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The role of glutamate signaling in the pathogenesis and treatment of obsessive–compulsive disorder

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ABSTRACT

Obsessive–compulsive disorder (OCD) is a common and often debilitating neuropsychiatric condition characterized by persistent intrusive thoughts (obsessions), repetitive ritualistic behaviors (compulsions) and excessive anxiety. While the neurobiology and etiology of OCD has not been fully elucidated, there is growing evidence that disrupted neurotransmission of glutamate within corticalstriatal–thalamocortical (CSTC) circuitry plays a role in OCD pathogenesis. This review summarizes the findings from neuroimaging, animal model, candidate gene and treatment studies in the context of glutamate signaling dysfunction in OCD. First, studies using magnetic resonance spectroscopy are reviewed demonstrating altered glutamate concentrations in the caudate and anterior cingulate cortex of patients with OCD. Second, knockout mouse models, particularly the DLGAP3 and Sltrk5 knockout mouse models, display remarkably similar phenotypes of compulsive grooming behavior associated with glutamate signaling dysfunction. Third, candidate gene studies have identified associations between variants in glutamate system genes and OCD, particularly for SLC1A1 which has been shown to be associated with OCD in five independent studies. This converging evidence for a role of glutamate in OCD has led to the development of novel treatment strategies involving glutamatergic compounds, particularly riluzole and memantine. We conclude the review by outlining a glutamate hypothesis for OCD, which we hope will inform further research into etiology and treatment for this severe neuropsychiatric condition.

1. Introduction

Obsessive–compulsive disorder (OCD) is a common, multidimensional, and often debilitating neuropsychiatric condition that affects 1–3% of the population worldwide (Kessler et al., 2005; Ruscio et al., 2010). The symptoms of OCD are characterized by persistent intrusive thoughts (obsessions), repetitive ritualistic behaviors (compulsions) and excessive anxiety (Calvocoressi et al., 1998). First line treatment for OCD includes pharmacotherapy and/or Cognitive Behavioral Therapy (CBT). CBT is at least as effective as pharmacotherapy in children and adults (Franklin and Foa, 2011). Current first line medications for OCD are the selective serotonin reuptake inhibitors (SSRIs) and clomipramine (SSRIs and clomipramine are classified together in general as "serotonin reuptake inhibitors" or SRIs to reflect their predominantly serotonergic mechanism of action). However only 40 to 50% of patients respond to current medications and those who do may continue to remain significantly impaired by their symptoms ("partial response") (Franklin and Foa, 2011). Furthermore, increasing concerns have been raised about potential adverse effects of SSRIs (e.g. behavioural activation in children for SRIs generally and more recently QT prolongation with citalopram). Despite the clear need for new and better targeted therapies, there has not been a novel class of medication approved for OCD since the early 1990s, and improved understanding of the neurobiology and etiology of OCD is needed in order to develop better treatment options.

While little is known about the neurobiology and etiology of OCD, there is strong evidence suggesting that it has a genetic basis. Twin studies reveal a higher concordance of OCD in monozygotic twins (80–87%) than in dizygotic twins (47–50%) (van Grootheest et al., 2005). Family and twin studies suggest an even stronger genetic component in pediatric OCD. In two controlled family studies using pediatric probands, the lifetime prevalence of OCD was significantly higher in case compared with control relatives (Hanna et al., 2005: 22.5% vs. 2.6%, do Rosario-Campos et al., 2005: 22.7% vs. 0.9%). The odds ratios from these two studies of 11.1 and 32.0 respectively are considerably higher than those reported in family studies with adult probands (Hettema et al., 2001). Twin studies provide heritability estimates for OCD symptoms in children ranging from 45% to 65%

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(van Grootheest et al., 2005). Thus, genetic factors appear to have a substantial role in the etiology of early-onset OCD.

Multiple lines of evidence implicate dysfunction within cortical–striatal–thalamocortical (CSTC) circuitry in OCD. Glutamate is the primary neurotransmitter within cortico-striatal-thalamic circuits (Bronstein and Cummings, 2001) with the majority of axon terminals in the striatum being glutamatergic (Parent and Hazrati, 1995). Increasing evidence has shown that the neurotransmission of glutamate within CTSC circuits is disrupted in OCD (see previous reviews: Ting and Feng, 2008; MacMaster, 2010; Rotge et al., 2010). This review will provide an updated highlight of the findings gathered from neuroimaging, animal model, candidate gene and novel treatment development studies in the context of glutamate signaling dysfunction, as well as to provide an overview of the current treatments of OCD that target the glutamate system. We will conclude by presenting a proposed model for how glutamate dysfunction may lead to development of this common and debilitating neuropsychiatric condition.

1.1. Neuroimaging studies

Proton magnetic resonance spectroscopy (^{1}H MRS) has provided a powerful tool for in vivo evaluation of glutamate function in OCD. Using ^{1}H MRS, studies in psychotropic-naive children with OCD patients have revealed greater left but not right caudate glutamatergic (Glx) concentrations (Rosenberg et al., 2000; Starck et al., 2008) and lower anterior cingulate cortex (ACC) Glx in pediatric and adult OCD patients regardless of medication status (Rosenberg et al., 2004; Yucel et al., 2008). Greater orbital frontal Glx has also been reported in adults with OCD (Whiteside et al., 2006). Reduced ACC Glx and increased caudate Glx in pediatric OCD patients may be consistent with a prior report of inverse correlations in OCD patients between ACC and striatal volume (Rosenberg and Keshavan, 1998). Glutamate plays an important role in ACC with high concentrations of Glu receptors compared to other neurotransmitter binding sites (Bozkurt et al., 2005). Taken together, these findings suggest a possible tonic–phasic dysregulation of Glx within cortico-striatal circuitry in OCD with reduced tonic Glx in ACC combined with phasic overactivity in the striatum and orbitofrontal cortex (Rosenberg et al., 2004). Further work using ^{1}H MRS is needed using more advanced imaging methods. In particular, early studies were limited by use of 1.5 Tesla (T) MRS, which enables measurement of Glx, a multi-peak signal including glutamate, glutamine, and gamma-amino butyric acid (GABA) rather than glutamate alone. Although Glx may be a reasonable proxy for glutamate (Provencher, 1993; Rosenberg et al., 2005) there is consensus in the field that the subcomponents of Glx are best resolved at higher field. Studies from our own group (unpublished reports) and others using higher field magnets have produced findings consistent with the earlier reports although definitive conclusions are premature until larger sample studies have been analyzed.

