cortical functions is under explored in pediatric OCD. Spatial-perceptual deficits similar to those of frontal lobe lesion patients were reported in OCD adolescents[7] but not replicated [4, 5]. Recently, deficits in visual attention and executive functioning were found in children with OCD [5]. There is more evidence for prefrontal oculomotor abnormalities in pediatric OCD [6, 7] including in: ability to suppress responses,

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Statistical Expert: None

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volitional execution of delayed responses, and anticipation of predictable events. Patients with OCD had more response-suppression failures than controls [6, 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 [6]. Woolley et al [8], using functional magnetic resonance imaging (fMRI) found that during the 'stop' task, OCD patients showed reduced activation in right orbitofrontal cortex, thalamus and basal ganglia compared to 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 [6, 7]. Indeed, pediatric OCD patients had significantly greater gray matter density in the orbital frontal cortex than healthy controls [9], confirmed by manual region of-interest (ROI) measurements. Furthermore, among patients, gray matter density in right lateral orbital frontal cortex correlated significantly with OCD symptom severity, but not with anxiety or depression [9].

Gray matter volume of the anterior cingulate is greater in pediatric OCD patients compared to age- and sex-matched controls [2, 10]. Anterior cingulate volume was positively correlated with age in controls but not in OCD patients [2]. There was no difference between groups for anterior cingulate white matter [10]. 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, 10], but not with VBM [9]. Converse to those reports [2, 9, 10], a VBM analysis by Carmona et al [11] found significantly lower gray matter density in OCD patients compared to healthy controls in the anterior cingulate bilaterally. This may indicate sensitivity issues with both techniques and fundamental differences in what is being measured [12]. Single-voxel proton magnetic resonance spectroscopy (^{1}H-MRS) of the anterior cingulate found lower glutamatergic concentrations (Glx) in OCD patients than in healthy controls [13]. Below-normal anterior cingulate Glx was also noted in adult females with OCD [14]. The lower anterior cingulate glutamate correlated with symptom severity in these patients. While no volumetric effects in dorsolateral prefrontal cortex (DLPFC) were noted [2], proton magnetic resonance spectroscopic imaging (^{1}H-MRSI) did reveal above-normal concentration of the putative neuronal marker, *N*-Acetyl-Aspartate (NAA) in left but not right DLPFC in pediatric OCD patients [15]. Higher NAA in left DLPFC may indicate abnormal cortical pruning in OCD.

Subcortical

Striatum/Basal Ganglia—OCD patients had significantly smaller striatal volumes than age- and sex-matched healthy controls [16]. In the OCD patients, striatal volumes correlated inversely with symptom severity but not with illness duration [16]. In a second sample, a smaller globus pallidus was noted in pediatric OCD patients than in healthy volunteers [10]. Interestingly, a VBM study showed above-normal gray matter density in the bilateral putamen in pediatric OCD patients [9]. It should be noted that VBM and manual tracing methods for evaluating brain volume have not been well validated against each other [12] and may not reflect identical aspects of brain morphology (see issues that require further study below). Above-normal striatal Glx concentrations, which normalized after successful treatment with an SSRI, were noted in pediatric OCD [17, 18]. This reduction in striatal Glx may persist after SSRI discontinuation [19]. Interestingly, cognitive behavioral therapy (CBT) did not change caudate Glx concentrations in pediatric OCD patients despite a reduction in symptoms [20]. Finally, subcortical hyperintensities occur more frequently in children with OCD than in controls [21].

Thalamus—Thalamic volume is larger in pediatric OCD patients than in age- and sex-matched controls [22]. After 12 weeks of treatment with paroxetine, thalamic volume normalized in OCD patients concurrent with a reduction in OCD symptoms. This reduction in thalamic volume in OCD appears specific to medication as no changes in thalamic volume were noted with CBT [23]. Interestingly, below-normal ratios of bilateral medial-thalamic NAA/Cr and

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NAA/Cho were noted in OCD [24]. Lower ratios could mean lower NAA. That might be inconsistent with the aforementioned above-normal overall thalamic volume in OCD [22], in so far as lower NAA could imply lower neuron mass and thus smaller thalamic volume. However, these results need not be associated with death or reduced size of neurons, A more advanced quantification technique, if fact, using validated phantom-replacement methodology that allowed for absolute quantification indicated greater medial-thalamic Cho [25, 26] and Cr [27] but not lower NAA [25–27] in OCD patients than in healthy controls. 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 lateral thalamus [25]. OCD patients differed not only from controls with regard to medial-thalamic Cho and Cr, but also from pediatric MDD patients [26, 27].

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 OCD patients than in controls [28]. Callosal area correlated significantly with OCD symptom severity but not with illness duration. Secondly, the age-related increase in callosal size observed in normal subjects was not present in OCD patients. MRI signal intensity, related to myelination in the corpus callosum, was lower in genu of the corpus callosum in OCD patients than in healthy controls [29]. 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 [28]. The genu connects ventral prefrontal cortex with striatum, regions noted above to be critical in pediatric OCD. Dysregulation of the limbic-hypothalamic-pituitary-adrenal (LHPA) axis has been reported in patients with OCD [30–33]. The pituitary gland is significantly smaller in treatment-naive pediatric OCD patients than in healthy controls, with a more prominent difference in males [34]. Interestingly, the smaller gland volume found in OCD contrasts with the enlarged pituitary seen in MDD [35, 36] and bipolar disorder [37]. It is not known if SSRI treatment changes pituitary volume in OCD as it does in MDD [38] or as antipsychotic medications do in schizophrenia [39].

