Published in final edited form as:
Pharmacol Ther. 2011 December ; 132(3): 314–332. doi:10.1016/j.pharmthera.2011.09.006.

GLUTAMATE ABNORMALITIES IN OBSESSIVE COMPULSIVE DISORDER: NEUROBIOLOGY, PATHOPHYSIOLOGY, AND TREATMENT

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Abstract

Obsessive compulsive disorder is prevalent, disabling, incompletely understood, and often resistant to current therapies. Established treatments consist of specialized cognitive-behavioral psychotherapy and pharmacotherapy with medications targeting serotonergic and dopaminergic neurotransmission. However, remission is rare, and more than a quarter of OCD sufferers receive little or no benefit from these approaches, even when they are optimally delivered. New insights into the disorder, and new treatment strategies, are urgently needed. Recent evidence suggests that the ubiquitous excitatory neurotransmitter glutamate is dysregulated in OCD, and that this dysregulation may contribute to the pathophysiology of the disorder. Here we review the current state of this evidence, including neuroimaging studies, genetics, neurochemical investigations, and insights from animal models. Finally, we review recent findings from small clinical trials of glutamate-modulating medications in treatment-refractory OCD. The precise role of glutamate dysregulation in OCD remains unclear, and we lack blinded, well-controlled studies demonstrating therapeutic benefit from glutamate-modulating agents. Nevertheless, the evidence supporting some important perturbation of glutamate in the disorder is increasingly strong. This new perspective on the pathophysiology of OCD, which complements the older focus on monoaminergic neurotransmission, constitutes an important focus of current research and a promising area for the ongoing development of new therapeutics.

Keywords

Obsessive-compulsive disorder; OCD; glutamate

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CONFLICT OF INTEREST STATEMENT

The authors are aware of no real or apparent conflict of interest that might influence the content of this review. C. Pittenger is a consultant to F. Hoffman-La Roche and has received research support from Pfizer Pharmacueticals. M. H. Bloch and K. Williams have no financial relationships to disclose.

1. INTRODUCTION

Obsessive-compulsive disorder (OCD) is a common, often debilitating neuropsychiatric disorder, with an estimated lifetime prevalence of 2.0–2.5% (Kessler et al., 2005; Robins et al., 1984; Ruscio, Stein, Chiu, & Kessler, 2010). OCD is characterized by obsessions and compulsions; most patients experience both, though either alone can justify the diagnosis (American Psychiatric Association. & American Psychiatric Association. Task Force on DSM-IV., 2000). *Obsessions* are frequent, intrusive, stereotyped thoughts. They are typically ego-dystonic in nature – that is, they are recognized as being foreign and unrealistic – and are associated with significant anxiety. *Compulsions* are repetitive, often ritualized behaviors, typically associated with specific obsessions and performed to alleviate this anxiety. The performance of compulsions can transiently improve obsessional anxiety, but they themselves then become a source of disability and distress. Affected individuals can spend hours a day in this cycle of obsession and compulsion, producing substantial morbidity (Jenike, 2004; Koran, Thienemann, & Davenport, 1996). In a recent epidemiological survey, 65% of patients reported that their symptoms produced significant role impairment (Ruscio et al., 2010). In severe cases, this level of distress contribute to a significant risk of suicidal behavior (Kamath, Reddy, & Kandavel, 2007); in profoundly treatment-refractory cases, patients and treaters increasingly turn to invasive treatment approaches such as ablative neurosurgery and deep brain stimulation (B. D. Greenberg, Rauch, & Haber, 2010).

Childhood-onset and adult-onset OCD may be distinct in important ways (Geller et al., 1998; Rosario-Campos et al., 2001). Early onset, before age 10, is more common among males (e.g. Ruscio et al., 2010), is more likely to be associated with tic disorders, and may be more heritable (Rosario-Campos et al., 2005). Adolescent onset is more typical in females (Ruscio et al., 2010). This difference in age of onset leads to a male preponderance among children and adolescents; among adults, the sex ratio is approximately 1:1 (Jenike, 2004). Onset after age 30 is uncommon (Jenike, 2004; Ruscio et al., 2010). The disorder is phenomenologically heterogeneous. OCD symptoms fall into recognizable symptom dimensions (M. H. Bloch, Landeros-Weisenberger, Rosario, Pittenger, & Leckman, 2008; Katerberg et al., 2009; Mataix-Cols, Rosario-Campos, & Leckman, 2005; Pinto, Greenberg, Murphy, Nestadt, & Rasmussen, 2009); it has been suggested that symptomatic subtypes may correspond to discrete patterns of abnormal brain activation (Mataix-Cols et al., 2004; van den Heuvel et al., 2009) and treatment response (e.g. Landeros-Weisenberger et al., 2010).

Numerous hypothesized contributors to the pathophysiology of OCD have been investigated, including genetic (M.H. Bloch & Pittenger, 2010), infectious and autoimmune (Swedo et al., 2010), endocrine (Leckman et al., 1994), post-partum (Uguz, Akman, Kaya, & Cilli, 2007), and post-ischemic (Carmin, Wiegartz, Yunus, & Gillock, 2002). No consensus has emerged regarding its etiology, which is likely to be heterogeneous. Genetic studies have indicated a heritability of 26–61% (M.H. Bloch & Pittenger, 2010).

There is, on the other hand, broad consensus that OCD is characterized by abnormalities of a particular brain network, the cortico-striato-thalamo-cortical (CSTC) circuitry (Figure 1). Functional imaging studies have revealed relative metabolic hyperactivity in the striatum (caudate and putamen), anterior thalamus, anterior cingulate cortex, and orbitofrontal cortex in patients with OCD (Maia, Cooney, & Peterson, 2008; Menzies et al., 2008); tellingly, in some studies this hyperactivity has been found to correlate with symptom severity and to resolve with symptomatic improvement upon treatment (e.g. Hansen, Hasselbalch, Law, & Bolwig, 2002). Morphometric studies have found abnormalities in the same group of brain regions (Menzies et al., 2008; Radua & Mataix-Cols, 2009); increased grey matter volume

of the caudate nucleus may be particularly specific for OCD, as opposed to anxiety disorders more generally (Radua, van den Heuvel, Surguladze, & Mataix-Cols, 2009). Although it is likely that abnormalities in brain structure and activation exist outside this canonical circuit (see for example Menzies et al., 2008), these functional and morphological data have focused attention on the CSTC circuitry as we strive to understand the neuropathophysiology of OCD and to develop novel treatment strategies. For example, invasive treatment strategies for refractory disease, such as DBS, typically target this circuitry (B. D. Greenberg et al., 2010).

Pharmacological treatment of OCD is targeted primarily at monoaminergic neurotransmission, particularly at the serotonin and dopamine systems. The specific serotonin reuptake inhibitors (SSRIs) are the mainstay of pharmacotherapy and are of benefit in 50–60% of patients (Koran, Hanna, Hollander, Nestadt, & Simpson, 2007; Soomro, Altman, Rajagopal, & Oakley-Browne, 2008). For reasons that remain unclear, high doses of these medications – in excess of the typical antidepressant dose range – are more efficacious and are often required (M. H. Bloch, McGuire, Landeros-Weisenberger, Leckman, & Pittenger, 2009). The older tricyclic antidepressant clomipramine, which has greater serotonin reuptake specificity than other tricyclics, is commonly prescribed and maybe slightly more effective, though its higher side effect burden can limit its use (Koran et al., 2007). In disease refractory to these agents, pharmacological augmentation with neuroleptic drugs, which antagonize the D2 dopamine receptor, can be efficacious (M. H. Bloch et al., 2006).

Neurobiological and genetic studies have similarly focused attention on these modulatory systems, and particularly on serotonin, as important in the pathophysiology of OCD and in its treatment. Linkage of OCD risk with polymorphisms in the serotonin transporter have been reported, though the finding has not been consistently replicated (M. H. Bloch, Landeros-Weisenberger, Sen et al., 2008). Increased serotonin in peripheral blood has been reported in OCD (Delorme et al., 2005; Yaryura-Tobias, Neziroglu, & Bhagavan, 1979). A few studies have implicated specific serotonin receptor subtypes in OCD. Agonists of the serotonin 1B and 1D receptors have been found to exacerbate OCD symptoms (Gross-Isseroff, Cohen, Sasson, Voet, & Zohar, 2004; Koran, Pallanti, & Quercioli, 2001; Zohar, Kennedy, Hollander, & Koran, 2004). PET studies suggest a reduction in the 5-HT_{2A} receptor in the cortex in drug-naïve patients (Perani et al., 2008). A smaller number of studies suggests abnormalities in dopamine neurotransmission in OCD; for example, a recent PET study found a reduction in the dopamine D2 receptor (Perani et al., 2008).

However, therapies aimed at modulating serotonin and dopamine prove inadequate in many cases of OCD; approximately 25% of patients get little benefit from available treatment strategies, and many of those who are classified as ‘responders’ continue to have significant symptoms and markedly reduced quality of life (M. H. Bloch et al., 2006; Jenike, 2004; Koran et al., 1996). It is therefore of critical importance that new insights into the neurochemical, anatomical, and functional abnormalities that contribute to OCD be developed, and that therapeutic strategies based on such insights be developed for the benefit of patients refractory to existing treatments.

We (Pittenger, Krystal, & Coric, 2006) and others (Carlsson, 2000, 2001; Chakrabarty, Bhattacharyya, Christopher, & Khanna, 2005; Rosenberg & Hanna, 2000; Rosenberg et al., 2000; Ting & Feng, 2008) have proposed that abnormalities in glutamate neurotransmission and homeostasis, especially in the CSTC circuitry, may contribute to OCD. Convergent evidence gives increasing support to this proposal. As a result, there is increasing interest in the use of glutamate-modulating agents in refractory OCD. Indeed, while no agent is yet supported by a definitive, placebo-controlled study, increasing evidence supports the

potential utility of riluzole, memantine, N-acetylcysteine, D-cycloserine, and other glutamate-modulating agents in the treatment of this disorder. In this review, we summarize current evidence supporting the existence of glutamate abnormalities in OCD, and we assess the potential utility of these glutamate-modulating pharmacological strategies in the treatment of refractory disease.

2. GLUTAMATE IN THE CENTRAL NERVOUS SYSTEM

Glutamate is the principal excitatory neurotransmitter in the adult brain. It is present in the central nervous system and in cerebrospinal fluid (CSF) at high concentrations, 8–10 mmol/kg or even higher (Danbolt, 2001; Sanacora, Gueorguieva et al., 2004; Snyder & Ferris, 2000). Glutamatergic projections participate in virtually all circuits in the adult central nervous system, including intracortical connections, cortical-subcortical connections, and subcortical systems such as the basal ganglia, cerebellum, thalamus, and brainstem circuits (Shepherd, 2004).

Glutamate functions as a classical neurotransmitter (Shepherd, 2004; see Figure 2). It is packaged into vesicles at the synaptic termini of glutamatergic neurons. Glutamatergic neurons are frequently, though not exclusively, projection neurons, whose axons extend to distant sites within the central nervous system. When such a neuron fires an action potential, glutamate-containing vesicles fuse with the presynaptic membrane, releasing their contents into the synaptic cleft. Glutamate rapidly diffuses across the synaptic cleft, where it can bind to postsynaptic receptors. It also binds to presynaptic receptors, which can provide negative feedback to limit further glutamate release.

