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NEUROBIOLOGICAL EVIDENCE SUPPORTING GLUTAMATE'S ROLE IN PEDIATRIC OBSESSIVE COMPULSIVE DISORDER

Frank P. MacMaster, PhD and

Assistant Professor, Cuthbertson and Fischer Chair in Pediatric Mental Health, Departments of Psychiatry and Pediatrics, University of Calgary, Calgary, AB, Canada

David R. Rosenberg, MD

Professor, Miriam L. Hamburger Endowed Chair of Child Psychiatry, Department of Psychiatry & Behavioral Neurosciences, Wayne State University, Detroit, MI, USA

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Obsessive-compulsive disorder (OCD) is a major public health problem - among the ten most disabling medical conditions worldwide (Murray & Lopez, 1996). The two fundamental reasons to focus on pediatric OCD are first, that OCD typically has its onset during childhood and adolescence (Pauls, Alsobrook, Goodman, Rasmussen & Leckman, 1995) and second, that pediatric OCD is continuous with adult OCD. The age of onset for pediatric OCD ranges from 9 to 11 years in boys to 11 to 13 years in girls (Hanna, 1995; Riddle *et al.*, 1990), with an earlier age of onset associated with a more negative outcome (Skoog & Skoog, 1999; Stewart *et al.*, 2004). There is a strong genetic component to OCD, with heritability estimates in children and adolescents ranging from 45% to 65% (van Grootheest, Cath, Beekman & Boomsma, 2005).

WHY IS TRANSLATIONAL RESEARCH INTO PEDIATRIC OCD NEEDED?

The two major obstacles for people suffering from OCD are first, getting an accurate diagnosis and second, access to effective treatment (Hollander *et al.*, 1996). At present, the serotonin reuptake inhibitors (SRI) are the only FDA approved medications for OCD. As noted in the companion article, SRIs are of limited positive effect in clinical practice (Jenike, 2004). Given the persistence of symptoms and partial levels of response to SRI treatment, it is apparent that the serotonin model of OCD does not fully account for the underlying neurobiology of the illness. Indeed, our understanding of the neurobiology of OCD has been limited until recently with the advent of non-invasive brain imaging tools.

Correspondence: David R. Rosenberg, M.D., Wayne State University, Psychiatry 9B, 4201 St. Antoine Boulevard, Detroit, MI 48201; Phone: 313-577-9000, FAX: 313-577-5900, drosen@med.wayne.edu.

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CAN BRAIN IMAGING INFORM TRANSLATIONAL RESEARCH?

In psychiatry, the usual strategy has been to go from the pharmacology of a disorder to the pathophysiology of a disorder. Indeed, the development of the serotonin paradigm of OCD is an example of this approach. Serotonergic medications were applied first and a neurophysiological explanation shaped around their effects. Unfortunately, this reverse engineering approach has failed to demonstrate real progress in our understanding of psychiatric illness (*Insel & Scolnick, 2006*). Developing the needed understanding of the physiology of psychiatric disorders has been difficult and access to the living brain remained limited until the development of brain imaging methodologies like magnetic resonance imaging (MRI), spectroscopy (MRS) and functional magnetic resonance imaging (fMRI). In the almost twenty years since the application of modern brain imaging to the study of OCD, tremendous progress has been made. However, getting these advances in our understanding of the disorder from the ‘bench’ to the clinic has been difficult. Translational research faces two hurdles (*Sung et al., 2003*). The first is in translating new understandings of the disorder into novel treatments, diagnostic tools, and prevention. The second is in getting these novel treatments, diagnostic and preventative methods to the clinic. As outlined below, substantial progress has been made in our understanding of the neurobiology of pediatric OCD. These advances, in turn, led to the novel application of agents to treat pediatric OCD - making this one of the rare instances in psychiatric research where knowledge has indeed moved from the ‘bench’ to the ‘bedside’. Whether or not these novel agents will ultimately have a role in the treatment of OCD remains to be seen, but exciting times lay ahead in our efforts to unravel the pathogenetic basis of OCD as it relates to treatment response, or lack thereof.

BASIC NEUROBIOLOGICAL MODEL OF PEDIATRIC OCD

The cortical-striatal-thalamic circuit has been consistently implicated in neurobiological studies of OCD (*Rauch & Savage, 1997; Rosenberg, MacMaster, Mirza, Easter & Buhagiar, 2007*) (see figure 1). 80% of all synapses in the striatum are cortical inputs (*Pasik, Pasik & DiFiglia, 1976*). Cortical regions that project to the striatum can be divided into ‘motor’ and ‘limbic associative’. Motor projections consist of somatosensory, motor, and premotor cortex. More relevant to OCD, the ‘limbic associative’ projections come from the amygdala, hippocampus, orbital frontal, cingulate, parietal, temporal, entorhinal and association cortex (*Mello & Villares, 1997*). One can subdivide the cortical-striatal connections into basic circuit loops: i.e., sensorimotor, oculomotor, dorsal cognitive, ventral cognitive, affective/motivational loops that extend from the cortex to the striatum to the thalamus and back to the cortex (*Rauch & Savage, 1997*). The anatomy and organization of these circuits have been reviewed elsewhere (*Alexander, 1994; Alexander & Crutcher, 1990; Alexander, DeLong & Strick, 1986; Gerfen, 1992a; 1992b; Graybiel, 1990*). These circuits progress in a self-repeating loop through distinct parts of the frontal cortex, basal ganglia, substantia nigra and the thalamus (*Alexander & Crutcher, 1990*). Two of the pathways act to insure appropriate behavioral responses to stimuli (*Alexander & Crutcher, 1990*). First, the “direct” pathway facilitates thalamic stimulation of the cortex. Second, the “indirect” pathway acts to inhibit the thalamus –permitting the cortex to shift sets and respond to new stimuli. In simple terms, OCD may result from excessive neural tone in the direct pathway relative to the indirect pathway.