GENETICS OF OBSESSIVE-COMPULSIVE DISORDER

Estimates of the heritability of obsessive-compulsive symptoms in children and adolescents range from 45% to 65% [40] 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 [41–43]. 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 [44, 45]. EAAT3/EAAC1 is present in cortex, basal ganglia, and hippocampus, and is detected in all parts of the neuron [46]. EAAT3/EAAC1 binds and transports cysteine more effectively than astrocyte glutamate transporters [47]. Furthermore, EAAT3 is localized to some GABAergic neurons, where it may play a role in regulating GABA synthesis [48]. In the adult brain, glutamate transport keeps extracellular glutamate below neurotoxic concentrations [49]. However, in adults EAAT3/EAAC1 exhibits rather low expression and is thought to make a minor contribution to the removal of synaptic glutamate compared to EAAT1 and EAAT2 [50]. 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 [50]. This role of EAAT3/EAAC1 in brain development is consistent with the

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linkage and association findings supporting SLC1A1 as a primary candidate gene in pediatric OCD [41–43] and in autistic spectrum disorders (Autism Genome Project Consortium, 2007). Expression of EAAT3/EAAC1 is regulated by testosterone and prolactin [45]. Increased expression of EAAT3/EAAC1 by testosterone is consistent with association of OCD with SLC1A1 being strongest in males [41, 42]. Mice deficient in EAAC1 develop dicarboxylic aminoaciduria [51], reduced neuronal glutathione and, with aging, brain atrophy, increased aggressiveness, and impaired self-grooming [44]. 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 might 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. Under-expression of SLC1A1, glutamate receptor agonists and EAAT3 antagonists, in contrast, could all aggravate OCD symptoms. Under-expression of SLC1A2 and SLC1A3 could produce OCD symptoms that would be aggravated by EAAT1 and EAAT2 antagonists, while enhanced expression of these genes or EAAT1 and EAAT2 agonism could have therapeutic effects. In adult OCD, cognitive-behavioral therapy (CBT) has multiple effects on MRS metabolites [52–54], including reduction of above-normal baseline glutamate in anterior cingulate [55]. Although different physiologic conditions may prevail in adult *vs.* 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 [56]. Additionally, 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 [57] consistent with regions demonstrating glutamatergic abnormalities in pediatric OCD patients [13, 18]. GRIN2B has also been linked to schizophrenia [58], attention deficit hyperactivity disorder [59] and bipolar disorder [60]. GRIN2B is thought to play a role in plasticity during cortical development [61]. Additionally, neurotoxic levels of glutamate during the neonatal period increase the expression of NMDA NR2B in the striatum and cortex [62]. The increased expression of GRIN2B in response to excess glutamate [63] suggests that pediatric OCD is associated with increased GRIN2B expression in the striatum.

NOVEL PHARMACOTHERAPY FOR OCD

Selective serotonin reuptake inhibitors (SSRI's) are the only FDA-approved medications for OCD. However, SSRI's are typically only effective in 40 to 60% of patients, leaving a substantial number still ill [64]. Indeed, as treatment response is defined by a 20 to 40% reduction in symptoms, many "responders" are still markedly symptomatic [64]. 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 [13, 14, 18, 41, 42, 56, 65–68]. Indeed, all of the ^{1}H-MRS and CSF measures of glutamate concentration in OCD demonstrated very large effect sizes ($d > 1.00$) indicating robust differences in regional glutamate concentrations in OCD patients as compared to controls (see figure 2). This neurobiological evidence has led to the search for agents that modulate glutamate [69]. Indeed, the glutamate-modulating agent riluzole (1-amino-6-trifluoromethoxybenzothiazole) has shown promise in neuropsychiatric disorders [70–75]. Riluzole is well tolerated and is FDA approved for treatment of amyotrophic lateral sclerosis (ALS; [76–78]). Riluzole is primarily an inhibitor of glutamate release but also inactivates voltage-dependant sodium channels in cortical neurons and blocks GABA reuptake [79–81]. In

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a case report [70] and an open-label trial in adults [71], riluzole has shown promise for ameliorating the symptoms of OCD. More recently, an open-label trial in children (8 to 16 years) with OCD found riluzole to be beneficial and well tolerated [82]. A larger placebo-controlled trial at NIMH is underway.

CONCLUSION

The Glutamate Hypothesis of Obsessive-Compulsive Disorder

In 1998, Rosenberg and Keshavan [2] first hypothesized a role for glutamate in pediatric OCD. The first reports of *in vivo* differences in Glx between pediatric OCD patients and healthy were published shortly thereafter [17, 18]. Since these initial reports, in OCD patients a lower concentration of glutamate has been noted in the anterior cingulate [13, 14] while greater Glx/Cr levels have been seen in orbital frontal white matter [65]. These neuroimaging reports found further support in genetic studies that noted an increased susceptibility to OCD in those expressing alterations in the neuronal glutamate transporter gene [41, 42] and certain glutamate receptor genes [56, 67]. Furthermore, peripheral markers [66] and animal models [68] have provided additional support for glutamate dysfunction in OCD. Clinically, glutamate-modulating agents are showing promise for OCD [70, 71, 82]. Hence, ^{1}H-MRS, CSF, genetic, animal and clinical studies have all 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 illness [83]. It is becoming clear that investigators need to combine strategies (genetic, neuroimaging, pharmacological, animal models, etc) to allow for the most advancement [83, 84]. 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 [83]. A roadmap of how to achieve these advances is only now coming into focus. The progress described in pediatric OCD in this review is a rare occurrence in psychiatry, an example where neurobiological studies of a disorder have directly informed its treatment. Indeed, if one compares what is known regarding diabetes and what we are starting to see in pediatric OCD, one can see how the disorder is coming into greater focus using multiple methods (see table 2). Brain imaging has demonstrated great potential for aiding in the diagnosis, treatment, prevention, and cure of neuropsychiatric disorders [85]. 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 (Glx)—To date, ^{1}H-MRS studies of OCD have reported the combined Glx measure (glutamate and glutamine) [13, 14, 17, 18, 65]. Given the differing physiological roles of glutamate and glutamine, techniques that allow for the separation of the two similar resonances need to be applied in OCD. Techniques include improved spectral editing [86–88] or the use of higher field MRI scanners [89].

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 illness [90]. 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 underway 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.

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Additional studies of glutamate related genes are required. These 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, as 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 [91]. 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), though unpublished negative findings may exist. These two astrocyte glutamate transporters may influence the pathophysiology of OCD and its pharmacologic regulation by regulating regional glutamate levels. Glutamate enters astrocytes through these transporters [50] and is rapidly converted to non-toxic glutamine [92] which thence is exported to neurons (through monocarboxylate transporters; [93, 94]) for re-conversion to glutamate [95]. 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 [17, 18]. Under-expression 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 Cycle [96] to sustain the higher metabolic rate, and lower overall levels of tissue Glx, as observed in the anterior cingulate in pediatric OCD [13]. Increased expression of SLC1A1 and the glutamate receptor gene GRIN2B (see above) might therefore be secondary responses, i.e., 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 [41]. It might 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.