Glutamate receptors are of two types, ionotropic and metabotropic. Ionotropic glutamate receptors, subtyped as AMPA, kainate, and NMDA receptors, are cation channels that open when they bind glutamate and thus electrically excite the postsynaptic cell. Metabotropic glutamate receptors, the mGluRs, do not directly open ion channels; rather, they are coupled to various intracellular signaling cascades that modulate neuronal function in diverse ways. Postsynaptic glutamate receptors are embedded in a matrix of structural proteins known as the postsynaptic density (PSD), which controls their positioning relative to one another; as reviewed below, certain molecular components of the PSD have been a recent focus of both animal and clinical studies of OCD and putatively OCD-related behaviors (Bienvenu et al., 2009; Welch et al., 2007; Zuchner et al., 2009). Glutamate receptor activity can be regulated in multiple ways, including by postsynaptic modifications such as phosphorylation and by insertion into, and removal from, the postsynaptic membrane.

The ionotropic NMDA receptor is of particular importance in portions of what follows (figure 2; for a more detailed review, see Pittenger, Sanacora, & Krystal, 2007). As discussed below, genetic studies have suggested an association between polymorphisms in the NMDA NR2B subunit and OCD risk (Arnold et al., 2004), and early pharmacological studies with the NMDA-blocking drug memantine have shown promise (Aboujaoude, Barry, & Gamel, 2009; Feusner, Kerwin, Saxena, & Bystritsky, 2009; Stewart et al., 2010). This heterotetrameric receptor has several unique properties. Its activation requires two coincident events: binding of glutamate to the receptor, and simultaneous depolarization of the postsynaptic cell in which the receptor resides. This requirement for simultaneous activating triggers makes the NMDA receptor ideally suited to be a coincidence detector, responding only when presynaptic and postsynaptic neurons are simultaneously activated. NMDA activation also requires binding of co-agonist glycine or D-serine to a distinct site on the receptor, providing an additional level of regulation. Pilot studies have investigated modulation at this site by the endogenous ligand glycine (W. M. Greenberg et al., 2009) and the exogenous co-agonist D-cycloserine (Kushner et al., 2007; Storch et al., 2010a; Wilhelm

et al., 2008) in the treatment of OCD, as will be reviewed below (see Figure 4 for an illustration of the primary sites of action of the glutamate-modulating drugs described in this review).

Glutamate can also diffuse out of the synaptic cleft; extrasynaptic glutamate binds to a distinct population of receptors and has distinct effects on neurons (reviewed, e.g., in Pittenger et al., 2007). In particular, while activation of postsynaptic NMDA-type glutamate receptors leads to synaptic transmission of information, synaptic plasticity, and trophic effects on neurons, activation of extrasynaptic NMDA receptors inhibits these processes and can lead to neuronal damage and death (Hardingham & Bading, 2010). Indeed, excess glutamate has long been known to lead to neuronal death, a phenomenon known as excitotoxicity (Olney, 1969). Glutamate concentration is therefore tightly regulated. The principal mode of regulation is through high-affinity glutamate transporters, which efficiently remove glutamate from the perisynaptic and extrasynaptic spaces (Danbolt, 2001). Quantitatively, glutamate transporters on glial cells – principally astrocytes – are responsible for the majority of glutamate removal; these astrocytic glutamate transporters are a target of the glutamate-modulating drug riluzole, which has shown promise in the treatment of refractory OCD (Pittenger, Coric et al., 2008). A smaller fraction of glutamate is removed by the neuronal glutamate transporter, EAAC1/EAAT3; as reviewed below, polymorphisms in the gene encoding this transporter have been repeatedly associated with OCD in recent studies (Arnold, Sicard, Burroughs, Richter, & Kennedy, 2006; Dickel et al., 2006; Shugart et al., 2009; Stewart et al., 2007). Finally, glutamate is also transported into glial cells in exchange for the oxidized amino acid cystine via the glutamate-cystine antiporter; under some circumstances the activity of this antiporter, which is influenced by the drug N-acetylcysteine, may be the principal determinant of baseline levels of extrasynaptic glutamate (Kalivas, 2009).

It is important to recognize that neurotransmitter glutamate, the focus of our attention here, represents a minority of total brain glutamate. As one of the basic 20 amino acids, glutamate is a building block of all proteins in the body. It is a single biochemical reaction removed from α-ketoglutarate and the Krebs cycle that is the core of mitochondrial energy metabolism. In addition, it is itself a precursor for the gamma aminobutyric acid (GABA), the principal inhibitory neurotransmitter in the brain, as well as for the amino acid glutamine and the endogenous antioxidant molecule glutathione (see Figure 3). Measurements of glutamate must be interpreted in this broader context, not simply as reflective of neurotransmission. And perturbations of glutamate homeostasis may be expected to have consequences beyond the modulation of excitatory communication between neurons.

3. GENETIC STUDIES

Several glutamate-related genes have been associated with OCD risk. While genetic studies were not the first to implicate glutamate neurotransmisison and homeostasis in the pathophysiology of OCD, they provide the strongest evidence for a causally important role for such perturbations. Other observed abnormalities in glutamate – reviewed below – could be either consequences or causes of the pathological change associated with OCD. Definitive association of genes implicated in glutamatergic neurotransmission with OCD risk, on the other hand, would be particularly clear evidence that perturbations of glutamate can be an important cause of OCD, at least in some cases. The evidence for such an association cannot yet be considered definitive, but it is growing in strength.

The genetic contribution to OCD has been recognized for decades (M.H. Bloch & Pittenger, 2010; Inouye, 1965). However, estimates of heritability vary (M.H. Bloch & Pittenger, 2010; Grabe et al., 2006), and the search for specific genetic contributors to the illness has

resulted in many leads, but many failures of replication (reviewed in M.H. Bloch & Pittenger, 2010).

SLC1A1

There has thus been substantial excitement surrounding the association of the glutamate transporter gene *Slc1A1* with OCD (Arnold et al., 2006; Dickel et al., 2006), and the subsequent replication and elaboration of this finding (Kwon et al., 2009; Liang et al., 2008; Samuels et al., 2011; Shugart et al., 2009; Stewart et al., 2007). The *Slc1A1* gene encodes the primary neuronal glutamate transporter EAAT3 (also known as EAAC1; see Figure 2). This transporter is estimated to be expressed on the postsynaptic membrane at 30–40% of the synapses in the mammalian brain (Nieoullon et al., 2006). As described above, the glutamate transporters play a critical role in terminating excitatory neurotransmission and in regulating extrasynaptic glutamate levels, limiting the activation of extrasynaptic neurotransmitter receptors and consequent excitotoxicity (Danbolt, 2001; Hardingham & Bading, 2010). Most glutamate reuptake is accomplished by the astrocytic glutmate transporters EAAT1 (GLT-1) and EAAT2 (GLAST); studies in mice suggest that these two transporters account for 90% of glutamate removal from the extracellular space (Bergles & Jahr, 1998; Rothstein et al., 1996; Tanaka et al., 1997).

The neuronal EAAT3 plays a more minor role; however, mice lacking the *Slc1A1* gene exhibit age-dependent loss of cortical neurons, confirming that this transporter, too, is essential for normal neuronal function and survival (Aoyama et al., 2006). It may also make unique contributions to glutamate homeostasis. Glutamate recovery from the extracellular space obviously requires the presences of the transporter in the cell membrane; but a disproportionate amount of EAAT3 protein is found intracellularly. It has been hypothesized that this intracellular EAAT3 plays a key role in regulating the production of glutathione and thereby protecting neurons from oxidative damage (Nieoullon et al., 2006). In the absence of EAAT3, glutathione is reduced, and oxidative damage may contribute to the consequent neuronal loss (Aoyama et al., 2006).

Slc1A1 emerged as a candidate OCD-related gene in the first genome-wide linkage study of the disorder, in which a region of the genome on chromosome 9p that contains the *Slc1A1* gene was identified as being of interest (though not at the threshold for genome-wide significance) in seven OCD pedigrees (Hanna et al., 2002). A subsequent study replicated suggestive linkage to this interval (Willour et al., 2004), though again without achieving genome-wide statistical significance. Then, in 2006, a pair of independent, well-powered studies specifically examining this locus found a significant association with single nucleotide polymorphisms (SNPs) in the 3’ end of the gene (Arnold et al., 2006; Dickel et al., 2006).

This association has now been investigated in a total of 9 studies (Arnold et al., 2006; Dickel et al., 2006; Kwon et al., 2009; Liang et al., 2008; Samuels et al., 2011; Shugart et al., 2009; Stewart et al., 2007; Wang et al., 2010; Wendland et al., 2009), with the majority confirming association of the *Slc1A1* gene with OCD – an unusually high level of replication for genetic studies of psychiatric conditions (M.H. Bloch & Pittenger, 2010). The specific SNPs and haplotypes associated with OCD risk have not been consistently reproduced across these studies; the most consistently implicated SNP is a 3’ polymorphism, rs3780412 (Dickel et al., 2006; Stewart et al., 2007). Interestingly, three of the studies have found association with OCD only with male probands, not females (Arnold et al., 2006; Dickel et al., 2006; Stewart et al., 2007). One study associated an *Slc1A1* haplotype with OCD symptoms triggered by antipsychotic treatment in schizophrenic patients, suggesting a complicated interaction between dopamine and glutamate signaling in this context (Kwon et al., 2009). Finally, one study has found evidence for an interaction between a polymorphism at the *Slc1A1* locus

and a locus on chromosome 14 in determining risk for hoarding symptoms (Liang et al., 2008). Findings of this sort may point the way towards elucidating distinct causal factors leading to symptomatic OCD subtypes (Mataix-Cols et al., 2005).

Such linkage and association studies provide evidence for a relationship between variants in *Slc1A1* and risk for OCD, but they provide limited insight into the nature of the putative functional *Slc1A1* abnormality that may account for the disorder. In particular, almost all of the identified SNPs are in non-translated DNA sequence, making the relationship between these sequence variants and functional abnormalities in gene expression or protein function particularly obscure. One recent study has begun to address this question (Wendland et al., 2009). Wendland and colleagues identified a haplotype at the *Slc1A1* locus, consisting of three linked SNPs, that was roughly twice as prevalent in OCD patients as in controls. They then tested RNA transcripts of the different haplotypes in cell culture, and found that one particular SNP, rs301430, resulted in a 50% decrease in *Slc1A1* mRNA expression. They went on to investigate the effect of this SNP on *Slc1A1* mRNA expression in post-mortem tissue from control patients and from schizophrenics (not from OCD patients). Here, too, they found the implicated SNP to be associated with a nominally significant decrease in mRNA. This study suggests a very provisional hypothesis about the association between *Slc1A1* polymorphisms and OCD: that polymorphisms leading to reduced expression of the transporter may be associated with increased risk of the disease.