1.2. Evidence from cerebrospinal fluid (CSF) studies

Further evidence for glutamatergic dysfunction in OCD comes from two studies on overlapping samples measuring levels of glutamate (and other amino acids) in cerebrospinal fluid (CSF) of OCD patients and matched psychiatrically normal controls (Chakrabarty et al., 2005; Bhattacharyya et al., 2009). In the first study, the CSF of 21 adult drug-naive OCD patients and 18 normal controls were examined. Glutamate concentrations in the CSF of OCD patients were significantly higher compared to normal controls. Furthermore, there were no effects of gender, age, duration of illness, or severity on the CSF glutamate levels. In the second study, the same group of investigators conducted a more comprehensive study on patients over the age of 15, including measurement of additional amino acids (GABA, taurine and glycine) in CSF and measurement of auto-antibodies directed against the basal ganglia (BG) and thalamus assayed in both the CSF and serum (Bhattacharyya et al., 2009). In addition to glutamate, they reported that glycine (a co-agonist of glutamate at NMDA receptors) was elevated in OCD patients compared with controls. Interestingly, the elevated glycine in OCD patients appeared to be entirely driven by patients who also had autoantibodies to BG or thalamus, suggesting a possible auto-immune mechanism driving the changes in glutamate and glycine. Although needing replication in larger samples, the CSF results are in line with ^{1}H MRS findings of altered Glx in various regions of the brain, suggesting that glutamate abnormalities may contribute to development of OCD.

1.3. Animal models

Several animal models have been developed for OCD using ethological, pharmacological, genetic and behavioural approaches. The use of genetic models (transgenic and knockout mice) in particular holds great promise for furthering our understanding of the neurophysiology of OCD. Since the specific genetic disruption is known a priori, investigators may conduct follow up studies using complementary approaches such as molecular genetic studies in humans. On the other hand, using animal models to identify candidate genes for human studies has two major limitations. First, in rodent models we are limited to grooming and other behaviors in which it is impossible to determine the subjective experience of the animal motivating the behaviour (Abramowitz et al., 2011). Validity of OCD animal models is increased when there is evidence for concurrent anxiety (increased face validity) or biological evidence of cortico-striatal dysfunction (construct validity). Second, conventional approaches in model organisms, such as "knocking out" a gene may not reflect more subtle changes in gene expression that are likely to be implicated in complex traits. Despite these limitations, there has been a recent proliferation in findings that may shed light on the manner in which glutamate dysfunction may lead to obsessive–compulsive symptoms. Here we review putative genetic animal models of OCD with mutations affecting glutamate neurotransmission, and also describe evidence for glutamate signaling abnormalities in a well-established behavioural model. For a more thorough review of animal models in OCD, we refer the reader to the growing number of excellent review articles that have been published recently (Ting and Feng, 2011; Albelda and Joel, 2011; Yang and Lu, 2011; Langen et al., 2011).

1.3.1. D1CT-7 transgenic mice

Generated by Campbell et al. (1999), D1CT-7 transgenic mice represent the first genetic mouse model for OCD and express an intracellular form of cholera toxin (CT) under the control of the D1 promoter. The CT toxin is a neuropotentiating agent that chronically activates stimulatory G-protein (Gs) signal transduction and cAMP synthesis. The use of D1 promoter restricts CT expression to D1 dopamine receptor subtype positive (D1+) neurons.

D1CT-7 mice display a constellation of compulsive behaviors including episodes of repetition or perseverance of normal behaviors, repetitive nonaggressive biting of siblings and repetitive leaping (Campbell et al., 1999). Furthermore, D1CT-7 mice also display tic-like movements with juvenile onset, which are increased in complexity and number compared with wild-type mice, can occur in flurries, and are more prevalent in males. These features suggest the suitability of the DICT-7 mouse as a model for Tourette's Syndrome (TS), a disorder that frequently co-occurs with OCD in humans (Nordstrom and Burton, 2002). Since the expression of CT in the brain of these mice overlaps with regions implicated with OCD, the authors suggest that chronic potentiation of D1+ neurons leads to over-activation of glutamatergic output to the striatum. This glutamatergic over-activation then induces complex compulsive behaviour similar to OCD in humans. Although the increase of glutamatergic output is not directly established, adding a non-competitive NMDA receptor antagonist that indirectly stimulates cortical-limbic glutamate output has been show to increase compulsive-like behaviour in the D1CT-7 model (McGrath et al., 2000).

1.3.2. Dlgap3 (SAPAP3) knock-out mice

SAP90/PSD95-associated proteins (SAPAP) are a family of proteins that form scaffolding complexes to regulate the trafficking and targeting of neurotransmitters to the post-synaptic membrane during excitatory synaptic transmission. Furthermore, the PSD95 family proteins are known to regulate the trafficking of both AMPA and NMDA types of glutamate receptors (Welch et al., 2007). DLGAP3, alternatively named SAPAP3, is the only member of the family that is highly expressed in striatum, a region implicated in OCD. Welch et al. (2007) showed that mice with DLGAP3 deletions knocking out the gene displayed OCD-like behaviour consisting of compulsive grooming behaviour leading to facial hair loss and skin lesions. Furthermore, the knockout mice displayed anxiety-like phenotypes on the open field, dark–light emergent and elevated zero maze tests. The anxiety phenotype strengthens the face validity of the repetitive grooming behaviors for human OCD-spectrum disorders, in which anxiety plays a prominent role.