VBM—It is not known why some VBM studies conflict with volumetric MRI studies using manual tracing methods [12]. For example, in the anterior cingulate in OCD patients Carmona et al [11] noted lower gray matter density bilaterally while Rosenberg and Keshavan [2] found greater gray matter volume. Interestingly, Szeszko et al [9] found greater anterior cingulate gray matter volume in patients as compared to healthy volunteers using volumetric MRI, but not with VBM. As the operational definition for gray matter density has not been resolved, it may be that the methods measure two very different things (i.e. volume vs. the statistical probability of a voxel being gray matter). Further work is needed to validate VBM and to resolve the conflict noted with traditional manual tracing techniques.

Future Directions

Given that the clinical phenomenology and nosology of OCD is, 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. Such studies may provide further 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 Institutes for Mental Health. Such approaches may lead to better understanding of pediatric OCD and, in turn, to new diagnostic and treatment approaches.

Acknowledgments

Acknowledgements: None

Financial Support: This work was supported in part by the State of Michigan Joe F. Young Sr. Psychiatric Research and Training Program, the Miriam L. Hamburger Endowed Chair of Child Psychiatry at Children's Hospital of Michigan and Wayne State University, Detroit, MI, and grants from the National Institute of Mental Health

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(R01MH59299, R01MH65122, R01MH081864, K24MH02037) and the Mental Illness Research Association (MIRA).

References

1. Pauls DL, Alsobrook JP 2nd, Goodman W, Rasmussen S, Leckman JF. A family study of obsessive-compulsive disorder. Am J Psychiatry Jan;1995 152(1):76–84. [PubMed: 7802125]
2. Rosenberg DR, Keshavan MS. A.E. Bennett Research Award. Toward a neurodevelopmental model of obsessive-compulsive disorder. Biol Psychiatry May 1;1998 43(9):623–640. [PubMed: 9582996]
3. Rosenberg, DR.; Mac, Master FP.; Mirza, Y.; Easter, PC.; Buhagiar, CJ. Neurobiology, neuropsychology and neuroimaging of child and adolescent obsessive-compulsive disorder. In: Storch, E.; Geffken, G.; Murphy, T., editors. A comprehensive handbook of child and adolescent obsessive-compulsive disorder. Lawrence Erlbaum Associates; 2007. p. 131-161.
4. Beers SR, Rosenberg DR, Dick EL, et al. Neuropsychological study of frontal lobe function in psychotropic-naive children with obsessive-compulsive disorder. Am J Psychiatry May;1999 156(5): 777–779. [PubMed: 10327915]
5. Chang SW, McCracken JT, Piacentini JC. Neurocognitive correlates of child obsessive-compulsive disorder and Tourette syndrome. J Clin Exp Neuropsychol Oct;2007 29(7):724–733. [PubMed: 17896198]
6. Rosenberg DR, Averbach DH, O'Hearn KM, Seymour AB, Birmaher B, Sweeney JA. Oculomotor response inhibition abnormalities in pediatric obsessive-compulsive disorder. Arch Gen Psychiatry Sep;1997 54(9):831–838. [PubMed: 9294374]
7. Rosenberg DR, Dick EL, O'Hearn KM, Sweeney JA. Response-inhibition deficits in obsessive-compulsive disorder: an indicator of dysfunction in frontostriatal circuits. J Psychiatry Neurosci Jan; 1997 22(1):29–38. [PubMed: 9002390]
8. Woolley J, Heyman I, Brammer M, Frampton I, McGuire PK, Rubia K. Brain activation in pediatric obsessive compulsive disorder during tasks of inhibitory control. Br J Psychiatry Jan;2008 192(1):25–31. [PubMed: 18174505]
9. Szeszko P, Christian C, Mac Master FP, et al. Gray matter structural alterations in psychotropic drug-naive pediatric obsessive-compulsive disorder: An optimized voxel based morphometry study. Am J Psychiatry. In Press
10. Szeszko PR, MacMillan S, McMeniman M, et al. Brain structural abnormalities in psychotropic drug-naive pediatric patients with obsessive-compulsive disorder. Am J Psychiatry Jun;2004 161(6):1049–1056. [PubMed: 15169693]
11. Carmona S, Bassas N, Rovira M, et al. Pediatric OCD structural brain deficits in conflict monitoring circuits: a voxel-based morphometry study. Neurosci Lett Jun 29;2007 421(3):218–223. [PubMed: 17573192]
12. Thacker, NA. Tutorial: A critical analysis of voxel based morphometry (VBM). Manchester: University of Manchester; 2005.
13. Rosenberg DR, Mirza Y, Russell A, et al. Reduced anterior cingulate glutamatergic concentrations in childhood OCD and major depression versus healthy controls. J Am Acad Child Adolesc Psychiatry Sep;2004 43(9):1146–1153. [PubMed: 15322418]
14. Yucel M, Wood SJ, Wellard RM, et al. Anterior cingulate glutamate-glutamine levels predict symptom severity in females with obsessive-compulsive disorder. Mol Psychiatry. In Press
15. Russell A, Cortese B, Lorch E, et al. Localized functional neurochemical marker abnormalities in dorsolateral prefrontal cortex in pediatric obsessive-compulsive disorder. J Child Adolesc Psychopharmacol 2003;13(Suppl 1):S31–38. [PubMed: 12880498]
16. Rosenberg DR, Keshavan MS, O'Hearn KM, et al. Frontostriatal measurement in treatment-naive children with obsessive-compulsive disorder. Arch Gen Psychiatry Sep;1997 54(9):824–830. [PubMed: 9294373]
17. Moore GJ, MacMaster FP, Stewart C, Rosenberg DR. Case study: caudate glutamatergic changes with paroxetine therapy for pediatric obsessive-compulsive disorder. J Am Acad Child Adolesc Psychiatry Jun;1998 37(6):663–667. [PubMed: 9628087]