What would this mean in the brain? As described above, glutamate transporters are critical for terminating excitatory synaptic transmission throughout the brain and for controlling the level of extrasynaptic glutamate and preventing excitotoxicity (Danbolt, 2001). However, knockout studies in mice have shown that the glial glutamate transporters are much more important in this regard, quantitatively, than the neuronal transporter (e.g. Rothstein et al., 1996). Knockout of *Slc1A1* does result in cumulative neurodegeneration in the cortex (Aoyama et al., 2006), but it is unclear that a more modest reduction in expression, such as that seen by Wendland and colleagues (Wendland et al., 2009), would have a similar effect; and there is minimal evidence of frank neurodegeneration in OCD. An alternative possibility is that reduced EAAT3 function leads to a maldistribution of glutamate, perhaps altering the synaptic-extrasynaptic glutamate ratio, and the ratio of NMDA activation, in particular brain circuits, and thereby leads to functional circuit abnormalities that fall short of neuronal death. Finally, it is possible that the relevant consequences of *Slc1A1* disruption are more indirectly related to glutamate levels; for example, as noted above, knockout of the *Slc1A1* gene reduces glutathione (Aoyama et al., 2006) and thereby presumably increases oxidative stress, which could lead to functional abnormalities. Much more research in this area is needed, both in functionally characterizing OCD-related *Slc1A1* alleles and in elucidating the neurobiological consequences of perturbation of this gene, in order to refine and test such pathophysiological hypotheses.

Sapap3

The *Sapap3* gene, which encodes a protein critical to the normal localization of ionotropic glutamate receptors in the PSD (see Figure 2), has been the target of substantial recent interest. Unlike the *Slc1A1* gene, which was first identified as a positional candidate from classical genetic studies (Hanna et al., 2002), interest in the *Sapap* gene derives from studies in animals (Welch et al., 2007). Its function at the glutamatergic synapse, and the intriguing phenotypes of mice in which it has been inactivated, are elaborated below in the discussion of animal models.

Three recent genetic studies have investigated genetic variants in *Sapap3* in OCD and in related grooming disorders, such as trichotillomania. The first such report, an association study, reported that four SNPs and three haplotype blocks within the *Sapap3* locus were

nominally associated with grooming disorders, though none was associated with OCD alone (Bienvenu et al., 2009). The second study used direct sequencing to look at *Sapap3* mutations in OCD patients with and without trichotillomania. Seven sequence variants were identified; variants were present in 4.2% of patients and only 1.1% of controls. Two variants were found in patients with OCD alone, providing the first clinical evidence potentially associating alterations in this gene with OCD itself, as opposed to with grooming disorders (Zuchner et al., 2009). A third study, examining a South African population, found a nominally significant association of two SNP markers with trichotillomania (though this did not survive correction for multiple comparisons), and an association between a particular *Sapap3* haplotype and age of onset in patients with OCD (Boardman et al., 2011). Such mutations are clearly rare; but these preliminary findings support the possibility that alterations in *Sapap3* may contribute to some cases of OCD and related disorders. Further investigation of this association is warranted, and is ongoing.

Glutamate receptors

The electrical response of a postsynaptic cell after activation of a glutamatergic synapse depends on the binding of glutamate to ionotropic and metabotropic glutamate receptors (see Figure 2). Several of these receptors have been investigated as candidate genes for OCD risk, with promising early results.

The *Grin2B* gene encodes one subunit of the NMDA glutamate receptor, NR2B. When NMDA receptors, which are heteromeric, incorporate this particular subunit they are more permeable to calcium, promoting both synaptic plasticity (Tang et al., 1999) and, potentially, excitotoxic cell damage (Hardingham & Bading, 2010). One early study found a *Grin2B* polymorphism, and one additional haplotype, to be associated with OCD transmission (Arnold et al., 2004). More recently, an association was observed between a *Grin2B* polymorphism and a magnetic resonance spectroscopy (MRS) measurement of anterior cingulate cortex *Glx*, a measure of glutamate and related molecules (Arnold et al., 2009; Carlsson, 2000; Moore, MacMaster, Stewart, & Rosenberg, 1998; MRS measurement of brain glutamate is discussed in detail below). These data provide weaker evidence of an association of *Grin2B* polymorphisms and the pathophysiology of OCD than, for example, the more extensive studies of the *Slc1A1* locus summarized above; but they do establish a suggestive relationship that merits further study.

Finally, two candidate gene studies have ionotropic kainate-class glutamate receptor gene *Grik2* (Jane, Lodge, & Collingridge, 2009). This receptor subunit has been associated in earlier genetic studies with both autism and schizophrenia. The first OCD study found no association of the *Grik2* gene or the related *Grik3* gene with OCD in the primary analysis; however, a secondary analysis found a single *Grik2* polymorphism, originally identified in autistic patients, to be undertransmitted in OCD (Delorme et al., 2004). A more recent candidate gene study found one haplotype at this locus to be significantly associated with OCD; in this case, the finding remained significant after correction for multiple comparisons (Sampaio et al., 2010). These findings are in need of replication; the *Grik2* locus is another gene involved in glutamate neurotransmission that merits further attention and investigation.

4. NEUROCHEMICAL STUDIES

As described above, morphological and functional imaging studies have identified abnormalities in the CSTC circuitry in patients with OCD (Maia et al., 2008; Menzies et al., 2008; Rotge et al., 2010). Over the past 10 years, several studies have used magnetic resonance spectroscopy (MRS) to investigate levels of glutamate and related molecules in this circuitry, and have produced some evidence of glutamate dysregulation in patients with OCD.

The CSTC circuitry uses both glutamate and GABA as its primary neurotransmitters. Excitatory glutamatergic projections from the cerebral cortex, as well as from thalamus and hippocampus, target the medium spiny neurons (MSNs) of the striatum. These glutamatergic synapses express NMDA and other glutamate receptor types. The MSNs, on the other hand, are GABAergic and inhibit their targets. The striatum also contains several types of interneuron (Kreitzer, 2009); however, it contains no glutamatergic neurons. Therefore, all glutamate in the striatum derives either from afferent projections (from cortex, hippocampus, and thalamus), or from metabolic pools and precursors to GABA.

Striatal MSNs project either to the globus pallidus pars externa (GPe), a projection known as the **indirect pathway**, or to the globus pallidus pars interna (GPi, equivalent to the rodent entopeduncular nucleus) and substantia nigra pars reticulata (SNr), a projection known as the **direct pathway**. Ultimately both projects modulate the firing of GABAergic cells of the GPi and SNr, which in turn inhibit glutamatergic neurons of the anterior thalamus. These thalamic neurons project back to frontal neocortex, including both the anterior cingulate and the orbitofrontal cortex. These pathways are illustrated in Figure 1.

Tentative inferences about glutamatergic tone can be made from the metabolic hyperactivity documented in this circuit in OCD. In particular, pathological hyperactivity of the ACC and OFC might be expected to increase glutamate release both in these structures (due to local collaterals) and in their target, the striatum. However, such inferences are limited; glutamate reuptake, primarily by astrocytes, is extremely efficient (reviewed in Pittenger, Coric et al., 2008), and therefore increased activity of glutamatergic neurons will not necessarily increase tonic concentrations of glutamate in tissue or in CSF.

CSF studies of glutamate in OCD

A general abnormality in glutamate balance, or a localized abnormality that overwhelms the brain's capacity to maintain homeostasis, may affect the concentration of glutamate and related compounds globally and be detectable in the cerebrospinal fluid (CSF). Two studies have examined glutamate concentrations in CSF of unmedicated OCD patients, thereby providing a measure of glutamate homeostasis that is molecularly precise, though anatomically nonspecific. In 2005, Chakrabarty et al (Chakrabarty et al., 2005) described measurements of glutamate in the CSF of 21 unmedicated adult patients and 18 controls; they found statistically significantly higher glutamate in patients, with no significant effect of age, gender, disease severity, or other covariates. Glutamate concentrations in the two groups overlapped substantially, and so this assessment is unlikely to prove of diagnostic utility; but it provides strong support for a general dysregulation in glutamate homeostasis in these patients. A follow-up study from the same group replicated and extended this finding (Bhattacharyya et al., 2009). Both glutamate and glycine were found to be elevated in a group of 23 unmedicated adult OCD patients, compared to 23 controls. As noted above, glycine functions as a co-agonist at the NMDA glutamate receptor (see Figure 2); elevations in glutamate and glycine might therefore synergize to produce excessive activation of brain NMDA receptors.

Ultimately, it would be of value to measure ambient glutamate concentrations in the various components of the CSTC circuitry of patients with OCD (Figure 1). This would be unacceptably invasive in patients – though it might become possible with the increased use of deep brain stimulation, DBS, in profoundly refractory cases (B. D. Greenberg et al., 2010); such an approach has begun to yield *in vivo* measurements of glutamate in other conditions (Cavus et al., 2005). It may also prove possible to measure glutamate and related molecules in *post mortem* tissue (e.g. Anderson et al., 1992), although such studies are fraught with the difficulties that attend the collection and characterization of such tissue. No such postmortem analysis of OCD has been reported.

Magnetic resonance spectroscopy

Magnetic resonance spectroscopy (MRS) complements these studies: it provides lower sensitivity and, in many cases, less molecular specificity than neurochemical analyses of CSF, but it permits investigation of levels of glutamate and related molecules in specific brain regions, which CSF analysis cannot do. A number of studies over the past 12 years have used MRS to probe glutamate levels in various brain regions in OCD.

MRS takes advantage of the distinct resonances in a magnetic field of hydrogen nuclei in different chemical contexts to measure the concentration of various small molecules in defined regions of brain (voxels). The most easily-measured cellular constituents are choline, creatine, inositol, and N-acetylasparatate; these are sometimes interpreted as reflecting neuronal viability, and some studies (beyond the scope of this review) have reported on them in OCD (e.g. Atmaca et al., 2009; Bedard & Chantal, 2011; Ebert et al., 1997; Sumitani, Harada, Kubo, & Ohmori, 2007; Yucel et al., 2008).

Glutamate, glutamine, and GABA are technically more difficult to measure, because they are present at lower concentrations, and because their molecular structures yield complex, overlapping resonances in MR spectra. Generating a clean measure of glutamate concentration is particularly difficult, if not impossible, at the low magnetic field strengths (typically 1.5 Tesla) employed by many scanners. Many studies – indeed, all MRS studies of OCD published to date – therefore do not cleanly disambiguate glutamate and glutamine; rather, they report a composite measure known as *Glx* (Yuksel & Ongur, 2010). This measure is often interpreted as reflecting glutamate concentration, but it is important to keep in mind that it is in fact a composite. Indeed, recent findings in depression suggest that the glutamate-glutamine ratio may be a particularly informative measure (Yuksel & Ongur, 2010); such detail is lost in studies that report only *Glx*. Higher field strengths and sophisticated analytic methods permit disambiguation of glutamate and glutamine, as well as measurement of GABA (e.g. Epperson et al., 2005; Sanacora, Gueorguieva et al., 2004; Yuksel & Ongur, 2010); however, these approaches are only now being applied to the study of OCD.

Another limitation of MRS, more difficult to overcome, is that it measures whole tissue glutamate. Glutamate in the brain is not only used as a neurotransmitter; it is also a protein building block, an intermediate in the biosynthesis of the inhibitory neurotransmitter GABA, the amino acid glutamine, and the antioxidant glutathione, and closely related to core processes of energy metabolism (Figure 3). Even within the neurotransmitter glutamate pool, MRS measures cannot distinguish between synaptic, extrasynaptic, and intracellular glutamate.