THE EVIDENCE SUPPORTING GLUTAMATE'S ROLE IN PEDIATRIC OCD PROTON MAGNETIC RESONANCE SPECTROSCOPY STUDIES (1H-MRS)

Glutamate is the core excitatory neurotransmitter of this cortical-striatal-thalamic circuit. Since Rosenberg and Keshavan (*Rosenberg & Keshavan, 1998*) first hypothesized a role for glutamate in pediatric OCD, evidence supporting glutamate abnormalities in OCD has been growing. Using proton magnetic resonance spectroscopy (1H-MRS), Rosenberg et al (2000) found greater striatal glutamatergic (Glx) concentrations in psychotropic naïve pediatric OCD patients as compared to controls. Increased Glx concentrations 'normalized' and returned to levels comparable to healthy pediatric controls after effective treatment with an SSRI. The decrease in striatal Glx concentration was associated with reduction in OCD symptom severity and may carry on after discontinuation of the SSRI (*Bolton, Moore, MacMillan, Stewart & Rosenberg, 2001*). Conversely, CBT - another treatment considered effective for OCD alone or in combination with SRI - did not alter caudate Glx concentrations in pediatric OCD patients despite a significant reduction in symptoms (*Benazon, Moore & Rosenberg, 2003*). In the anterior cingulate, again using single-voxel 1H-MRS, Rosenberg et al (2004) observed lower Glx concentrations in pediatric OCD patients compared to healthy controls. This finding was replicated and extended in adults, where lower than normal anterior cingulate Glx was observed (*Yucel et al., 2008*). In this sample, lower anterior cingulate glutamate correlated with OCD symptom severity. In another sample of adult OCD patients, Whiteside, Port, Deacon and Abramowitz (2006) found greater Glx in orbital frontal white matter in patients as compared to healthy controls. These effects appear to be regional rather than global with no differences noted in the occipital cortex - a brain region not characteristically implicated in the pathophysiology of OCD (*Rosenberg et al., 2000*). In summary numerous in vivo studies of the cortical-striatal-thalamic circuit in OCD have implicated glutamate directly (see figure 2).

ANIMAL MODELS AND PERIPHERAL MARKER STUDIES

Findings from the aforementioned neuroimaging studies have been bolstered by studies using other methods and models. For example, Chakrabarty, Bhattacharyya, Christopher and Khanna (2005) studied the concentration of glutamate in the cerebral spinal fluid (CSF) of 21 psychotropic naïve adults with OCD and 18 healthy controls. In OCD patients, CSF glutamate concentration was significantly greater as compared to control subjects. Furthermore, indirect support for glutamate's association with OCD has been provided by rodent models of obsessive-compulsive (*Nordstrom & Burton, 2002; Welch et al., 2007*) and stereotypic behaviors (*Presti, Watson, Kennedy, Yang & Lewis, 2004*).

GLUTAMATE TRANSPORTER AND RECEPTOR POLYMORPHISMS

Consistent genetic markers have been largely elusive for most psychiatric disorders. In OCD however, three independent groups have observed that the 3' region of the glutamate transporter gene, solute carrier family 1, member 1 (*SLC1A1*), may contain a susceptibility allele for OCD (*Arnold, Sicard, Burroughs, Richter & Kennedy, 2006; Dickel et al., 2006; Stewart et al., 2007*). *SLC1A1*'s protein product is the high-affinity neuronal and epithelial transporter (EAAT3, EAAC1). EAAT3/EAAC1 transports L-glutamate, L- and D-aspartate,