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18. 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 Sep;2000 39(9):1096–1103. [PubMed: 10986805]
19. Bolton J, Moore GJ, MacMillan S, Stewart CM, Rosenberg DR. Case study: caudate glutamatergic changes with paroxetine persist after medication discontinuation in pediatric OCD. J Am Acad Child Adolesc Psychiatry Aug;2001 40(8):903–906. [PubMed: 11501689]
20. Benazon NR, Moore GJ, Rosenberg DR. Neurochemical analyses in pediatric obsessive-compulsive disorder in patients treated with cognitive-behavioral therapy. J Am Acad Child Adolesc Psychiatry Nov;2003 42(11):1279–1285. [PubMed: 14566164]
21. Amat JA, Bronen RA, Saluja S, et al. Increased number of subcortical hyperintensities on MRI in children and adolescents with Tourette's syndrome, obsessive-compulsive disorder, and attention deficit hyperactivity disorder. Am J Psychiatry Jun;2006 163(6):1106–1108. [PubMed: 16741215]
22. Gilbert AR, Moore GJ, Keshavan MS, et al. Decrease in thalamic volumes of pediatric patients with obsessive-compulsive disorder who are taking paroxetine. Arch Gen Psychiatry May;2000 57(5): 449–456. [PubMed: 10807485]
23. Rosenberg DR, Benazon NR, Gilbert A, Sullivan A, Moore GJ. Thalamic volume in pediatric obsessive-compulsive disorder patients before and after cognitive behavioral therapy. Biol Psychiatry Aug 15;2000 48(4):294–300. [PubMed: 10960160]
24. Fitzgerald KD, Moore GJ, Paulson LA, Stewart CM, Rosenberg DR. Proton spectroscopic imaging of the thalamus in treatment-naive pediatric obsessive-compulsive disorder. Biol Psychiatry Feb 1;2000 47(3):174–182. [PubMed: 10682215]
25. Rosenberg DR, Amponsah A, Sullivan A, MacMillan S, Moore GJ. Increased medial thalamic choline in pediatric obsessive-compulsive disorder as detected by quantitative in vivo spectroscopic imaging. J Child Neurol Sep;2001 16(9):636–641. [PubMed: 11575601]
26. Smith EA, Russell A, Lorch E, et al. Increased medial thalamic choline found in pediatric patients with obsessive-compulsive disorder versus major depression or healthy control subjects: a magnetic resonance spectroscopy study. Biol Psychiatry Dec 15;2003 54(12):1399–1405. [PubMed: 14675804]
27. Mirza Y, O'Neill J, Smith EA, et al. Increased medial thalamic creatine-phosphocreatine found by proton magnetic resonance spectroscopy in children with obsessive-compulsive disorder versus major depression and healthy controls. J Child Neurol Feb;2006 21(2):106–111. [PubMed: 16566872]
28. Rosenberg DR, Keshavan MS, Dick EL, Bagwell WW, MacMaster FP, Birmaher B. Corpus callosal morphology in treatment-naive pediatric obsessive compulsive disorder. Prog Neuropsychopharmacol Biol Psychiatry Nov;1997 21(8):1269–1283. [PubMed: 9460091]
29. MacMaster FP, Keshavan MS, Dick EL, Rosenberg DR. Corpus callosal signal intensity in treatment-naive pediatric obsessive compulsive disorders. Prog Neuropsychopharmacol Biol Psychiatry May; 1999 23(4):601–612. [PubMed: 10390719]
30. Altemus M, Cizza G, Gold PW. Chronic fluoxetine treatment reduces hypothalamic vasopressin secretion in vitro. Brain Res Oct 16;1992 593(2):311–313. [PubMed: 1450938]
31. Monteleone P, Catapano F, Tortorella A, Maj M. Cortisol response to d-fenfluramine in patients with obsessive-compulsive disorder and in healthy subjects: evidence for a gender-related effect. Neuropsychobiology 1997;36(1):8–12. [PubMed: 9211437]
32. Monteleone P, Catapano F, Tortorella A, Di Martino S, Maj M. Plasma melatonin and cortisol circadian patterns in patients with obsessive-compulsive disorder before and after fluoxetine treatment. Psychoneuroendocrinology 1995;20(7):763–770. [PubMed: 8848522]
33. Catapano F, Monteleone P, Fuschino A, Maj M, Kemali D. Melatonin and cortisol secretion in patients with primary obsessive-compulsive disorder. Psychiatry Res Dec;1992 44(3):217–225. [PubMed: 1289919]
34. MacMaster FP, Russell A, Mirza Y, et al. Pituitary volume in pediatric obsessive-compulsive disorder. Biol Psychiatry Feb 1;2006 59(3):252–257. [PubMed: 16140279]
35. MacMaster FP, Kusumakar V. Pituitary gland volume in adolescent depression. J Psychiatr Res. 2004
36. MacMaster FP, Russell A, Mirza Y, et al. Pituitary volume in treatment-naive pediatric major depressive disorder. Biol Psychiatry Oct 15;2006 60(8):862–866. [PubMed: 16876142]