DLGAP3 knockout mice were found to have changes in NMDA receptor composition including increased NR1 (*GRIN1*), NR2B (*GRIN2B*) subunits and decreased NR2A (*GRIN2A*) subunits in the postsynaptic density (PSD) of striatal neurons, as well as reduced cortical–striatal transmission. Their evidence suggests that defects in cortical–striatal neurotransmission, where glutamate served as the primary excitatory neurotransmitter, may contribute to the compulsive behaviors in these mice. In addition to OCD, these behaviors have good face validity for human grooming disorders, such as trichotillomania (compulsive hair pulling), which frequently co-occur with OCD and are considered by many to form part of an OCD "spectrum" of disorders (Feusner et al., 2009a). In the *DLGAP3* knockouts, the expression of the gene in the striatum using lentiviral vectors rescued the synaptic defect and OCD-like behaviour, suggesting that the absence of *DLGAP3* is the cause of the synaptic and behavioural phenotypes (Welch et al., 2007).

1.3.3. Slitrk5 knock-out mice

Recently, another mouse model demonstrated that impaired cortical–striatal circuitry and associated glutamate abnormalities can lead to OCD-like behaviors. Shmelkov et al. (2010) generated KO mice with deletions in the *Sltrk5* gene, an experiment which was suggested by human genetic studies that showed association between *Sltrk1* and TS (Abelson et al., 2005). They found behavioural phenotypes in these mice which were similar compared to the *DLGAP3* KO mice, specifically older *Sltrk5* −/− mice showed facial hair loss and severe skin lesions due to excessive grooming. Although the function of *Slitrk5* remains largely unknown, Shmelkov et al. (2010) showed that it is predominanly expressed in neural tissues in a variety of regions including the cortex and striatum. Finally, the evaluation of histology, function and anatomy of cortex and striatum in these mice revealed increased orbital frontal cortex activity, reduced striatal volume and altered expression of glutamate receptor subunits NR2A, NR2B, GluR1, and GluR2 (Shmelkov et al., 2010), consistent with the hypothesis of altered cortical–striatal transmission in OCD patients.

Although the phenotype was remarkably similar to the *DLGAP3* knockout mice, there were important differences that must be considered when formulating models of how glutamate dysfunction within CSTC circuits may lead to OCD. For example, striatal expression of both NR2A and NR2B subunits was reduced in the *SLTRK5* knockouts, whereas in *DLGAP3* knockout mice the expression of NR2A was reduced but NR2B expression was increased. The difference in glutamate receptor composition alterations between the two models are difficult to explain. However there were differences in the structural consequences of knocking out *SLITRK5* and *DLGAP3* which may be linked with their different influences on NMDA subunit composition as either cause or consequence. For example, *SLTRK5* knockout mice had structural changes in the striatum compared with their wildtype counterparts including reduced striatal volume and decreased dendritic complexity of medium spiny neurons, neither of which were found in DLGAP3 knockout mice (Shmelkov et al., 2010; Welch et al., 2007). Despite the differences in structural and functional effects, the behavioural similarities of these knockout mice remain striking and both models support a pivotal role of altered cortical–striatal glutamate neurotransmission in OCD.

1.3.4. Signal attenuation model

The signal attenuation model is another animal model that has interesting implications for glutamate signaling in OCD. In this behavioural paradigm, rats continue to engage in lever pressing during extinction training, after the attenuation of an external signal associated with food and without an accompanying effort to obtain a reward (Joel et al., 2004). The lever pressing in this experiment is postulated as a model of the excessive and unreasonable behaviour that characterizes human OCD. The compulsive lever pressing is reduced by SSRIs, but not by drugs known to be less effective for human OCD such as desipramine and diazepam (Joel et al., 2004). Interestingly, rats in this model that are treated with D-cycloserine (DCS), an NMDA receptor agonist, display decreased compulsive lever pressing; whereas the treatment of MK 801, an NMDA antagonist, has no effect on lever pressing (Albelda et al., 2010). Based on these findings, the authors hypothesized that under normal physiological conditions, NMDA receptor activity does not play a role in the production of compulsive behaviors. However, pharmacological activation of these receptors may exert an anti-compulsive effect (Albelda et al., 2010).

1.4. Genetic association studies in humans with OCD

The glutamate hypothesis suggests that genes involved in glutamatergic neurotransmission are good candidates for genetic association studies. Based on evidence from animal models, neuroimaging studies and prior genome-wide linkage studies, several investigators have studied specific candidate genes in the glutamate system using a genetic association approach.

1.4.1. SLC1A1

Solute Carrier, Family 1, Member 1 (*SLC1A1*), which codes for the neuronal glutamate transporter excitatory amino acid carrier 1 (EAAC1/EAAT3), represents one of the most well-supported candidate genes for OCD. In the first genome-wide linkage study of OCD, Hanna et al. (2002) examined 56 family members from seven pedigrees ascertained through pediatric probands. Using 349 microsatellite markers, the strongest signal was on the chromosomal region 9p24, with a multipoint LOD score of 2.25. This finding was replicated in a separate linkage study by Willour et al. (2004) in which markers were typed only in the 9p24 region in 50 pedigrees with OCD. While the 9p24 region contains many known genes, *SLC1A1* is the only gene with obvious glutamatergic effects in the brain. Furthermore, *SLC1A1* is highly expressed in the cerebral cortex, striatum and thalamus, which are the brain regions implicated in the CSTC model (Kanai and Hediger, 2004; Arnold et al., 2006). As a follow up to the linkage studies, five independent family-based association studies (Arnold et al., 2006; Dickel et al., 2006; Stewart et al., 2007; Shugart et al., 2009; Samuels et al., 2011) and one case–control study (Wendland et al., 2009) found that *SLC1A1* may contain a susceptibility allele for OCD. The four family-based studies more specifically implicated the 3′ region of the gene and reported that the associations were male-specific after stratifying for gender. Our group has conducted a meta-analysis of published and unpublished data from multiple OCD populations, and preliminary results suggest that no single *SLC1A1* allele is associated with OCD across samples (E. Stewart et al., unpublished results).