These caveats aside, MRS investigations provide some of the earliest and most intriguing evidence indicative of glutamate dysregulation in OCD (Rosenberg, MacMillan, & Moore, 2001). Rosenberg and colleagues initially described elevations in *Glx* in a caudate voxel in 11 pediatric patients with OCD (Moore et al., 1998; Rosenberg et al., 2000). There was no between-group difference in *Glx* measurements from the occipital cortex, suggesting some anatomical specificity to this abnormality. Remarkably, elevated *Glx* normalized after pharmacotherapy with paroxetine (Moore et al., 1998; Rosenberg et al., 2000); in a case report, this normalization was found to persist for many months, including for three months after medication discontinuation (Bolton, Moore, MacMillan, Stewart, & Rosenberg, 2001). In contrast, the elevation in caudate *Glx* did not normalize after CBT in a similar population, despite clear symptomatic improvement (Benazon, Moore, & Rosenberg, 2003), suggesting (as had earlier studies using PET imaging of cerebral metabolism; Brody et al., 1998) that pharmacotherapy and psychotherapy produce symptomatic improvement through distinct mechanisms. These early reports of increased glutamate-related compounds in a major node

of the circuit implicated in OCD were highly influential and spurred early interest in a possible role for glutamate dysregulation in the disorder.

Subsequent studies, however, paint a more complicated picture. An early MRS study of the caudate in adult OCD patients found an abnormality in N-acetylaspartate but no difference from controls in *Glx* (Bartha et al., 1998). Similarly, two later studies in adults failed to find any difference between OCD patients and controls in caudate *Glx* (Starck et al., 2008; Whiteside, Port, Deacon, & Abramowitz, 2006), although one of the two (Starck et al., 2008) did report a correlation between caudate *Glx* and OCD symptom severity. No published reports after the original studies of Rosenberg and colleagues have re-examined caudate *Glx* in pediatric patients. It remains unclear, therefore, whether the discrepancy between the initial positive findings and the subsequent failures of replication reflect the small sample sizes in these studies, limitations inherent in the technique employed (especially the use of the compound measure *Glx* and the relatively low signal-to-noise ratio achieved at low field strength), or a fundamental difference between pediatric and adult OCD.

The anterior cingulate cortex (ACC), another often-reported node of hyperactivity in OCD (Maia et al., 2008; Menzies et al., 2008; Rotge et al., 2010), has been reported to have decreased *Glx* in pediatric OCD (Rosenberg et al., 2004). This abnormality parallels the decrease in ACC glutamate that has been more regularly reported in major depressive disorder (Auer et al., 2000; Price et al., 2009; Rosenberg et al., 2005; Yuksel & Ongur, 2010), but it was observed in euthymic OCD patients (Rosenberg et al., 2004), suggesting an etiology independent of mood pathology. More recently, the same group reported that this reduction in ACC Glx may be modulated by a specific NMDA glutamate receptor polymorphism (Arnold et al., 2009). A reduction in ACC *Glx* that correlated with symptom severity was replicated in one MRS study in adults with OCD, though only in women (Yucel et al., 2008); a second study in adults found no difference between OCD patients and controls in ACC *Glx* (Starck et al., 2008). As in the case of studies targeting the caudate nucleus, it remains unclear whether these discrepancies reflect the small size of the studies, their technical limitations, or true clinical differences between subpopulations of OCD patients. We have recently reported, using disambiguated measurements of glutamate and glutamine, that ACC glutamate is reduced only in adult OCD patients without significant comorbid mood and anxiety symptoms (Pittenger et al., 2011). Carefully controlling for these comorbid symptoms may help clarify the clinical correlates of reduced ACC glutamate in future studies.

An investigation in unmedicated adults found elevated *Glx* in orbitofrontal white matter of OCD patients, relative to controls; *Glx* correlated with OCD symptom severity (Whiteside et al., 2006). However, a more recent study (examining 8 patients and 8 controls) found no *Glx* difference in OFC (Bedard & Chantal, 2011). Finally, several studies have examined *Glx* in occipital cortex. While the canonical circuit and the initial study of Rosenberg and colleagues (Rosenberg et al., 2000) would suggest that occipital *Glx* should be normal in OCD, one study in adults found a strong negative correlation between OCD symptomatology and occipital *Glx* (Starck et al., 2008).

In sum, MRS studies of glutamate and related compounds in OCD are tantalizing but remain quite limited. All studies to date have been relatively small, with the largest examining 20 patients, have used low field-strength MRS, and have reported only *Glx*, not a disambiguated glutamate signal. Clarification of the various conflicting results will require larger studies using more powerful analytic methods. Nevertheless, the majority of studies have suggested some abnormality in glutamate regulation within the CSTC circuit implicated in OCD. Despite their limitations, these imaging studies clearly contribute further

evidence for the hypothesis that glutamate dysregulation contributes importantly to the disorder.

5. ANIMAL MODELS

Assessing animal models

Modeling OCD in experimental animals poses particular challenges. Some of these challenges are inherent to the modeling of psychiatric disease in general (Nestler & Hyman, 2010), but they are acute in the case of OCD.

Animal models of disease are commonly assessed on the basis of three criteria. Face validity describes the extent to which a model recapitulates the symptomatology of a pathological condition. This is a challenge in any psychiatric condition, given the inherently subjective nature of the symptoms; some symptom clusters are more readily modeled than others. For example, in the case of major depression, the symptoms of anhedonia and 'behavioral despair' have been extensively used in animal studies and possess a degree of face validity for the clinical disorder, whereas the DSM-IV symptoms of guilt and suicidality are virtually impossible to evaluate in an animal (Nestler & Hyman, 2010). In the case of OCD, claims of face validity have been made for repetitive or perseverative behaviors (e.g. Eilam, Zor, Szechtman, & Hermesh, 2006; Joel, 2006; Thomas et al., 2009), including grooming (Campbell et al., 1999; Greer & Capecchi, 2002; Shmelkov et al., 2010; Welch et al., 2007); anxiety-related behaviors (e.g. Shmelkov et al., 2010; Welch et al., 2007); sensory processing abnormalities such as prepulse inhibition (Shanahan et al., 2009); and cognitive abnormalities such as working memory deficits (e.g. Anderson et al., 1992). None of these 'symptoms' are remotely specific for OCD, and putative models that rely on face validity are thus limited; the defining symptoms of OCD – the presence of obsessions, with their characteristic intrusive and irrational nature, and the execution of compulsions as an anxiety-relieving response – is not subject to ready evaluation in animals.

The predictive validity of an animal model refers to its ability to distinguish between medications that are efficacious in the modeled disorder and those that are not. In the case of OCD, predictive validity is often claimed when an observed behavioral effect is reversed by treatment with SSRIs (e.g. Joel, 2006; Shmelkov et al., 2010; Welch et al., 2007). Conclusions from such responsivity are limited by the lack of specificity of these agents, which are used to treat a wide range of mood and anxiety disorders. Modulation of behavioral models by glutamate-targeting medications has been interpreted as supportive of the idea that glutamate pathology contributes to these models and therefore, by inference, to OCD itself (e.g. Egashira et al., 2008; McGrath, Campbell, Parks, & Burton, 2000).

The construct validity of an animal model describes the extent to which it recapitulates a plausible pathophysiological theory of the modeled disorder. Here, as in most neuropsychiatric conditions, studies have been limited by the paucity of well-specified etiological theories of OCD and related disorders. Nevertheless, animal models have been described that claim construct validity on the basis of circuit-level (e.g. Campbell et al., 1999), pharmacological (Andersen, Greene-Colozzi, & Sonntag, 2010), and behavioral manipulations (e.g. Joel, 2006).

It would be beyond our scope here to enumerate every model that has been proposed for OCD, or to evaluate them critically; rather, this framework is reviewed to provide a context for a more focused treatment of specific findings in animals that lend support to the idea that glutamate dysregulation can contribute to OCD. The most compelling models of OCD, or of any disorder, partake of all three domains of validity outlined above. Ultimately, the test of any animal model is its ability to provide new insights into the pathophysiology of the

modeled disorder that can be validated in affected patients and, ultimately, may lead to new therapeutic or preventative approaches. This has been an elusive goal.

Glutamate modulation of behavioral models of OCD

Glutamate modulators (agonists and antagonists, including some therapeutic drugs) have been investigated in a variety of behavioral models of OCD. All of these models have limitations, as reviewed above. Nevertheless, the ability of a glutamate-targeting agents to mitigate or exacerbate putative OCD-related behaviors provides support for the idea that targeting of glutamatergic neurotransmission in humans may be similarly efficacious in OCD treatment.

The signal attenuation model—The signal attenuation model is based on the hypothesis that OCD derives from a deficit in a feedback signal indicating task completion; in the absence of this signal, it is suggested, the urge to perform a task is not alleviated by performance and becomes an obsession (Szechtman & Woody, 2004). This sequence of events is modeled in rats through a series of purely behavioral manipulations in an operant chamber; the result is a 'compulsive' repetition of unproductive activity despite a lack of reward (Joel, 2006). In this model, D-cycloserine (DCS), a partial agonist at the glycine co-agonist site on the NMDA receptor (see Figure 4), decreased compulsive lever-pressing (Albelda, Bar-On, & Joel, 2010).

Marble burying—Marble burying describes the tendency of mice to dig repetitively when placed in a cage with deep bedding; in the presence of inert objects (typically marbles), this can be quantified as the number of objects buried in a given interval of time. This behavior, which is of clear ethological relevance for rodents, has been widely used in pharmacological studies due in part to its methodological accessibility (Deacon, 2006). It has been variably interpreted as reflecting anxiety or compulsivity (Thomas et al., 2009); marble burying abnormalities can be produced by perturbation of the serotonin system (Andersen et al., 2010), and the behavior is attenuated both by anxiolytics and by serotonergic antidepressants (Deacon, 2006) – though it is also affected by a variety of other medications, including methamphetamine (Bespalov et al., 2008), so predictive specificity of this model for OCD may be limited.

Recently, marble burying was observed to be attenuated by several antagonists of the NMDA glutamate receptor, but not by AMPA agonists or the glutamate modulator riluzole (Egashira et al., 2008). Marble burying is also attenuated by the presynaptic mGluR II/III receptor agonists LY-341495 (Bespalov et al., 2008) and LY-404039 (Rorick-Kehn et al., 2007); by activating presynaptic mGluRs, these agents are predicted to reduce glutamate synaptic outflow. While the precise relevance of this species-specific behavior for OCD is unclear and its predictive validity may be limited, these results may be interpreted as supportive of the idea that modulators of glutamate neurotransmission can affect repetitive behaviors.

Obsessive grooming and other behaviors in dogs—Compulsive behaviors, including excessive grooming ('acral lick syndrome'), tail-chasing, and other behaviors, have been described in dogs and may represent a naturally occurring OCD-like condition (Luescher, 2003; Overall & Dunham, 2002); similar compulsive behaviors, often associated with anxiety, are seen in other species. The efficacy of serotonin reuptake inhibitors in these conditions lends support to the phenomenological resemblance of such canine disorders to OCD (Seksel & Lindeman, 2001; Wynchank & Berk, 1998). Recent anecdotal evidence suggests that the glutamate modulator memantine may be of benefit in these OCD-like conditions in dogs (Holden & Travis, 2011). Rigorous studies have not been described; but

naturally-occuring OCD-like conditions such as acral lick syndrome may prove a valuable model for future study.