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37. MacMaster FP, Leslie R, Rosenberg DR, Kusumakar V. Pituitary gland volume in adolescent and young adult bipolar and unipolar depression. Bipolar Disord Feb;2008 10(1):101–104. [PubMed: 18199247]
38. Mac Master, FP.; Easter, PC.; Rix, C.; Kmiecik, L.; Buhagiar, CJ.; Rosenberg, DR. Society for Biological Psychiatry. Washington, DC: 2008. Regional volumetric changes with treatment in pediatric major depression.
39. MacMaster FP, El-Sheikh R, Upadhyaya AR, Nutche J, Rosenberg DR, Keshavan M. Effect of antipsychotics on pituitary gland volume in treatment-naive first-episode schizophrenia: A pilot study. Schizophr Res May;2007 92(1–3):207–210. [PubMed: 17337162]
40. van Grootheest DS, Cath DC, Beekman AT, Boomsma DI. Twin studies on obsessive-compulsive disorder: a review. Twin Res Hum Genet Oct;2005 8(5):450–458. [PubMed: 16212834]
41. Arnold PD, Sicard T, Burroughs E, Richter MA, Kennedy JL. Glutamate transporter gene SLC1A1 associated with obsessive-compulsive disorder. Arch Gen Psychiatry Jul;2006 63(7):769–776. [PubMed: 16818866]
42. Dickel DE, Veenstra-VanderWeele J, Cox NJ, et al. Association testing of the positional and functional candidate gene SLC1A1/EAAC1 in early-onset obsessive-compulsive disorder. Arch Gen Psychiatry Jul;2006 63(7):778–785. [PubMed: 16818867]
43. Stewart SE, Fagerness JA, Platko J, et al. Association of the SLC1A1 glutamate transporter gene and obsessive-compulsive disorder. Am J Med Genet B Neuropsychiatr Genet Dec 5;2007 144(8):1027–1033. [PubMed: 17894418]
44. Aoyama K, Suh SW, Hamby AM, et al. Neuronal glutathione deficiency and age-dependent neurodegeneration in the EAAC1 deficient mouse. Nat Neurosci Jan;2006 9(1):119–126. [PubMed: 16311588]
45. Franklin RB, Zou J, Yu Z, Costello LC. EAAC1 is expressed in rat and human prostate epithelial cells; functions as a high-affinity L-aspartate transporter; and is regulated by prolactin and testosterone. BMC Biochem 2006;7:10. [PubMed: 16566829]
46. Guillet BA, Velly LJ, Canolle B, Masmejean FM, Nieoullon AL, Pisano P. Differential regulation by protein kinases of activity and cell surface expression of glutamate transporters in neuron-enriched cultures. Neurochem Int Mar;2005 46(4):337–346. [PubMed: 15707698]
47. Zerangue N, Kavanaugh MP. Interaction of L-cysteine with a human excitatory amino acid transporter. J Physiol Jun 1;1996 493(Pt 2):419–423. [PubMed: 8782106]
48. Rothstein JD, Martin L, Levey AI, et al. Localization of neuronal and glial glutamate transporters. Neuron Sep;1994 13(3):713–725. [PubMed: 7917301]
49. Kanai Y, Smith CP, Hediger MA. A new family of neurotransmitter transporters: the high-affinity glutamate transporters. FASEB J Dec;1993 7(15):1450–1459. [PubMed: 7903261]
50. Nieoullon A, Canolle B, Masmejean F, Guillet B, Pisano P, Lortet S. The neuronal excitatory amino acid transporter EAAC1/EAAT3: does it represent a major actor at the brain excitatory synapse? . J Neurochem Aug;2006 98(4):1007–1018. [PubMed: 16800850]
51. Peghini P, Janzen J, Stoffel W. Glutamate transporter EAAC-1-deficient mice develop dicarboxylic aminoaciduria and behavioral abnormalities but no neurodegeneration. EMBO J Jul 1;1997 16(13): 3822–3832. [PubMed: 9233792]
52. O'Neill, J.; Gorbis, E.; Feusner, J., et al. 1H MRSI study of effects of cognitive-behavioral therapy on obsessive-compulsive disorder. Paper presented at: ISMRM 15th Scientific Meeting and Exhibition; Berlin. 2007.
53. O'Neill, J.; Gorbis, E.; Feusner, J., et al. 1H MRSI study of effects of cognitive-behavioral therapy on obsessive-compulsive disorder. Paper presented at: Organization For Human Brain Mapping; Chicago. 2007.
54. O'Neill, J.; Gorbis, E.; Feusner, J., et al. Effects of cognitive-behavioral therapy on regional neurometabolism in obsessive-compulsive disorder. Paper presented at: ISNR 15th Annual Conference; San Diego. 2007.
55. Zurowski, B.; Fahr, WW.; Freyer, T., et al. Neurochemical abnormalities in patients with obsessive-compulsive disorder diminish in the course of behavior therapy . Paper presented at: Society for Neuroscience 37th Annual Meeting; San Diego. 2007.

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56. Arnold PD, Rosenberg DR, Mundo E, Tharmalingam S, Kennedy JL, Richter MA. Association of a glutamate (NMDA) subunit receptor gene (GRIN2B) with obsessive-compulsive disorder: a preliminary study. Psychopharmacology (Berl) Aug;2004 174(4):530–538. [PubMed: 15083261]
57. Loftis JM, Janowsky A. The N-methyl-D-aspartate receptor subunit NR2B: localization, functional properties, regulation, and clinical implications. Pharmacol Ther Jan;2003 97(1):55–85. [PubMed: 12493535]
58. Li D, He L. Association study between the NMDA receptor 2B subunit gene (GRIN2B) and schizophrenia: a HuGE review and meta-analysis. Genet Med Jan;2007 9(1):4–8. [PubMed: 17224684]
59. Dorval KM, Wigg KG, Crosbie J, et al. Association of the glutamate receptor subunit gene GRIN2B with attention-deficit/hyperactivity disorder. Genes Brain Behav Jul;2007 6(5):444–452. [PubMed: 17010153]
60. Martucci L, Wong AH, De Luca V, et al. N-methyl-D-aspartate receptor NR2B subunit gene GRIN2B in schizophrenia and bipolar disorder: Polymorphisms and mRNA levels. Schizophr Res Jun;2006 84(2–3):214–221. [PubMed: 16549338]
61. Sheng M, Cummings J, Roldan LA, Jan YN, Jan LY. Changing subunit composition of heteromeric NMDA receptors during development of rat cortex. Nature Mar 10;1994 368(6467):144–147. [PubMed: 8139656]
62. Beas-Zarate C, Rivera-Huizar SV, Martinez-Contreras A, Feria-Velasco A, Armendariz-Borunda J. Changes in NMDA-receptor gene expression are associated with neurotoxicity induced neonatally by glutamate in the rat brain. Neurochem Int Jul;2001 39(1):1–10. [PubMed: 11311443]
63. Ueda Y, Doi T, Tsuru N, Tokumaru J, Mitsuyama Y. Expression of glutamate transporters and ionotropic glutamate receptors in GLAST knockout mice. Brain Res Mol Brain Res Aug 15;2002 104(2):120–126. [PubMed: 12225864]
64. Jenike MA. Clinical practice. Obsessive-compulsive disorder. N Engl J Med Jan 15;2004 350(3): 259–265. [PubMed: 14724305]
65. Whiteside SP, Port JD, Deacon BJ, Abramowitz JS. A magnetic resonance spectroscopy investigation of obsessive-compulsive disorder and anxiety. Psychiatry Res Mar 31;2006 146(2):137–147. [PubMed: 16507346]
66. Chakrabarty K, Bhattacharyya S, Christopher R, Khanna S. Glutamatergic dysfunction in OCD. Neuropsychopharmacology Sep;2005 30(9):1735–1740. [PubMed: 15841109]
67. Delorme R, Krebs MO, Chabane N, et al. Frequency and transmission of glutamate receptors GRIK2 and GRIK3 polymorphisms in patients with obsessive compulsive disorder. Neuroreport Mar 22;2004 15(4):699–702. [PubMed: 15094479]
68. Nordstrom EJ, Burton FH. A transgenic model of comorbid Tourette's syndrome and obsessive-compulsive disorder circuitry. Mol Psychiatry 2002;7(6):617–625. 524. [PubMed: 12140785]
69. Pittenger C, Krystal JH, Coric V. Glutamate-modulating drugs as novel pharmacotherapeutic agents in the treatment of obsessive-compulsive disorder. NeuroRx Jan;2006 3(1):69–81. [PubMed: 16490414]
70. Coric V, Milanovic S, Wasylink S, Patel P, Malison R, Krystal JH. Beneficial effects of the antiglutamatergic agent riluzole in a patient diagnosed with obsessive-compulsive disorder and major depressive disorder. Psychopharmacology (Berl) May;2003 167(2):219–220. [PubMed: 12658528]
71. Coric V, Taskiran S, Pittenger C, et al. Riluzole augmentation in treatment-resistant obsessive-compulsive disorder: an open-label trial. Biol Psychiatry Sep 1;2005 58(5):424–428. [PubMed: 15993857]
72. Zarate CA Jr, Payne JL, Quiroz J, et al. An open-label trial of riluzole in patients with treatment-resistant major depression. Am J Psychiatry Jan;2004 161(1):171–174. [PubMed: 14702270]
73. Zarate CA Jr, Quiroz JA, Singh JB, et al. An open-label trial of the glutamate-modulating agent riluzole in combination with lithium for the treatment of bipolar depression. Biol Psychiatry Feb 15;2005 57(4):430–432. [PubMed: 15705360]
74. Sanacora G, Kendell SF, Fenton L, Coric V, Krystal JH. Riluzole augmentation for treatment-resistant depression. Am J Psychiatry Nov;2004 161(11):2132. [PubMed: 15514421]