The consistency of positive associations for the gene combined with lack of consistency for single variants suggest substantial allelic

heterogeneity (different variants within a single locus or gene causing a disorder) which may include multiple, as yet undiscovered rare variants in *SLC1A1*, or non-allelic (locus) heterogeneity involving other brain-expressed genes in the 9p24 linkage region . Our group and others are beginning to search for rare variants of large effect which are more likely to be of causal significance, even if present only in subset of OCD patients. Rare variants identified to date include a rare 11 bp deletion located just 3′ of SLC1A1 (Dickel et al., 2006) and a single rare SNP identified through mutation screening of over 300 OCD patients (Wang et al., 2010). In addition, a recent study of dicarboxylic aminoaciduria, a rare autosomal recessive renal disorder, identified rare mutations in *SLC1A1*, which were shown to impede glutamate transport in the kidney mediated by the EAAC1 protein expressed in the kidney. One of the probands in this study had longstanding behaviors strongly suggestive of obsessive–compulsive traits, although he declined formal evaluation for OCD. This individual harbored a coding mutation in exon 12 of *SLC1A1*, in close proximity to common variants previously identified in earlier studies of OCD (Arnold et al., 2006; Wendland et al., 2009). There are no reports of sequencing the entire *SLC1A1* gene in a sample of OCD-affected individuals, an approach which is now feasible with "next-generation" sequencing methods and should be applied to *SLC1A1* and other top glutamate candidate genes in OCD.

1.4.2. GRIN2B

GRIN2B, which codes for the NR2B subunit of NMDA receptors, has been associated with OCD, although it has not been studied as extensively as *SLC1A1*. *GRIN2B* is located on chromosome 12p and expressed at relatively high levels in the striatum and the prefrontal cortex, which are regions with reported glutamatergic abnormalities in neuroimaging studies of OCD (Arnold et al., 2004). In a preliminary study, Arnold et al. (2004) found a significant association between OCD and variants within a specific 3′ untranslated region in *GRIN2B*, as well as an even stronger association with a haplotype block in the same region. An independent group has also reported association between GRIN2B variation and OCD, although the specific polymorphisms and haplotypes differed (Stewart et al., 2008). In a study of glutamatergic concentration (measured using ^{1}H MRS) in children with OCD, Arnold et al. (2009b) found a significant association between a *GRIN2B* single nucleotide polymorphism and glutamatergic concentration in the ACC but not the occipital cortex. These findings were consistent with the previously reported ^{1}H MRS findings of decreased glutamatergic concentration in the ACC of OCD patients, with the "risk" variant found more commonly in OCD patients correlating with the "risk" phenotype of decreased ACC glutamatergic concentration (Arnold et al., 2009b).

1.4.3. GRIK2/GRIK3

Like NMDA receptors, kainate receptors are a subtype of the ionotropic glutamate receptor family. They are highly expressed in the CNS and have been implicated in various brain functions (Jane et al., 2009). *GRIK2* and *GRIK3* encode for subunits 2 and 3 of kainate receptors and have been implicated in genetic association studies of autism and schizophrenia (Jamain et al., 2002; Ahmad et al., 2009; Begni et al., 2002). Delorme et al. (2004) reported that *GRIK2* SNP I867 (rs2227283), which has previously been associated with autism, was undertransmitted in OCD trios, supporting a functional role for this variant. To follow up on the finding in *GRIK2*, Sampaio et al. (2010) studied 47 OCD probands and their parents in a family-based genetic association study. While they did not replicate the findings from the Delorme study, they found a different polymorphism, rs1556995 and a two marker haplotype rs1556995/rs1417182 significantly associated with OCD. Since there have only been two studies reporting the association between *GRIK2* and OCD, further studies using independent and larger samples are needed.

1.4.4. DLGAP3

Based on the promising *DLGAP3* KO mouse model (Welch et al., 2007), a large family based association study with 1600 participants (383 families) was conducted to examine the role of *DLGAP3* in OCD and grooming disorders (GD) (Bienvenu et al., 2009). Grooming disorders in this study included trichotillomania (TTM), pathological nail biting, and pathological skin picking. Six common SNPs were genotyped in this study. No association was found between *DLGAP3* and OCD. Two of the six SNPs showed nominal association with various forms of GD (Bienvenu et al., 2009). Using a similar study design and sample size (1575 subjects from 308 families recruited from six different sites), Arnold et.al recently reported (at the World Congress of Psychiatric Genetics, 2009) nominal association between sequence variation in or near the *DLGAP3* gene and OCD.

Using a different approach, Zuchner et al. (2009) resequenced *DLGAP3* in patients with OCD and trichotillomania (TTM), resulting in detection of seven novel nonsynonymous heterozygous variants (Zuchner et al., 2009). Since each variant was rare, these investigators conducted a pooled analysis to determine the proportion of case and control individuals who were heterozygous for at least one novel variant. This analysis revealed that a significantly greater proportion of TTM/OCD patients had at least one rare variant (4.2% of cases vs. 1.1% of controls). The majority of the variants were missense mutations, and therefore more likely to directly affect the function of the gene and subsequent development of OCD and TTM than the common SNPs (with unknown function) identified in the other studies of this gene. Further validation in larger samples is required to determine whether other OCD patients harbor rare variants in *DLGAP3*, and additional study will be required to determine the functional significance of rare variants in this gene.

1.4.5. Summary of genetic evidence

In summary, there is good evidence that *SLC1A1* variation is implicated in OCD, with multiple studies identifying associations with SNPs in this gene. However, the actual SNPs associated with OCD have been inconsistent across studies. This lack of consistency of SNP associations may be due to the fact that variants conferring risk to OCD are relatively rare and vary between populations (multiple rare variant hypothesis), suggesting that further studies including targeted sequencing are warranted. Other genes, including *GRIN2B*, *GRIK2*, and *DLGAP3* may be associated with OCD but require further studies in larger samples. Ultimately, whole genome approaches (genome-wide association, whole exome and whole genome sequencing) should reveal whether glutamate system genes are implicated in OCD and, if so which genes should be further examined in functional studies, both in vitro and in animal models. An international collaborative genome-wide association study (GWAS) of OCD, currently underway should suggest common variants associated with OCD, although recent experience with genetics of complex traits suggests that the common variants covered by GWAS SNP arrays typically have very small effect sizes in common disorders and therefore require very large sample sizes (thousands of subjects) to detect. The problem of small effect sizes for common variants may be partly addressed by studying endophenotypes, heritable biological markers with large effects on phenotype. Our group is currently conducting studies, based on the glutamate hypothesis, in which we are genotyping children with OCD and matched controls with regional glutamatergic concentrations measured using ^{1}H MRS (Arnold et al., 2009a,b). Ultimately, whole exome or whole-genome sequencing approaches and analyses of copy number variants (CNVs) may be required to identify a broader spectrum of both common and rare genetic variants in OCD. Until whole-genome data is available we will continue to be constrained by very limited a priori evidence regarding which glutamate genes are most likely to be relevant to OCD. Whole-genome approaches are becoming technologically feasible with the advent of increasingly dense genotyping arrays

(enabling CNV detection) and next-generation sequencing methods. Continuing advances in technology and genomic statistical approaches, combined with further decreases in costs, will make large-scale sequencing studies increasingly commonplace over the next 5 to 10 years.