Pharmacological models

A variety of drug-induced behavioral abnormalities in mice have been described that may model aspects of OCD. Such models typically claim construct validity through their targeting of neuromodulatory systems thought to be involved in OCD, and face validity from the production of repetitive behaviors thought to model aspects of compulsions. Most models described to date derive from pharmacological manipulation of neurotransmission through dopamine (Szechtman, Sulis, & Eilam, 1998) or serotonin (Anderson et al., 1992; Shanahan et al., 2009; Tsaltas et al., 2005). To date, no systematic investigations of the impact of glutamate-modulating agents in these models have been described, nor has any model of OCD produced by treatment with a directly glutamate-modulating drug been proposed.

Genetically modified mice

Over the past decade, a number of genetically modified mice (either transgenic or knockout) have been described to exhibit behaviors reminiscent of OCD. With one exception, the pathophysiological link between the genetic modification and the biology of OCD has been *post-hoc* – behaviors have been observed in genetically modified mice that are taken to resemble OCD, and this link then motivates further investigation of both the phenotype and its underlying etiology. Insofar as abnormalities in glutamate homeostasis or neurotransmission are characterized in such models they provide evidence supportive of a glutamate-centered hypothesis of OCD. However, more robust construct validity – specifically, a clearer connection between the targeted genes and the pathophysiology of OCD in patients – is requisite before strong mechanistic links can be made.

D1CT-7 mice—As summarized above, multiple studies suggest hyperactivity in the CTSC circuitry interconnecting frontal cortex and basal ganglia in OCD (Maia et al., 2008; Menzies et al., 2008; Rotge et al., 2008). In an effort to model this hyperactivity, Burton and colleagues generated transgenic mice expressing the neuropotentiating subunit of the cholera toxin under control of the D1 dopamine receptor promoter (Campbell et al., 1999). This leads to constitutive hyperactivity of cortical afferents projecting to the striatum. The strength of this model is its construct validity – it is based on a specific hypothesis of the pathophysiology of OCD, that is, that it is caused by hyperactivity in these circuits. A weakness is the relative lack of specificity of the potentiation: it is unclear whether either the specific neurons targeted by the transgene, or the nature of their increased firing, realistically recapitulate the elevated neuronal activity seen in functional imaging studies of human OCD. Regardless, a variety of ‘OCD-like’ behaviors have been described in these mice: perseverative repetition of normal behaviors; nonaggressive biting during grooming; repetitive leaping (Campbell et al., 1999); anxiety (McGrath, Campbell, Veldman, & Burton, 1999); and tic-like stereotypies (Nordstrom & Burton, 2002).

Since the transgene expressed in these mice is expressed in glutamatergic cells and enhances their excitability, it is to be expected that they would show abnormalities in glutamate homeostasis. Consistent with this prediction, D1CT-7 mice exhibit a reduced seizure threshold, suggestive of a shifted balance between excitation and inhibition in the cortex (Campbell, Veldman, McGrath, & Burton, 2000). MK-801, a noncompetitive antagonist of the NMDA-type glutamate receptor, was found to worsen the behavioral phenotypes in this mouse (McGrath et al., 2000). Since NMDA antagonists can increase extracellular glutamate in the prefrontal cortex (Moghaddam & Adams, 1998) as well as in the CSF

(Schmidt et al., 2009), this effect is consistent with an exacerbation by MK-801 of an underlying hyperglutamatergic state.

SAPAP3 knockout mice—In an influential recent study, Feng and colleagues investigated the consequences of knockout of the gene encoding SAPAP3, a postsynaptic scaffolding protein involved in linking the postsynaptic density with the actin cytoskeleton at glutamatergic synapses (Welch et al., 2007). There are four SAPAPs in the mouse brain; SAPAP3 is expressed broadly but is the only one of the four that is expressed at significant levels in the striatum – a key component of the CSTC circuitry (Welch, Wang, & Feng, 2004).

Knockout of this gene produces pathological grooming and elevated anxiety, two behaviors that are suggestive of an OCD-like phenotype. Both of these phenotypes are reversed after rescuing SAPAP3 expression in the striatum, confirming the association of the phenotype with abnormalities the CSTC circuitry, and after chronic treatment with the SSRI fluoxetine. This knockout also leads to abnormalities in glutamatergic corticostriatal synapses in the striatum, as would be predicted after disruption of an integral component of the postsynaptic structure. These synapses showed narrowed postsynaptic densities by electron microscopy, altered electrophysiological properties, and elevated expression of the NR1 and NR2B subunits of the NMDA glutamate receptor (Welch et al., 2007). Together, these phenotypes clearly show that targeted disruption of components of glutamatergic synapses within the CSTC circuitry can produce anxiety and compulsive behaviors.

As noted above, several genetic studies have found mutations in the SAPAP3 gene in clinical populations (Bienvenu et al., 2009; Boardman et al., 2011; Zuchner et al., 2009), although the mutations are rare and have been more commonly found in association with trichotillomania and other grooming disorders than with OCD.

SliTrk5 knockout mice—More recently, a very similar phenotype was found in mice with a knockout of the gene for the neuron-specific transmembrane protein Siltrk5 (Shmelkov et al., 2010). The function of this protein is unknown; however, proteins of the Slitrk family have been a focus of great recent interest to psychiatric geneticists since the *Slitrk1* gene was first associated with Tourette syndrome (Abelson et al., 2005; Epelbaum, 2005; O'Roak et al., 2010). *Slitrk5* knockout mice exhibited pathological grooming and anxiety, similarly to *SAPAP3* knockouts. These behaviors were normalized by chronic fluoxetine. *Slitrk5* mice showed reduced transmission at corticostriatal synapses but, in contrast to *SAPAP3* knockout mice, showed reduced levels of NR1 and NR2B at corticostriatal synapses (Shmelkov et al., 2010). There is as yet no genetic evidence in humans linking the *Slitrk5* gene with OCD or related disorders.

Taken together with the earlier investigation in *SAPAP3* knockouts (Welch et al., 2007), these effects of *Slitrk5* knockout show how distinct genetic perturbations can lead to different abnormalities in CSTC glutamatergic neurotransmission, and yet to similar and interesting behavioral phenotypes. Better understanding of the neurobiological changes in the CSTC circuitry, and throughout the brain, in these mouse models will doubtless help advance our understanding of how normal and abnormal CSTC functioning contributes to the regulation of behavior and may thereby yield new insights into the neurobiology of OCD.

5. CLINICAL STUDIES

The various lines of evidence summarized above have motivated substantial interest in the use of glutamate-modulating agents in the treatment of OCD, especially in disease that

proves refractory to standard pharmacotherapy and psychotherapy. Fortunately, a number of glutamate-modulating agents have been developed in recent decades for other indications and are available for investigational and off-label use in this context. This has permitted a number of small clinical investigations in academic settings. The molecular targets of various glutamate-modulating medications are shown in Figure 4.

While numerous glutamate-modulating agents have been investigated in small trials in OCD, only a single placebo-controlled study has been completed to date; and the results of that study were equivocal. Impressions regarding the potential efficacy of glutamate-modulating agents therefore rest, for the present, on case series and open-label studies. These may be more informative in the case of OCD than in many other conditions, as the placebo response rate in OCD – especially in the treatment-refractory cases typically represented in pharmacological augmentation studies – is particularly low (McDougle, Epperson, Pelton, Wasylink, & Price, 2000; McDougle et al., 1994). Nevertheless, conclusions from such small, open-label studies are inherently limited. Controlled studies of some glutamate-modulating agents are underway at our site and elsewhere; the outcome of such controlled trials will provide greater clarity as to whether glutamate modulation will prove a clinically important new therapeutic strategy in the treatment of OCD.

Riluzole

The first observations suggestive of a beneficial effect from glutamate modulators in refractory OCD used the glutamate-modulating drug riluzole (Coric et al., 2003; Coric et al., 2005; Pittenger, Kelmendi, Wasylink, Bloch, & Coric, 2008). Riluzole has been approved by the U.S. FDA and by other regulatory agencies for the treatment of amyotrophic lateral sclerosis, in which it has a modest but clear beneficial effect (Miller, Mitchell, Lyon, & Moore, 2007). It appears to modulate neuronal glutamate through several mechanisms; we have recently reviewed this literature in detail (Pittenger, Coric et al., 2008). Numerous mechanisms have been described *in vitro*; the two mechanisms appear to be most relevant at clinically realistic concentrations (Figure 4; (Pittenger, Coric et al., 2008)). First, riluzole inhibits certain voltage-gated sodium channels; this attenuates action potential invasion of the axon terminal and thus reduces transmitter release. This mechanism, which is similar to the mechanism of lamotrigine, is thought to preferentially affect excitatory neurons (Prakriya & Mennerick, 2000). More recently, riluzole has been shown to potentiate reuptake of extrasynaptic glutamate by glial cells (Frizzo, Dall'Onder, Dalcin, & Souza, 2004; Fumagalli, Funicello, Rauen, Gobbi, & Mennini, 2008). Elevated extrasynaptic glutamate levels have been linked to neuronal damage and even cell death and may contribute to neuropathogy in a number of contexts (Hardingham & Bading, 2010; Pittenger et al., 2007); reduction of extrasynaptic glutamate and normalization of the synaptic:extrasynaptic glutamate ratio may therefore be of particular therapeutic importance (Pittenger, Coric et al., 2008). These speculations, however, are based largely on extrapolation from *in vitro* studies; their relevance to riluzole's *in vivo* effects and to any benefit it proves to have in OCD remains to be established.

Our group initially reported benefit from riluzole augmentation in a single case of comorbid OCD and major depression in 2003 (Coric et al., 2003). This was followed up by a 12-week open-label study of SRI augmentation with riluzole in similarly severely affected and refractory patients (Coric et al., 2005). All other medications were held constant; no formal psychotherapy was delivered during the study period. A positive clinical response (defined as a 35% improvement in the Y-BOCS score) was seen in 7 of the 13 patients in this original study. While there was no control group included, the placebo response in such refractory patients is notoriously low, and this response rate therefore is quite encouraging. A second cohort of similarly refractory patients was treated more naturalistically in a follow-up case series; a similar response rate of ~50% was seen (Pittenger, Kelmendi et al., 2008). In

pediatric OCD, a small case series from the NIMH suggests similar benefit (156, 157). Placebo-controlled studies of riluzole in refractory OCD and ongoing both in adults (clinicaltrials.gov: NCT00523718) and in children (clinicaltrials.gov: NCT00251303).

Riluzole is in general well tolerated; common side effects include mild sedation and nausea. The agent can lead to asymptomatic transaminitis and, rarely, to clinically significant hepatotoxicity; regular blood monitoring is required to avoid this complication. Two cases of pancreatitis have occurred in children treated with riluzole for OCD; this effect has not been seen in adults. Pharmacokinetics, dosing, and side effects have recently been reviewed in detail (P. Grant, Song, & Swedo, 2010; Pittenger, Coric et al., 2008).