and cysteine (Aoyama *et al.*, 2006; Franklin, Zou, Yu & Costello, 2006). EAAT3/EAAC1 is located in cortex, basal ganglia, and hippocampus, and all parts of the neuron (Guillet *et al.*, 2005). Glutamate transport keeps extracellular glutamate below neurotoxic concentrations in adults (Kanai, Smith & Hediger, 1993). Interestingly, EAAT3/EAAC1 makes only a minor contribution to the removal of synaptic glutamate when compared to EAAT1 and EAAT2 (Nieoullon *et al.*, 2006). In initial brain development, EAAT3/EAAC1 is expressed before astrocytes are functional. This suggests that EAAT3/EAAC1 plays a role in the developmental function of glutamate (Nieoullon *et al.*, 2006). The expression of EAAT3/EAAC1 is regulated by testosterone and prolactin (Franklin *et al.*, 2006). Testosterone increasing expression of EAAT3/EAAC1 is consistent with the association of OCD with *SLC1A1* being most robust in males (Arnold *et al.*, 2006; Dickel *et al.*, 2006). With regard to the possible function of the polymorphism, it has been noted that mice deficient in EAAC1 develop impaired self-grooming (Aoyama *et al.*, 2006). This is suggestive that EAAT3/EAAC1 changes in pediatric OCD may be associated with increased EAAT3/EAAC1 expression. Interestingly, the *SLC1A1* rs3056 variant was associated with increased total, left and right thalamic volume (Arnold *et al.*, 2009b).

The 5072T/G variant (5072G–5988T haplotype) of N-methyl-D-aspartic acid (NMDA) subunit 2B gene (*GRIN2B*) has also been associated with OCD in pediatric patients (Arnold *et al.*, 2004). *GRIN2B*, found on chromosome 12p, encodes for the NR2B subunit of the NMDA receptor. Consistent with regions demonstrating glutamatergic abnormalities in pediatric OCD patients (Rosenberg *et al.*, 2000; Rosenberg *et al.*, 2004), it is expressed mainly in the striatum and the prefrontal cortex (Loftis & Janowsky, 2003). *GRIN2B* has also been linked to attention deficit hyperactivity disorder (Dorval *et al.*, 2007), schizophrenia (Li & He, 2007), and bipolar disorder (Martucci *et al.*, 2006). During brain development, *GRIN2B* plays a role in plasticity (Sheng, Cummings, Roldan, Jan & Jan, 1994). Furthermore, neurotoxic levels of glutamate in the neonatal period cause an increase in the expression of NMDA NR2B in the striatum and cortex (Beas-Zarate, Rivera-Huizar, Martinez-Contreras, Feria-Velasco & Armendariz-Borunda, 2001). With regard to function, the increased expression of *GRIN2B* in reaction to excess glutamate (Ueda, Doi, Tsuru, Tokumaru & Mitsuyama, 2002) is suggestive that pediatric OCD is associated with greater, rather than lesser *GRIN2B* expression in the striatum. A significant association has also been identified between the rs1019385 polymorphism of *GRIN2B* and decreased anterior cingulate cortex Glx, but not occipital Glx, in pediatric OCD patients (Arnold *et al.*, 2009a). Furthermore, the rs1805476 variant of *GRIN2B* was associated with left but not right orbital frontal cortex and right but not left anterior cingulate cortex volume (Arnold *et al.*, 2009b).

LIMITATIONS TO THE GLUTAMATE HYPOTHESIS

Of course, a single neurochemical hypothesis of a psychiatric disorder is limited, as neurotransmitters often operate in concert. The response of OCD patients to SSRI's has spawned the "serotonin" hypothesis of OCD and there is also supporting neurobiological evidence (Sallee, Richman, Beach, Sethuraman & Nesbitt, 1996). In spite of this, the persistence of OCD symptoms despite serotonin-based interventions demonstrates the limits of the serotonin hypothesis (Geller, 2007; Jenike, 2004). Furthermore, glutamate and serotonin interact in the frontal striatal circuit (Becquet, Faudon & Hery, 1990).

CONCLUSIONS

In the twelve years since the glutamate hypothesis was first proposed, there is converging biological evidence supporting the role of glutamate in the symptoms of OCD (Arnold *et al.*, 2006; Arnold *et al.*, 2004; Chakrabarty *et al.*, 2005; Delorme *et al.*, 2004; Dickel *et al.*, 2006; Nordstrom & Burton, 2002; Rosenberg *et al.*, 2000; Rosenberg *et al.*, 2004; Stewart *et al.*, 2007; Whiteside *et al.*, 2006) (see figure 3). As seen in the companion piece to this review, pharmacologically modulating glutamate has been shown to have an effect on OCD symptoms (Coric *et al.*, 2003; Coric *et al.*, 2005; Grant, Lougee, Hirschtritt & Swedo, 2007). In summary, 1H-MRS, CSF, genetic, animal and clinical studies have all implicated glutamate in OCD, indicating a clear link between glutamate and OCD. The ongoing work on the glutamate hypothesis in pediatric OCD is a strong example of Dr. Tomas Insel's call for "rational therapeutics" for psychiatric illness (Society for Biological Psychiatry, 2008). The usual strategy of going from pharmacology to pathophysiology failed to advance the understanding and treatment of psychiatric illness (Insel & Scolnick, 2006). New approaches - moving from in vivo neurobiology to treatment - may allow for progress that is more substantial.

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Figure 1.
The cortical-striatal-thalamic circuit implicated in neurobiological studies of obsessive-compulsive disorder.

Figure 2.

Findings from in vivo proton spectroscopy studies of obsessive-compulsive disorder. Glx = glutamate/glutamine

Figure 3. Summary schematic of the convergence of research methods used to examine the role of glutamate in obsessive-compulsive disorder.