Finally, another promising area of future research is epigenetic mechanisms, which may include DNA methylation or other DNA modifications that are distinct from primary DNA nucleotide sequence changes but that can influence gene expression and be influenced by environmental stimuli. Epigenetic factors have been demonstrated to play key roles in other neuropsychiatric disorders as well as normal brain processes (Graff et al., 2011). Epigenetic mechanisms have not yet been systematically investigated in OCD, and represent a particularly interesting line of inquiry as they may help explain how genes and environment (e.g. early life stressors, infection) can interact in the development of obsessive–compulsive symptoms (Real et al., 2011).

1.4.6. Autoimmune hypothesis

Autoimmune factors have been postulated to play a role in the pathogenesis of OCD, and recently there have been some reports suggesting that autoimmune factors may combine with glutamate dysfunction in predisposing individuals to develop OC symptoms. Some of the most compelling evidence for immune factors in OCD comes from studies of putative subtype of OCD and other childhood neuropsychiatric disorders known as Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS) (Murphy et al., 2011). Swedo et al. (1998) first described a detailed case series of 50 children with OCD temporally related to streptococcal infections. This syndrome is believed to be triggered by the production of auto-antibodies that react with proteins in the basal ganglia following Group A beta-hemolytic Streptococcal (GABHS) infection, although investigators have not yet been able to definitively identify autoantibodies in PANDAS (e.g. Brilot et al., 2011).

Although much remains to be learned about PANDAS, interest in this subgroup of OCD cases has triggered a more general search for autoimmune factors in OCD with some suggestive results. The role of glutamate as a regulator of T-cell function (Pacheco et al., 2007), may provide the missing link between the glutamate and autoimmune hypotheses and lead to a more comprehensive explanatory model (as proposed by Rotge et al., 2010 in a comprehensive review of this subject). Two other preliminary lines of evidence suggest that further research in this area as warranted. Firstly, as noted above, elevated glycine in s study of the CSF of OCD patients appeared to be entirely driven by patients who also had autoantibodies to BG or thalamus, suggesting a possible auto-immune mechanism driving changes in glutamate and glycine (Bhattacharyya et al., 2009). Secondly, in another study, a German research group identified circulating immune complexes (CICs) specific to Borna disease virus (BDV-CICs), an infectious agent known to increase extracellular glutamate in the striatum in patients with mood disorders and OCD (Bode et al., 1996, 2001; Ovanesov et al., 2007). These same investigators went on to demonstrate that levels of these CICs distinguished OCD patients compared with controls, and also correlated with event-related brain potentials over the anterior cingulate cortex during performance of a Go/NoGo task (Dietrich et al., 2005). In summary, it is possible that genetic variation in glutamate system genes may interact with immunological reactions to infectious agents, which may then result in cortical–thalamic alterations that lead OCD symptoms (for a detailed review of this hypothesis, see Rotge et al., 2010). Investigation of this intriguing hypothesis will require independent replication of the initial findings on which it is based (e.g. the BDV studies) and studies of larger samples in which detailed genetic and immunological data is collected from the same OCD patients.

1.5. Pharmacological evidence

Given multiple lines of evidence implicating glutamatergic dysfunction in the pathophysiology of OCD, investigators have shown increasing interest in the use of glutamate targeting agents for the treatment of OCD (Pittenger et al., 2006). While serotonin reuptake inhibitors (SRI) still remain the first line pharmacological treatment, evidence has been accumulating in recent years for the potential effectiveness of agents which modulate glutamatergic activity. Here we provide a brief overview of some preliminary clinical studies of glutamatergic agents in OCD.

1.5.1. Riluzole

Riluzole is approved by the FDA for the treatment of Amyotrophic Lateral Sclerosis (ALS). It is thought to reduce glutamatergic neurotransmission through the inhibition of voltage-dependent sodium channels (Urbani and Belluzzi, 2000) and the inhibition of P/Q-type calcium channels at the axon terminal, thereby inhibiting synaptic glutamate release (Wang et al., 2004) and stimulating glutamate uptake by astrocytes (Frizzo et al., 2004). Several open-label trials have been conducted on riluzole augmentation therapy for both adult and pediatric OCD patients and found riluzole to be effective in reducing OCD symptoms (Coric et al., 2005; Grant et al., 2007). In total, slightly more than half of the reported patients with OCD treated open-label with riluzole have shown significant improvement (Ting and Feng, 2008). A double blind clinical trial with riluzole in SSRI-refractory OCD is currently recruiting patients (Clinicaltrial.gov, identifier: NCT01204918).

1.5.2. N-acetylcysteine (NAC)

NAC is an amino acid derivative with hepatoprotective antioxidant properties. It is converted to cystine in the body, which then acts as a substrate for the glutamate/cystine antiporter located on glial cells and results in an increase of extracellular glutamate (Dean et al., 2011). The rise of glutamate in the extrasynaptic space is thought to activate mGluR2/3 receptors on glutamatergic nerve endings which reduce synaptic glutamate release (Moran et al., 2005). One case study reports that the use of NAC in augmentation with fluoxetine resulted in marked decrease of OCD symptoms (Lafleur et al., 2006). A double blinded clinical study is currently recruiting patients with this agent (ClinicalTrials.gov, Identifier: NCT00539513).