Riluzole has also been used recently in a number of conditions related to or commonly comorbid with OCD. Open-label studies suggest efficacy in major depressive disorder, bipolar depression, and generalized anxiety (Mathew et al., 2005; Sanacora, Kendell, Fenton, Coric, & Krystal, 2004; Sanacora et al., 2007; C. A. Zarate, Jr. et al., 2004; C. A. Zarate, Jr. et al., 2005; C. A. Zarate & Manji, 2008); no controlled studies for these indications have been reported. Case reports have also suggested efficacy in patients with self-injurious behavior (Pittenger, Krystal, & Coric, 2005) and in trichotillomania and other grooming disorders (Coric et al., 2007; Sasso et al., 2006). However, these potential uses of riluzole have not yet been corroborated in larger samples, let alone in controlled studies, and they must therefore be interpreted with great caution.

NMDA pore blockers

There has been substantial interest in recent years in the use of antagonists and modulators of the NMDA glutamate receptor as treatments for psychiatric disease (Berman et al., 2000; Pittenger et al., 2007; C. A. Zarate, Jr., Singh, Carlson et al., 2006; C. A. Zarate, Jr., Singh, Quiroz et al., 2006). The rationale for using such agents in OCD is threefold. First, in light of the hypothesis that glutamate is generally elevated in OCD (Bhattacharyya et al., 2009; Chakrabarty et al., 2005), it may be therapeutic to reduce the activation of a glutamate receptor whose excessive activation can lead to neurotoxic sequelae (Hardingham & Bading, 2010). As elaborated above, glutamate dysregulation in OCD is unlikely to be as simple as global excess – witness, for example, reports of reduced glutamate, as measured by low field-strength MRS, in the anterior cingulate cortex in pediatric OCD (Rosenberg et al., 2005). Nevertheless, the availability of well-tolerated, FDA-approved agents such as memantine (Kavirajan, 2009) whose off-label use in OCD can be readily investigated has made this an attractive area of clinical research. Second, as summarized above, polymorphisms in the gene for the NMDA NR2B subunit have been associated with OCD in early candidate gene studies (Arnold et al., 2004; M.H. Bloch & Pittenger, 2010).

A final motivation for targeting the NMDA receptor in OCD derives from the apparent relationship between OCD and major depressive disorder (MDD). OCD and MDD are commonly comorbid (Ruscio et al., 2010), and the mainstay of pharmacotherapy for OCD remains the SSRI antidepressants (Koran et al., 2007). Furthermore, abnormalities in glutamate homeostasis have been repeatedly documented in MDD (Sanacora, Gueorguieva et al., 2004; Yuksel & Ongur, 2010). The recent finding that single-dose treatment with a potent NMDA antagonist, ketamine, can lead to a rapid antidepressant response in refractory depressed patients, lasting a week or more, has engendered enormous excitement (Berman et al., 2000; Pittenger et al., 2007; C. A. Zarate, Jr., Singh, Carlson et al., 2006). It is therefore of great interest to investigate whether the same agents, and the same molecular targets, are of therapeutic relevance in OCD.

Memantine—Case reports and case series suggest that there may be benefit from augmentation with the NMDA blocker memantine in OCD (Figure 4). As is the case for

riluzole, blinded, controlled studies are lacking; but the agent has attracted considerable ongoing interest. Memantine is a low-affinity open-pore NMDA blocker with a rapid receptor off-time; these characteristics have been argued to be the reason that it does not possess the psychotomimetic properties of the more potent pore-blocking agents phencyclidine and ketamine. Memantine is approved by the FDA and other regulatory agencies for the treatment of moderate-severity Alzheimer's disease and is widely used for this indication (Kavirajan, 2009). A controlled study found no evidence for efficacy in major depressive disorder, at a single moderate dosage (C. A. Zarate, Jr., Singh, Quiroz et al., 2006); but explorations of the utility of the agent continue in neurodegenerative disorders beyond Alzheimer's disease (e.g. Ondo, Shinawi, Davidson, & Lai, 2011), in neuropathic pain (Collins, Sigtermans, Dahan, Zuurmond, & Perez, 2010), and in other conditions.

In OCD, early case reports suggested benefit from memantine augmentation of standard SSRI pharmacotherapy in refractory adults (Pasquini & Biondi, 2006; Poyurovsky, Weizman, Weizman, & Koran, 2005) and, subsequently, children (Hezel, Beattie, & Stewart, 2009). These observations, along with suggestive observations in behavioral animal models (Egashira et al., 2008; Wald, Dodman, & Shuster, 2009), have motivated several subsequent studies. Aboujaoude and colleagues (Aboujaoude et al., 2009) described an open-label trial of 15 refractory OCD patients who were treated with 12 weeks of memantine augmenation; 42% were judged to be treatment responders, defined as a 25% improvement from symptom baseline. In another open-label trial, Feusner and colleagues (Feusner et al., 2009) compared the effect of 12 weeks of memantine in 10 patients with OCD to those on 7 similar patients with generalized anxiety disorder (GAD). They found substantially greater improvement in the OCD patients (40.6% Y-BOCS improvement for the group) than in the GAD patients (22.4% improvement in the Hamilton Anxiety Rating Scale). This suggests that benefit from memantine may be specific to OCD, and not a nonspecific effect on anxiety.

Most recently, Stewart and colleagues described a series of 22 patients treated with memantine augmentation, in conjunction with other pharmacological management and with intensive inpatient behavioral treatment at the McLean Hospital OCD Institute (Stewart et al., 2010). They compared these patients with 22 retrospectively-identified control subjects in the same treatment program. A greater improvement in Y-BOCS scores was seen among memantine-treated patients (27%) than among controls (16.5%), suggesting benefit. This study is limited by its retrospective nature, by incomplete blinding of both patients and treaters, and by the uniquely refractory patient population and the intenstive behavioral and pharmacological management the patients were receive simultaneously; despite these caveats, it represents an important step towards the necessary goal of fully blinded, controlled, prospective studies to explore the efficacy of this and other glutamate-modulating agents. Overall, the evidence for benefit from memantine augmentation is comparable to that for rilzuole, consisting of a handful of promising but suboptimally controlled open-label studies.

Ketamine—As noted above, single-dose infusion with the potent NMDA blocker ketamine has been found to have a remarkable, rapid antidepressant effect in refractory patients (Berman et al., 2000; C. A. Zarate, Jr., Singh, Carlson et al., 2006). This has engendered considerable interest in whether a similar therapeutic effect can be seen in OCD. A single recent case report has begun to provide data on this question (Rodriguez, Kegeles, Flood, & Simpson, 2011). A 24 year-old patient with severe, refractory OCD received ketamine and saline infusions, a week apart from one another, following the protocol used in multiple studies of depression. There was no effect of saline infusion on OCD symptoms, as measured using a visual analog scale. After ketamine infusion, however, there was a substantial, ~50% reduction in self-reported obsessions, which lasted at least 3 days. This

initial report, from a single patient, is suggestive that ketamine infusion may have benefit in OCD paralleling that seen in refractory depression. More research on this question is needed.

NMDA glycine-site coagonists: chronic treatment

There has been equal interest in the field in agents that enhance NMDA receptor function, primarily through action on the NMDA glycine co-agonist site. The fact that both NMDA antagonists and NMDA enhancers are being actively investigated in OCD is testament to the nascent state of our understanding of the nature of glutamate dysreguation in this disorder.

The glycine co-agonist site on the NR1 subunit of the NMDA receptor is thought to play an important modulatory role *in vivo*. Activation of the NMDA receptor requires three coincident events: binding of glutamate to the primary agonist site; depolarization of the postsynaptic neuron; and binding of glycine (or the related molecule D-serine, which may be the principal co-agonist *in vivo*). Glycine/D-serine is thought to be present at fairly constant (or at least slowly-changing) levels, in contrast to the rapid changes in synaptically released glutamate). Enhancing glycine/D-serine concentrations, therefore, is expected to potentiate NMDA signaling; but this activation should be phasically gated by glutamate release and postsynaptic neuronal depolarization, avoiding the neurotoxic effects of chronic receptor activation seen with pharmacological activation of the glutamate agonist site itself.

From a theoretical point of view, the strategy of potentiating NMDA function using an agonist at the glycine site is less easy to justify than an anti-NMDA strategy; in particular, it is counterintuitive in the context of data suggesting elevated glutamate in unmedicated patients with OCD (Bhattacharyya et al., 2009; Chakrabarty et al., 2005). Preclinical models, however, lend some support to the strategy. NMDA antagonists lead to a paradoxical increase in frontal cortical glutamate (presumably by preferentially inactivating inhibitory interneurons), illustrating the potentially counterintuitive effect of agents acting at this receptor (Moghaddam & Adams, 1998). NMDA antagonism exacerbates repetitive behaviors in the D1CT-7 mice, described above (McGrath et al., 2000). Of more direct relevance, as summarized below, pilot clinical data with several different glycine-site agonists show promise in OCD. No definitive studies targeting this site have been performed, but it clearly merits further attention and study.

Should chronic NMDA potentiation prove efficacious in OCD, it would speak to the complexity of the poorly understood alterations in excitatory neurotransmission in the disorder. It is likely to be insufficient to merely think of glutamate as being ‘up’ or ‘down’ in the brain of patients with OCD. Rather, as emphasized above, complexities such as the distinction between effects in different brain regions (Rosenberg et al., 2000; Rosenberg et al., 2004), alterations of synaptic versus extrasynaptic glutamate (Hardingham & Bading, 2010), and the balance of glutamate and other neurotransmitters such as GABA are likely to be critical to understanding how excitatory neurotransmission is perturbed in patients with OCD.

Glycine—Greenberg and colleagues performed a small, placebo-controlled study in which patients were given oral glycine, at high doses previously shown to affect brain glycine levels and NMDA activation (W. M. Greenberg et al., 2009). The high doses required lead to an unpleasant taste and substantial nausea that is difficult for patients to tolerate; the dropout rate in this study was correspondingly high (7 of 12 patients within the glycine-treated group). The nausea produced by the glycine also makes it difficult to maintain blind in a study such as this. With these substantial caveats, however, the results of this study – the only double-blind, placebo-controlled study of a glutamate-modulating agent in OCD published to date – were encouraging. The five completers showed a 6-point improvement

in Y-BOCS, compared to a 1-point change in 9 placebo-treated completers; the difference in this analysis approached statistical significance. No intent-to-treat analysis was presented in this study, and clearly any such analysis would be compromised by the low completion rate.

A single case report lends further anecdotal evidence for the potential utility of this therapeutic strategy. Cleveland et al (Cleveland, DeLaPaz, Fawwaz, & Challop, 2009) report the case of a young man, with somewhat atypical but quite disabling OCD, whose symptoms improved with high-dose glycine treatment. Treatment continued on-and-off for five years; symptomatic worsening accompanied glycine discontinuation in a few instances, though the correlation was not perfect.

These reports are best considered proof-of-concept for the general mechanism of glycine agonism; given the low tolerability, it is unlikely that high-dose glycine will become a clinically useful treatment, the above-mentioned case report notwithstanding. It is quite encouraging, however, of the general strategy of targeting the NMDA glycine site as a potential glutamate-modulating therapy for OCD.