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75. Sanacora G, Kendell SF, Levin Y, et al. Preliminary evidence of riluzole efficacy in antidepressant-treated patients with residual depressive symptoms. Biol Psychiatry Mar 15;2007 61(6):822–825. [PubMed: 17141740]
76. Bensimon G, Lacomblez L, Meininger V. A controlled trial of riluzole in amyotrophic lateral sclerosis. ALS/Riluzole Study Group. N Engl J Med Mar 3;1994 330(9):585–591. [PubMed: 8302340]
77. Lacomblez L, Bensimon G, Leigh PN, et al. A confirmatory dose-ranging study of riluzole in ALS. ALS/Riluzole Study Group-II. Neurology Dec;1996 47(6 Suppl 4):S242–250. [PubMed: 8959996]
78. Lacomblez L, Bensimon G, Leigh PN, Guillet P, Meininger V. Dose-ranging study of riluzole in amyotrophic lateral sclerosis. Amyotrophic Lateral Sclerosis/Riluzole Study Group II. Lancet May 25;1996 347(9013):1425–1431. [PubMed: 8676624]
79. Stefani A, Spadoni F, Bernardi G. Differential inhibition by riluzole, lamotrigine, and phenytoin of sodium and calcium currents in cortical neurons: implications for neuroprotective strategies. Exp Neurol Sep;1997 147(1):115–122. [PubMed: 9294408]
80. Jehle T, Bauer J, Blauth E, et al. Effects of riluzole on electrically evoked neurotransmitter release. Br J Pharmacol Jul;2000 130(6):1227–1234. [PubMed: 10903959]
81. Urbani A, Belluzzi O. Riluzole inhibits the persistent sodium current in mammalian CNS neurons. Eur J Neurosci Oct;2000 12(10):3567–3574. [PubMed: 11029626]
82. Grant P, Lougee L, Hirschtritt M, Swedo SE. An open-label trial of riluzole, a glutamate antagonist, in children with treatment-resistant obsessive-compulsive disorder. J Child Adolesc Psychopharmacol 2007;17(6):761–767. [PubMed: 18315448]
83. Insel TR, Scolnick EM. Cure therapeutics and strategic prevention: raising the bar for mental health research. Mol Psychiatry Jan;2006 11(1):11–17. [PubMed: 16355250]
84. Insel TR, Quirion R. Psychiatry as a clinical neuroscience discipline. JAMA Nov 2;2005 294(17): 2221–2224. [PubMed: 16264165]
85. Wong DF, Grunder G, Brasic JR. Brain imaging research: does the science serve clinical practice? . Int Rev Psychiatry Oct;2007 19(5):541–558. [PubMed: 17896234]
86. Rosenberg DR, MacMaster FP, Mirza Y, et al. Reduced anterior cingulate glutamate in pediatric major depression: a magnetic resonance spectroscopy study. Biol Psychiatry Nov 1;2005 58(9):700–704. [PubMed: 16084860]
87. Provencher SW. Automatic quantitation of localized in vivo 1H spectra with LCModel. NMR Biomed Jun;2001 14(4):260–264. [PubMed: 11410943]
88. Kanowski M, Kaufmann J, Braun J, Bernarding J, Tempelmann C. Quantitation of simulated short echo time 1H human brain spectra by LCModel and AMARES. Magn Reson Med May;2004 51(5): 904–912. [PubMed: 15122672]
89. Barker PB, Hearshen DO, Boska MD. Single-voxel proton MRS of the human brain at 1.5T and 3.0T. Magn Reson Med May;2001 45(5):765–769. [PubMed: 11323802]
90. Hariri AR, Weinberger DR. Imaging genomics. Br Med Bull 2003;65:259–270. [PubMed: 12697630]
91. Schiffer HH. Glutamate receptor genes: susceptibility factors in schizophrenia and depressive disorders? . Mol Neurobiol Apr;2002 25(2):191–212. [PubMed: 11936559]
92. Martinez-Hernandez A, Bell KP, Norenberg MD. Glutamine synthetase: glial localization in brain. Science Mar 25;1977 195(4284):1356–1358. [PubMed: 14400]
93. Chaudhry FA, Reimer RJ, Krizaj D, et al. Molecular analysis of system N suggests novel physiological roles in nitrogen metabolism and synaptic transmission. Cell Dec 23;1999 99(7):769–780. [PubMed: 10619430]
94. Varoqui H, Zhu H, Yao D, Ming H, Erickson JD. Cloning and functional identification of a neuronal glutamine transporter. J Biol Chem Feb 11;2000 275(6):4049–4054. [PubMed: 10660562]
95. Kvamme E, Torgner IA, Svenneby G. Glutaminase from mammalian tissues. Methods Enzymol 1985;113:241–256. [PubMed: 4088067]
96. Petroff OA, Mattson RH, Rothman DL. Proton MRS: GABA and glutamate. Adv Neurol 2000;83:261–271. [PubMed: 10999208]
97. Szeszko PR, MacMillan S, McMeniman M, et al. Amygdala volume reductions in pediatric patients with obsessive-compulsive disorder treated with paroxetine: preliminary findings. Neuropsychopharmacology Apr;2004 29(4):826–832. [PubMed: 14970831]

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98. Gilbert AR, Keshavan M, Diwadkar VA, et al. Gray matter differences between pediatric obsessive-compulsive disorder patients and high-risk siblings: A preliminary voxel-based morphometry study . Neurosci Lett. In Press

99. Association AP. Diagnostic and statistical manual of psychiatric disorders. Vol. 4. Washington, D.C: American Psychiatric Association; 1994.