1.5.3. NMDA glutamate receptor targeting agents

Memantine is a non-competitive NMDA receptor antagonist that has received FDA approval for the treatment of Alzheimer's disease. It has shown efficacy as an augmenting agent in refractory OCD in several case reports (Poyurovsky et al., 2005; Pasquini and Biondi, 2006; Hezel et al., 2009), as well as open-label trials (Feusner et al., 2009b; Aboujaoude et al., 2009). Recently, a single blind, case–control study reported memantine was an effective augmenting agent to standard Intensive Residential Treatment (IRT) in severe OCD (Stewart et al., 2010). It is interesting to note that amantadine, another NMDA antagonist, has been shown to reduce marble-burying behaviour in mice with greater effectiveness compared to memantine and riluzole (Egashira et al., 2008). Although there has not been any reported trial of amantadine in OCD, amantadine has been reported to induce hallucinations, delusions, increased aggression and nausea/vomiting in a minority of patients (Green et al., 2004). Although many of these adverse effects were reported in geriatric patients or those with concurrent medical or neurological issues, exceptions exist (Smith, 2008) and therefore caution would be warranted in any trial of this NMDA antagonist.

D-cycloserine (DCS) is a partial agonist of the NMDA receptor. DCS has been shown to accelerate extinction learning in rodents (Walker et al., 2002), suggesting it may help facilitate behavioural therapy for OCD where extinction is an important component for reducing anxiety.

Two groups have reported successful use of DCS in augmentation with exposure therapy for adult patients (Kushner et al., 2007; Wilhelm et al., 2008). A third group reported no effect in a study in which adult subjects were given 250 mg of DCS or placebo 4 h before each of the 12 total therapy sessions. Another recent report showed DCS in augmentation with cognitive behavioural therapy(CBT) in children

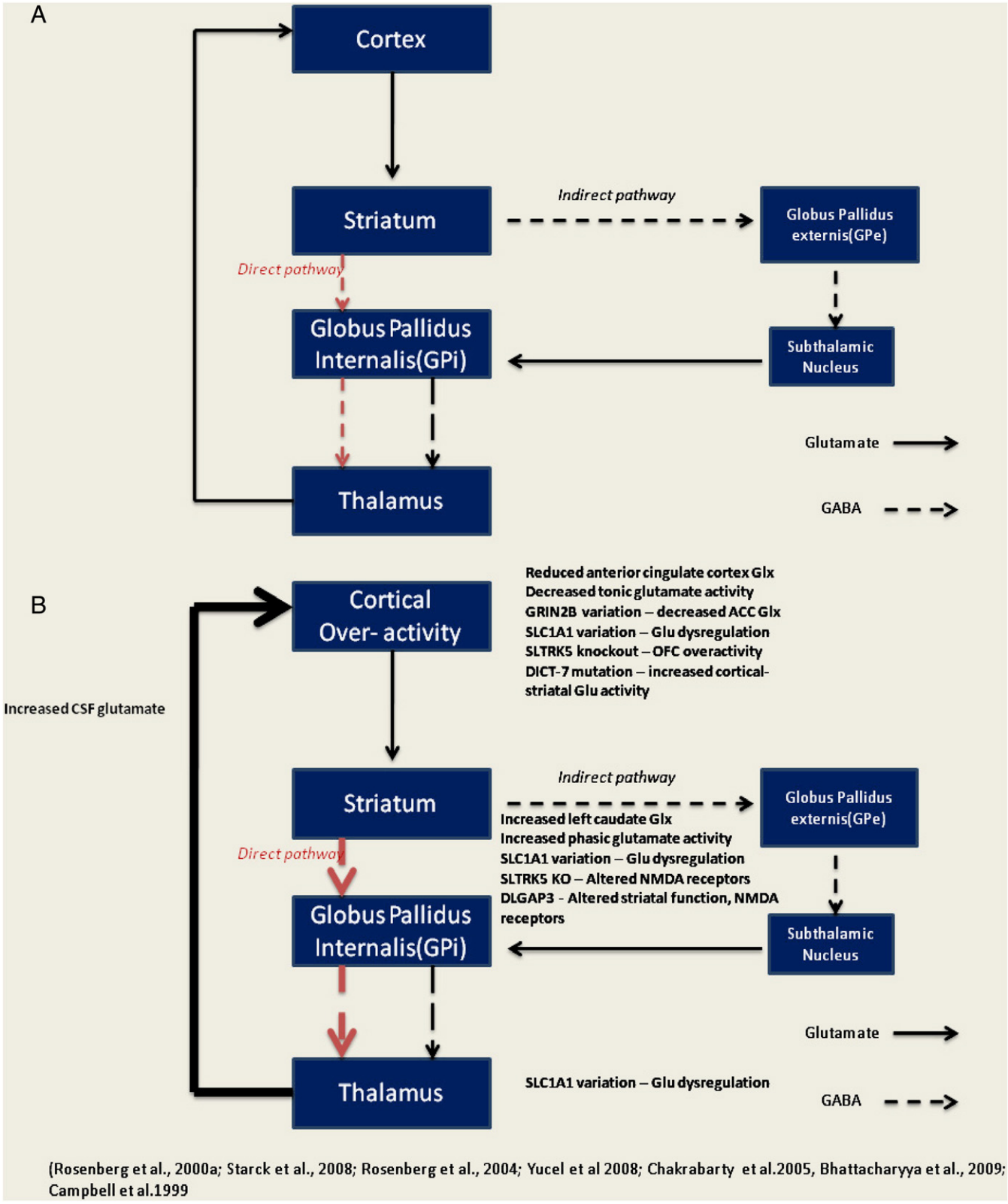

Fig. 1. Proposed glutamate dysfunction model and pharmacological evidence A) A simplified diagram of the Cortical Striatal Thalamic Cortical (CSTC) circuit B) Proposed glutamate dysfunction model. Evidence supporting various components of the model outlined with references listed below C) Glutamate in OCD: proposed pharmacological sites of action. The mechanisms of action for each pharmacological agent are also given.