Gly-T1 inhibition: sarcosine—An alternative strategy to enhance glycine tone *in vivo* is to reduce the reuptake and/or breakdown of endogenous glycine. Glycine is removed from the extracellular space by the glycine transporter Gly-T, primarily by Gly-T1. Pharmacological inhibition of Gly-T1 therefore represents a potential therapeutic strategy to positively modulate NMDA function in OCD. Gly-T1 inhibitors have received increasing attention recently, primarily in the context of studies of schizophrenia (Hashimoto, 2011). Sarcosine, or N-methylglycine, is a naturally occurring Gly-T1 inhibitor that has been explored in this context (Wu, Tang, Lane, Tsai, & Tsai, 2011). Unlike high-dose glycine required to affect levels in the brain, sarcosine is reasonably well tolerated.

In a recent open-label study, Wu and colleagues investigated the potential benefit of sarcosine, either as monotherapy or augmentation, in OCD. 25 subjects treated for 10 weeks showed a mean Y-BOCS improvement of 20%; eight were judged treatment responders, by the criterion of having achieved a 35% improvement in Y-BOCS. A single subject withdrew due to headache; the agent was otherwise well tolerated.

N-acetylcysteine

The antioxidant amino acid N-acetylcysteine (NAC), which has glutamate-modulating properties, has received increasing attention recently as a potential therapeutic agent in neuropsychiatric disease. The published evidence for its utility in OCD is extremely thin, consisting of a single case report (Lafleur et al., 2006). However, as this is an area of active research, its mechanisms are briefly reviewed here (Figure 4).

NAC has long been used for its antioxidant properties, including as a treatment for oxidative liver damage in acetaminophen poisoning. Its glutamate-modulating properties have been appreciated more recently (Dean, Giorlando, & Berk, 2011; Sansone & Sansone, 2011). In the brain, NAC is converted to cystine, which is a substrate for the glial cystine-glutamate antiporter. Treatment with NAC is therefore expected to increase extrasynaptic glutamate. Such an effect has been clearly demonstrated in studies in rat, in which NAC can normalize depressed extrasynaptic glutamate in the nucleus accumbens of cocaine-exposed rats; this normalized glutamate acts on presynaptic type 2/3 metabotropic glutamate receptors to moderate pathologically elevated synaptic glutamate release (Moran, McFarland, Melendez, Kalivas, & Seamans, 2005). It remains unclear whether this same mechanism operates in other brain regions and under other biological circumstances. Effects of NAC in the brain on glutamate and on oxidation state are likely to be related: glutamate is a biochemical precursor of glutathione, the brain's primary antioxidant; and genetic manipulations of

glutamate homeostasis in mice – in fact, genetic disruption of the *Slc1A1* gene – can alter both glutathione levels and oxidative stress (Aoyama et al., 2006).

As in the case of NMDA potentiators, the ability of NAC to trigger glutamate efflux from glia makes it a somewhat counterintuitive target as an OCD treatment. In light of clinical evidence suggesting elevated glutamate in OCD, summarized above, elevating glial glutamate efflux may not be desirable – indeed, this is the opposite of the proposed mechanism of riluzole in enhancing reuptake of extrasynaptic glutamate (Pittenger, Coric et al., 2008). Nevertheless, NAC's attractive clinical characteristics (it is inexpensive, is available without a prescription, and is extremely well tolerated), as well as the animal literature indicating that it can attenuate compulsive drug-related behaviors (Kalivas, 2009), have motivated considerable interest in the agent.

Several years ago, we described a single case of clinical improvement in refractory OCD after augmentation with NAC (Lafleur et al., 2006). This remains the only published report of NAC in OCD. Subsequently, however, a well-controlled trial showed striking benefit in adult patients with trichotillomania (J. E. Grant, Odlaug, & Kim, 2009). Case reports suggest benefit in other grooming disorders, as well (Odlaug & Grant, 2007).

Other small controlled studies have suggested benefit from NAC treatment in pathological gambling (J. E. Grant, Kim, & Odlaug, 2007) and bipolar depression (Berk et al., 2008). Because of these several positive studies in other conditions, interest in this agent continues to be substantial. Controlled studies are needed.

Other glutamate-modulating agents

The off-label use of a variety of other available glutamate-modulating agents in OCD has been reported, at the level of case reports and small case series. The evidence for the utility of these agents is not strong, but some of them may prove fruitful targets of future study.

Lamotrigine inhibits certain voltage-gated sodium channels, limiting action potential invasion of the axon terminal and therefore reducing neurotransmitter release (Lingamaneni & Hemmings, 1999). This resembles one of the two mechanisms reviewed above by which riluzole appears to reduce glutamate levels (Pittenger, Coric et al., 2008). Case reports of lamotrigine augmentation suggest benefit in OCD (Kumar & Khanna, 2000; Uzun, 2010); benefit has also been reported in schizoaffective patients with clinically significant OCD symptoms, in an open-label case series (Poyurovsky, Glick, & Koran, 2010). A controlled study also suggests benefit in a subset of patients with pathological skin picking (J. E. Grant, Odlaug, Chamberlain, & Kim, 2010). However, an early open-label case series suggested no benefit (Kumar & Khanna, 2000); and OCD-like symptoms after lamotrigine treatment in bipolar 2 have been reported (Kemp, Gilmer, Fleck, & Dago, 2007; Kuloglu, Caykoylu, Ekinci, & Yilmaz, 2009).

The antiepileptic agent topiramate also has glutamate-modulating properties. Augmentation with topiramate has been of reported benefit in refractory OCD in case reports (Hollander & Dell'Osso, 2006; Vinkers & van der Wee, 2008). In a retrospectively-evaluated open-label case series, 11 of 16 patients treated with topiramate augmentation were judged to be much improved or very much improved on the Clinical Global Impression scale (Van Ameringen, Mancini, Patterson, & Bennett, 2006). A second, prospective, open-label trial reported similar results, finding a clinical response (defined as a 30% improvement in the Y-BOCS) in 10 of 12 patients treated with topiramate augmentation (Rubio, Jimenez-Arriero, Martinez-Gras, Manzanares, & Palomo, 2006). More recently, however, a controlled study reported no statistically significant benefit in overall Y-BOCS score, although a small, statistically significant improvement in the obsessions subscale of the Y-BOCS was found

(Van Ameringen et al., 2006). The side effects of topiramate are more significant than those of some of the other glutamate-modulating agents described here; in the recently-described controlled study, 28% of topiramate-treated patients dropped from the trial due to side effects, and 39% required a dose reduction during the study (Berlin et al., 2010). Induction of OCD symptoms by topiramate has been reported in individual cases (Ozkara, Ozmen, Erdogan, & Yalug, 2005; Thuile, Even, & Guelfi, 2006).

D-cycloserine augmentation of cognitive-behavioral therapy

Specialized cognitive behavioral therapy (CBT) is highly effective in many cases of OCD and is a first-line treatment (Koran et al., 2007). CBT is structured learning, and in recent years there has been increasing interest in using biological insights into the neural mechanisms of learning to identify strategies for pharmacological enhancement of CBT (Choi, Rothbaum, Gerardi, & Ressler, 2010; Ganasen, Ipser, & Stein, 2010; Norberg, Krystal, & Tolin, 2008). The NMDA glutamate receptor is critical to the mechanisms of most experimental forms of synaptic plasticity; pharmacological or genetic enhancement of NMDA function in animals can enhance several forms of learning in animals (Tang et al., 1999; Walker, Ressler, Lu, & Davis, 2002). Most studies of pharmacological augmentation of psychotherapy have therefore focused on NMDA potentiation using D-cycloserine (DCS), a partial agonist of the modulatory glycine co-agonist site (see Figure 4). A landmark study by Ressler and colleagues demonstrated benefit from D-cycloserine augmentation of behavioral therapy in patients with acrophobia; pharmacological treatment improved both the rate of extinction-based psychotherapy and the persistence of symptomatic benefit (Ressler et al., 2004). Since that initial study, a number of similar studies have used a similar approach in a variety of anxiety disorders and other conditions (Norberg et al., 2008). Four studies attempting DCS augmentation of psychotherapy in OCD have been reported to date (Kushner et al., 2007; Storch et al., 2007; Storch et al., 2010b; Wilhelm et al., 2008).

The logic of this treatment strategy is quite different from pharmacological treatment through chronic activation of this site, using an agonist such as glycine (W. M. Greenberg et al., 2009) or D-serine, which is why it is being described separately here. Chronic glycine-site agonist treatment, a strategy that has been described above, aims to correct or compensate for a hypothesized abnormality in NMDA function or some other aspect of glutamate neurotransmission. DCS has proven a problematic agent for such an approach, as repeated treatment leads to a reduced behavioral effect (i.e. tachyphylaxis; Goff et al., 2008; Parnas, Weber, & Richardson, 2005), probably because of agonist-induced NMDA receptor internalization (Nong et al., 2003).

DCS augmentation of psychotherapy, in contrast, entails intermittent dosing, typically shortly before a psychotherapy session; the goal is to enhance the mechanisms of synaptic plasticity transiently during the session, not chronically. No fundamental abnormality of glutamate neurotransmission or homeostasis is presumed; indeed, the assumption is that the normal NMDA-dependent mechanisms of learning are intact and available. Because of the intermittent dosing, tachyphylaxis is not expected to be an issue (Goff et al., 2008; Parnas et al., 2005). However, the intermittent dosing leads to an increased number of variables in clinical trials: not only drug dose, but also the interval between drug dose and the psychotherapy session (as well as the frequency and specific form of the psychotherapy session itself) must be specified (Rothbaum, 2008). This broadened range of treatment parameters may contribute to the heterogeneity in outcome that has been seen in DCS augmentation studies in OCD. A full evaluative review of these variables is beyond the scope of this review; we simply provide a summary of the four treatment studies published to date.

The first study attempting DCS augmentation of CBT in OCD found no benefit. 24 adult patients received standardized psychotherapy; half received DCS augmentation 4 hours before therapy sessions, in a blinded, placebo-controlled fashion. Neither the rate of improvement nor the total improvement achieved differed between treatment groups (Storch et al., 2007). At about the same time, a separate, similar study randomized 32 adult OCD patients (25 completers) to receive either DCS or placebo in conjunction with therapy, and found more rapid improvement in patients receiving augmentation treatment; placebo-treated patients achieved similar final levels of improvement, after additional sessions (Kushner et al., 2007). A major difference between the two studies was that patients in this successful trial took DCS 2 hours before their therapy sessions, rather than 4; this may be a critical variable (Rothbaum, 2008). Subsequently, a third study randomized 23 patients to receive either DCS or placebo one hour before twice-weekly treatment sessions. Patients receiving augmentation again showed more rapid improvement; at the end of treatment, OCD symptoms in the two groups were similar, but depression was more improved in DCS-treated patients (Wilhelm et al., 2008). Finally, a recently reported study extended this approach to pediatric OCD. In a similar trial design, 30 pediatric patients received either DCS or placebo, one hour before therapy sessions. DCS-treated patients tended to improve more, and more rapidly, though the difference did not reach statistical significance (Storch et al., 2010b).

As a whole, these four studies provide exciting evidence that pharmacological augmentation of psychotherapy through targeting of the glutamate system may significantly speed the response to psychotherapy in OCD. Whether this can then lead to symptomatic benefit at the end of treatment remains unclear; but even if it does not, an accelerated treatment response is clinically valuable.