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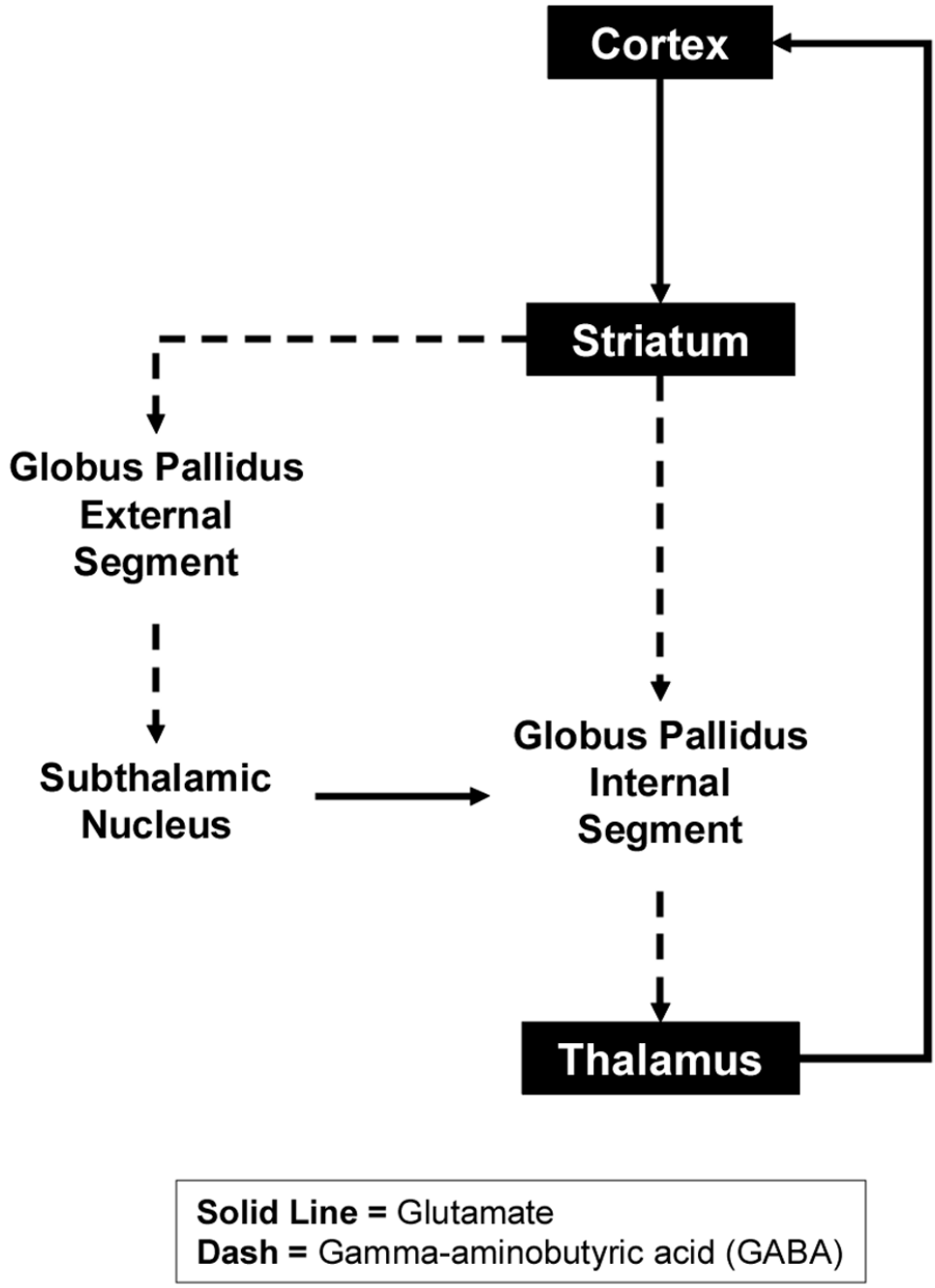

Figure 1.
Basic schematic of the frontal – striatal – thalamic circuit.

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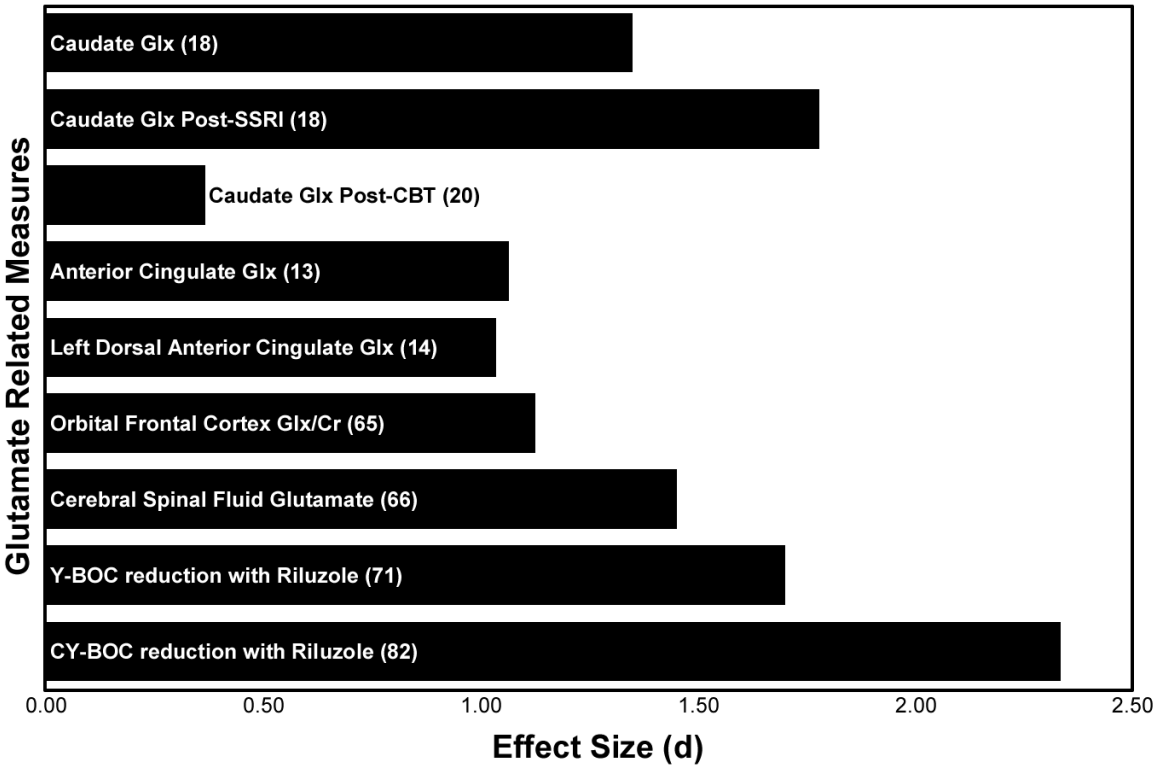