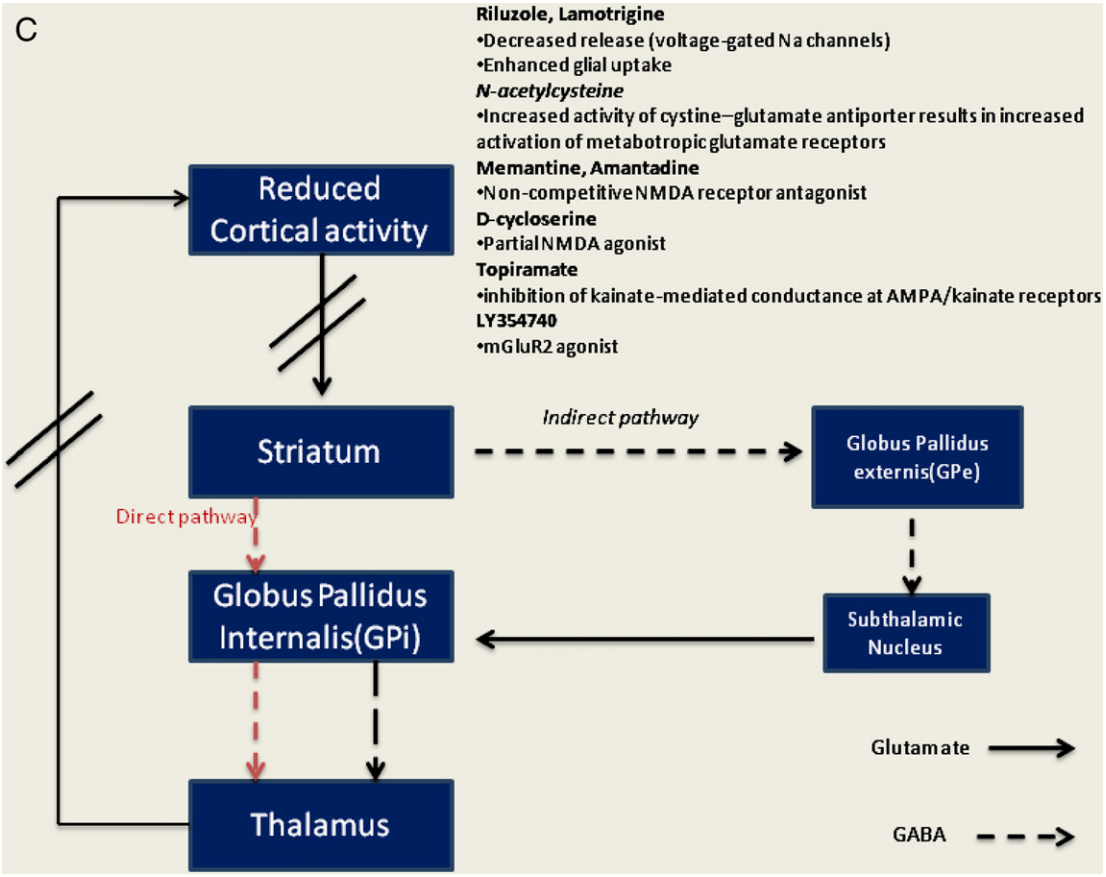

Fig. 1 (*continued*).

resulted in a trend towards improved treatment effect compared to placebo based on several symptom severity indices, although these effects were not statistically significant (Storch et al., 2010).

1.5.4. Other glutamatergic agents

Anticonvulsant drugs with glutamatergic effects, have shown some promise in open trials for treating OCD patients. These primarily include topiramate for which there has been one small randomized controlled trial (Mowla et al., 2010) and a number of open trials (Hollander and Dell'Osso, 2006; Van Ameringen et al., 2006; Berlin et al., 2010). There are also cases report of efficacy for lamotrigine augmentation of SRI medication, with a case series of eight patients showing larger negative results (Kumar and Khanna, 2000) and a single more recent case report with a positive outcome (Uzun, 2010). These largely negative findings combined with rare instances of severe dermatological reactions including Stevens-Johnson syndrome (particularly in children, Seo et al., 2011) suggest caution is warranted when using lamotrigine. It has also been suggested that metabotropic receptor agents may be helpful in OCD. For example, El Mansari and Blier (2006) noted that the mGluR2 agonist LY354740, located extrasynaptically, has been shown to attenuate excessive glutamate release and therefore might prove useful in OCD. Interestingly, the same authors predicted that riluzole would prove effective for similar reasons, a prediction which has been supported by more recent evidence as described above.

1.5.5. Medications which induce obsessive–compulsive symptoms and possible role of glutamate mechanisms

It is well established that obsessive–compulsive symptoms can be induced in some patients treated with atypical antipsychotic drugs (AAP), particularly when these agents are used for treatment of psychotic disorders (Lim et al., 2007). . An intriguing finding by Kwon et al. (2009) suggests that development of AAP-induced OC symptoms may be influenced by pharmacogenetic factors. Specifically, these investigators found that variation in *SLC1A1* was associated with induction of obsessive–compulsive symptoms during AAP treatment. Although typically considered to act through combined serotonin and dopamine blockade, there is preclinical evidence that the prototypical AAP clozapine downregulates the protein produced by *SLC1A1* (EAAC1) in the cingulate cortex of the rat (Schmitt et al., 2003). Further pharmacogenetic studies are needed to determine if other genetic variants in glutamate system genes help predict AAP-induced obsessive–compulsive symptoms. Paradoxically, AAPs which can induce OC symptoms in a subset of individuals are also used to augment treatment by serotonin reuptake inhibitors (SRIs) in treatment-refractory patients with OCD, yet they only work in approximately a third of cases and are associated with significant adverse effects (particularly metabolic side effects and weight gain) (Bloch et al., 2006). Pharmacogenetic studies of *SLC1A1* and other glutamate system genes which enable prediction of which patients will respond to these medications (and for whom the risk–benefit ratio may be favorable) would potentially be very helpful in clinical practice.

As with AAPs, there are case reports of topiramate (Ozkara et al., 2005; Thuile et al., 2006) inducing obsessive–compulsive symptoms and lamotrigine inducing tics with or without obsessive–compulsive symptoms (Seemuller et al., 2006; Alkin et al., 2007). Although not studied as extensively as AAPs, if OC symptoms are induced by topiramate and lamotrigine one might speculate that individual genetic differences (e.g. variation in *SLC1A1*) play a role in which patients benefit from these medications as opposed to developing new or worsened OC symptoms.

1.6. Towards a glutamate hypothesis

Based on the pivotal role of glutamate in CSTC models of OCD, Rosenberg and Keshavan (1998) reasoned that glutamate dysfunction might be implicated in the pathogenesis of OCD. Their hypothesis was based on the integral role of glutamate as the key neurotransmitter within CSTC circuits. One of the leading models of OCD is based on the balance between direct and indirect pathways within CSTC circuits (Saxena et al., 2001). According to this theory, reciprocal interaction between direct (ultimately leads to thalamic stimulation of cortex) and indirect (ultimately leads to thalamic inhibition of cortex) normally resulted in a dynamic balance with no one pathway predominating. Hyperactivity of the direct pathway, or hypoactivity of the indirect pathway was thought to lead to disinhibition of CSTC circuits and consequent release of hardwired behaviors (compulsions) and cognitions (obsessions) that were normally held in check. Rosenberg and others at the time (also see Carlsson, 2001) reasoned that over-activity of the direct pathway and associated hyperactivity of glutamate (the major excitatory neurotransmitter in this pathway).

Further indirect support for the role of glutamate dysfunction in OCD was also provided by the DICT-7 mouse model, which amounted to a test of the CSTC hypothesis in mice, since it was based on engineering transgenic mice in which glutamatergic neurons in the direct pathway (which express D1) were chronically hyperstimulated. In DICT-mice OCD- and tic-like behaviour were observed to be associated with stimulation of direct CSTC circuits; furthermore, as noted above this behaviour was exacerbated by NMDA antagonists (Campbell et al., 1999; McGrath et al., 2000). The group investigating the DICT-7 mice outlined a "cortical–limbic glutamatergic neuron (CGN)" hyperactivity model of tic and OCD symptoms, which elaborated on earlier CSTC models of OCD and attempted to account for the role of glutamate, dopamine and serotonin within direct and indirect CSTC pathways (Nordstrom and Burton, 2002).

While the DICT-7 model was being developed, more direct evidence for glutamatergic dysfunction in OCD was being gathered by Rosenberg and colleagues in their series of MRS studies described above (Rosenberg et al., 2000, 2004). Their findings were consistent with their earlier predictions, and led them to propose that they had identified a reversible (with treatment), glutamatergically mediated thalamo-cortical-striatal dysfunction in OCD (Rosenberg et al., 2001). Their initial findings of increased Glx in caudate taken together with findings of elevated glutamate of CSF in patients with OCD (Chakrabarty et al., 2005), seemed consistent with the CGN model of general glutamatergic hyperactivity in OCD within CSTC circuits. However, importantly Rosenberg and others found that Glx concentrations were not uniformly activated but showed regional specificity. Based on these findings, Rosenberg et al. (2004) hypothesized that OCD was associated with tonic-phasic dysregulation of glutamate within CSTC circuits, including reduced tonic glutamate levels in ACC (as evidenced by decreased Glx) which in turn led to phasic overactivity in the striatum and orbitofrontal cortex (as evidenced by increased Glx in both regions) (Rosenberg et al., 2004).

Although there has been accumulating evidence for glutamatergic dysfunction in OCD, until recently there were no studies that could help elucidate the nature of this dysfunction. As pointed out by Pittenger et al. (2006), there could be many possible causes for the altered glutamate levels seen in MRS studies, including presynaptic and/or post-synaptic neuronal mechanisms and/or altered glial functioning. However, there is now evidence from both candidate gene studies and animal models which suggest that post-synaptic dysfunction in glutamate signaling represents the most likely candidate mechanism at the molecular level to explain the higher order changes seen in CSTC glutamate transmission (for a recent review discussing this hypothesis see Ting and Feng, 2008). First, the most replicated gene finding in OCD is an association with *SLC1A1*, which encodes the EAAT3/EAAC1 glutamate transporter predominantly expressed on the post-synaptic and peri-synaptic membrane. Another candidate gene with some evidence for association, *GRIN2B* encodes the NMDA-2B subunit which is expressed predominantly in the same cellular location and interacts with *SLC1A1* (Scimemi et al., 2009). Second, the two animal knockout models of *DLGAP3* and *SLTRK5* indicate that changes in genes involved in post-synaptic scaffolding and glutamate signaling can produce remarkably similar compulsive behaviors. Furthermore, both mouse models yielded direct evidence of altered glutamate receptor expression and electrophysiological changes known to reflect glutamate signaling. Finally, the emerging findings in OCD are consistent with the mounting evidence in autistic spectrum disorders of glutamatergic post-synaptic dysfunction (van Spronsen and Hoogenraad, 2010). This overlap in putative mechanisms is intriguing given the known phenotypic overlap in these disorders characterized by repetitive behaviors.

In this era of evidence based medicine it can take years to translate basic science discoveries to clinical practice. However, in the case of the glutamate hypothesis, the translation of research findings to development of novel therapeutic strategies has been quite rapid. The first case–control MRS study identifying glutamatergic dysfunction in OCD was reported by Rosenberg et al. (2000). Since that time, we have seen converging evidence from animal models, genetic studies, and most recently imaging genetic studies provide the rationale for novel treatment development trials (See Fig. 1 for an overview of proposed dysfunction model). To date, riluzole and memantine are under active study. Memantine has already shown promise in a small randomized trial, whereas riluzole is being investigated in a randomized, double-blind placebo-controlled trial at the NIMH. Both medications are being used regularly in clinics in North America and other glutamatergic compounds are being studied. The translation of findings from "bench" to "bedside" in this case has therefore taken between 5 and 10 years. This remarkably rapid progress provides an excellent example of translational research in which neuroimaging, genetics and treatment studies all have the potential to inform one another and lead to accelerating discovery of novel medications and improved understanding of pathogenesis.

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