Figure 2.
Graph of the effect sizes (x – axis) for glutamate related measures (y – axis) in obsessive-compulsive disorder.

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Table 1

Summary of Imaging Studies of Pediatric Obsessive-Compulsive Disorder

Study	Sample	Note	Finding
Rosenberg et al [16]	19 OCD 19 Healthy Controls	Treatment naive 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 [28]	21 OCD 21 Healthy Controls	Treatment naive Case-control matched	⇑ Corpus callosum area and all sub-regions (except isthmus) in OCD
MacMaster et al[29]	21 OCD 21 Healthy Controls	Treatment naive Case-control matched	⇓ Genu signal intensity in OCD patients; possibly indicating greater myelinization of region
Rosenberg et al [2]	21 OCD 21 Healthy Controls	Treatment naive Case-control matched	⇑ Anterior cingulate cortex in OCD patients; 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 [18]	11 OCD 11 Post-SSRI 11 Healthy Controls	Treatment naive Paroxetine (12 weeks) Case-control matched	⇑ Caudate Glx concentrations in OCD patients that declined after SSRI treatment. Decrease in striatal Glx was associated with reduction in OCD symptom severity. Occipital Glx did not differ.
Benazon et al [20]	21 OCD 21 Post- Treatment	Treatment naive Cognitive Behavioral Therapy (12 weeks)	No change in caudate Glx concentrations in OCD patients after cognitive behavioral therapy, despite a reduction in symptoms.
Gilbert et al [22]	21 OCD 10 Post-SSRI 21 Healthy Controls	Treatment naive Paroxetine (12 weeks) Case-control matched	⇑ Thalamic volumes in OCD patients that declined after SSRI treatment. Decrease in thalamic volume was associated with reduction in OCD symptom severity.
Rosenberg et al[23]	11 OCD 11 Post- Treatment	Cognitive Behavioral Therapy (12 weeks)	No significant change in thalamic volume was observed in OCD patients after cognitive behavioral therapy.
Fitzgerald et al [24] Rosenberg et al[25]	11 OCD 11 Healthy Controls	Treatment naive Case-control matched	⇓ Medial thalamic NAA/Cho and NAA/Cr in OCD. However, using a validated phantom method to achieve absolute measures, greater choline [25, 26] and creatine [27] were found, calling into question the NAA ratio findings.
Smith et al [26] Mirza et al [27]	27 OCD 18 MDD 18 Healthy Controls	Treatment naive	⇑ Bilateral medial thalamic choline and creatine in OCD compared with both healthy controls and MDD. Medial thalamic choline and creatine concentrations did not differ between MDD and controls.
Russell et al [15]	15 OCD 15 Healthy Controls	Treatment naive Case-control matched	⇑ NAA in left but not right DLPFC in OCD patients. No significant differences in Cho or Cr were observed.
Rosenberg et al[13]	20 OCD 14 MDD 14 Healthy Controls	Treatment naive	⇓ Anterior cingulate Glx in both OCD and MDD patients compared with controls. Glx did not differ between OCD and MDD patients.
Szeszko et al [10]	23 OCD 27 Healthy Controls	Treatment naive	⇓ 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 [97]	11 OCD 11 Post – SSRI 11 Healthy Controls 11 Controls Time 2	Treatment naive Paroxetine (16 weeks) No intervention	Patients demonstrated significant asymmetry of the amygdala (L>R) as compared to controls at baseline. ⇓ Left amygdala volume in OCD patients following 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 healthy comparison subjects between scans.
MacMaster et al[34]	31 OCD 31 Healthy Controls	Treatment naive Case-control matched	⇓ Pituitary in OCD; effect more pronounced in males.

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Study	Sample	Note	Finding
Gilbert et al [98]	10 OCD 10 Siblings 10 Healthy Controls	Treatment naive Unaffected	Using voxel-based morphometry (VBM), OCD showed greater gray matter density in the right putamen as compared to unaffected siblings.
Szeszko et al [9]	37 OCD 26 Healthy Controls	Treatment naive	Using VBM, OCD showed greater gray matter density in the putamen and orbital prefrontal cortex.
Carmona et al [11]	18 OCD 18 Healthy Controls	Matched by gender 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 Healthy Controls	fMRI	During a 'stop' task, OCD showed reduced activation in right orbitofrontal cortex, thalamus and basal ganglia.

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Table 2

Model of Obsessive Compulsive Disorder as compared to Diabetes [83, 84]

Item	Diabetes	Obsessive-Compulsive Disorder
Trigger	Genetics - IDDM1 to IDDM18 (type 1) and CAPN10 and HNF4A (type II) Environment - viruses, early diet, obesity	Genetics – evidence for GRIN2B [56] and SLC1A1 [41–43], more may follow. Environment – stress, unknown
Primary Pathology	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 keytones in urine	⇑ Striatal [18] and orbital frontal glutamate [65]. ⇓ Anterior cingulate glutamate [13]
Behavioral Ramifications	Increased thirst, urination Hunger Weight changes Fatigue Blurred vision	Core DSM Criteria [99] - Recurrent/persistent thoughts, impulses or images Intrusive and inappropriate causing anxiety/stress Repetitive behaviors, driven to perform by obsessions