6. CONCLUSIONS AND SYNTHESIS

The case for dysregulation of glutamate neurotransmission and/or homeostasis in obsessive-compulsive disorder remains inconclusive; but convergent data from the many approaches summarized above are making it progressively stronger. Much remains to be established. We conclude our review by summarizing major outstanding conceptual and technical issues, to put this growing literature into context

How strong is the evidence?

The various lines of evidence summarized above are of varying strength. The clearest evidence for a fundamental dyregulation of glutamate in OCD derives from the neurochemical analysis of cerebrospinal fluid from unmedicated OCD patients (Bhattacharyya et al., 2009; Chakrabarty et al., 2005). The direct detection of glutamate in this pair of studies, both from the same group, avoids many of the interpretative pitfalls inherent in less direct measurements. In contrast, CSF analysis does not permit any localization as to where in the brain the glutamate is coming from, and it provides only very limited evidence as to the nature of the abnormality that leads to the observed increase in CSF glutamate. Local measurements of glutamate are possible using MRS; but the MRS evidence of glutamate dysregulation must be interpreted with caution. As summarized above, all MRS studies published to date have used low magnetic field strength and have reported a compound measure, *Glx*, rather than glutamate itself. There has been substantial inconsistency among the various MRS studies that have been published to date (Rosenberg et al., 2000; Rosenberg et al., 2004; Starck et al., 2008; Whiteside et al., 2006; Yucel et al., 2008).

The genetic investigations summarized above remain limited in important ways. Most candidate gene associations have not been consistently replicated (M.H. Bloch & Pittenger,

2010). The best-replicated finding remains the association of OCD risk with variants in the neuronal glutamate transporter EAAT3, encoded by the *Slc1A1* gene (Arnold et al., 2006; Dickel et al., 2006; Kwon et al., 2009; Liang et al., 2008; Shugart et al., 2009; Stewart et al., 2007; Wang et al., 2010; Wendland et al., 2009). However, caveats are necessary for even this multiply-replicated association. Most disease-associated SNPs that have been identified are merely markers; causative mutations and their biochemical effects remain largely unknown (Wendland et al., 2009). Furthermore, the specific SNPs associated with OCD risk have not been consistent across studies. This could very likely result from differences among the specific populations studied; but it raises lingering doubts about the validity of the association. Further replication in much larger samples is needed (M.H. Bloch & Pittenger, 2010).

The animal models provide intriguing evidence that perturbations of glutamate-related signaling processes in the basal ganglia can lead to anxiety and grooming abnormalities, but only weak evidence that they do contribute to clinical OCD. An enormous challenge in such animal models is to establish the relevance of the mechanisms elucidated to OCD in humans.

The clinical studies summarized above are quite preliminary: larger, well-controlled studies are essential. If validated, these novel glutamate-targeting therapies could be of immense clinical importance. However, modulation of glutamate neurotransmission could be of benefit in patients even in the absence of a core glutamate-related abnormality, by counterbalancing an abnormality in some other system. Therefore, while ongoing exploration of the clinical utility of glutamate-modulating agents is critical, it is unlikely to provide as robust support for a ‘glutamate hypothesis’ of OCD as neurochemical and genetic studies may.

Cause or consequence?

A separate question is whether abnormalities in glutamate are a fundamental cause of OCD, or whether they are a downstream consequence of other processes that are more primary to the pathophysiology. This is not a question that need necessarily have a single answer – it is possible, even likely, that perturbation of glutamate may be an important cause of OCD in some cases, but a downstream consequence of other events in others.

The strongest evidence for glutamate homeostasis as a cause of OCD derives from the genetic association of the *Slc1A1* glutamate transporter gene with OCD risk. A functional abnormality in this glutamate transporter could, in principle, produce the elevated glutamate observed in neurochemical studies: a reduction in glutamate reuptake would presumably leave more glutamate in the extracellular space and, ultimately, in the CSF. In addition, since glutamate taken back up into neurons may be available for re-use as a neurotransmitter, reduced reuptake might also lead to a requirement for enhanced synthesis, and consequently to an increase in whole-tissue glutamate. These connections are speculative, but they begin to paint a picture of how abnormalities in glutamate transport might lead to some of the other abnormalities in glutamate measures described above. How these abnormalities could then lead to the symptoms of OCD remains obscure and an important area for ongoing research.

Are glutamate abnormalities in OCD an epiphenomenon of neuronal hyperactivity?—It is widely accepted that OCD is characterized by neuronal hyperactivity, or at least increased metabolism, in certain key brain areas – chiefly the orbitofrontal cortex, the caudate nucleus, and the anterior cingulate cortex (Maia et al., 2008; Rotge et al., 2010). It is possible that the observed abnormalities in glutamate in patients with OCD are simply a consequence of this hyperactivity: increased neuronal firing implies

increased synaptic glutamate release, which may lead both to increased synthesis as well as to increased levels in the CSF. According to this hypothesis, glutamate dysregulation in OCD would be real, and potentially a useful therapeutic target, but would be a secondary consequence of neuronal hyperactivity that derived from some other pathophysiological process.

Several considerations – not conclusive – suggest that altered glutamate may not simply be an epiphenomenon. First, neuronal and glial glutamate reuptake is extraordinarily efficient (Danbolt, 2001). Elevations in CSF glutamate in OCD (Bhattacharyya et al., 2009; Chakrabarty et al., 2005) therefore may indicate an abnormality in how glutamate is buffered and metabolized in the brain, and not merely elevated synaptic activity. Second, both the genetic association with the *Slc1A1* gene and the findings from specific animal models suggest that primary perturbations in glutamate signaling within this circuit can lead to OCD, or at least to OCD-like behaviors.

Third, the heterogeneity in brain glutamate suggested by MRS implies that things cannot be so simple. Studies published to date suggest, inconsistently, elevated glutamate (or *Glx*) in the caudate nucleus and orbitofrontal cortex, but reduced *Glx* in anterior cingulate cortex (Rosenberg et al., 2000; Rosenberg et al., 2005; Starck et al., 2008; Whiteside et al., 2006; Yucel et al., 2008). Elevated metabolic activity is seen in all three of these structures (Maia et al., 2008; Menzies et al., 2008; Rotge et al., 2008). Assuming that these glutamate measures hold up in future studies, this suggests a dissociation between pathological elevations in neuronal activity and perturbations in whole-tissue glutamate. Unlike the cortex, the striatum contains no glutamatergic neurons (Kreitzer, 2009), and all glutamate in this structure therefore represents either metabolic pools – including glutamate as a precursor in the biosynthesis of GABA – or neurotransmitter glutamate derived from afferents. But this cannot explain why glutamate should be differently affected in orbitofrontal and cingulated cortices (Rosenberg et al., 2004; Whiteside et al., 2006; Yuksel & Ongur, 2010). This dissociation suggests that regional perturbations in glutamate reflect something other than simple neuronal hyperactivity.

It is equally plausible that the causality of this relationship is in the other direction: that the observed elevation in metabolic activity in the OCD-related circuit is a consequence of glutamate dysregulation. Glutamate reuptake is energetically costly (Danbolt, 2001); increased extracellular glutamate, which would drive increased reuptake, could therefore directly increase the metabolic rate of a particular brain region, in addition to indirectly increasing metabolism through activation of neuronal firing.

A connection between glutamate and autoimmunity?—There is a long though controversial literature associating OCD, at least in some circumstances, with abnormalities in immune function (Swedo & Grant, 2005; Swedo, Leonard, & Rapoport, 2004) (Dietrich et al., 2005; Rotge et al., 2010) (Bhattacharyya et al., 2009). One recent proposal is that elevated glutamate can potentiate autoimmune responses in the brain (Rotge et al., 2010). It has been suggested that glutamate can function as a T-cell regulatory by binding on metabotropic glutamate receptors present on the T-cell surface (Pacheco, Gallart, Lluis, & Franco, 2007). The mGluR1 glutamate receptor, in particular, is induced when T-cells are activated; enhanced glutamate may thus enhance cytokine production after activation of T-cells by viral infection or other means (Rotge et al., 2010). This intriguing proposal lacks clear empirical support, but it illustrates an interesting potential role for elevated glutamate in the etiology of OCD beyond the simple activation or modulation of neuronal function.

Cellular and circuit-level effects of glutamate dysregulation—If glutamate dysregulation accompanies OCD, as cause, consequence, or even epiphenomenon – what

might be the effects? Any attempt to address this question is necessarily speculative. One possibility, outlined above, is that abnormalities in glutamate transport lead to maldistribution of glutamate, resulting in excessive activation of extrasynaptic NMDA receptors. This suggestion is not specific to OCD: a very similar hypothesis has been explored to explain glutamate dysregulation in major depressive disorder and in animal models of chronic stress (Banasr et al., 2010; Pittenger et al., 2007).

In a recent modeling study, Rolls and colleagues explored the potential consequences of excessive glutamatergic neurotransmission in artificial neural networks (Rolls, Loh, & Deco, 2008). They propose that pathologically enhanced neuronal functional connectivity, through excessive stimulation of NMDA and/or AMPA glutmate receptors, leads to the presence of 'strong attractors' within decision-making networks. These attractors are network states that represent particular cognitions or action patterns; if they are maladaptively stabilized, such that the network settles into such a state repeatedly, such attractors might explain the obsessions and cognitive inflexibility seen in patients with OCD.

Diagnostic and treatment considerations

Clinical subtypes—OCD is a heterogeneous disorder. Two patients with OCD can qualify equally well for the diagnosis, yet have no specific symptoms in common. This observation has led to increasing interest in recent years as to whether OCD can better be described as a cluster of overlapping conditions, or by a series of quasi-independent symptom dimensions (M. H. Bloch, Craiglow et al., 2009; Leckman, Bloch, & King, 2009; Mataix-Cols et al., 2005). In this light, whether glutamate dysregulation is more associated with one putative subtype or symptom dimension than with others is an interesting and important clinical question. Unfortunately, no studies have directly addressed this question to date. A single study suggests a genetic interaction between the *Slc1A1* locus and another genetic locus on chromasome 14q that has been associated with hoarding (Liang et al., 2008), suggesting the possibility of a particular relationship with hoarding symptoms. Neurochemical studies performed to date – both CSF and MRS – have not been large enough to detect differential glutamate abnormalities in OCD subtypes.

Therapeutic import—The ultimate therapeutic import of the hypothesis that glutamate dysregulation contributes to OCD remains to be seen. As noted repeatedly above, no studies published to date are definitive: most are case reports or small open-label studies, and those controlled studies that have been described are either retrospective or have failed to show statistically convincing results. Nevertheless, the hope for therapeutic benefit from such agents, especially in the large fraction of patients refractory to established treatment approaches, drives continued interest (Pittenger, Coric et al., 2008; Pittenger et al., 2006). Larger, controlled studies are urgently needed.

If glutamate dysregulation proves to be characteristic of a meaningful clinical subtype of OCD, this may prove to usefully inform therapy with non-glutamatergic agents, as well. For example, glutamate dysregulation may serve as a biomarker to identify cases of OCD that are differentially responsive to SSRI treatment or to behavioral therapy. To date, no studies have rigorously examined this idea.

Conclusion

The suggestion that glutamate dysregulation may contribute to OCD has now been with us for more than a decade (Carlsson, 2000; Moore et al., 1998). Definitive evidence supporting (or contradicting) it has been slow to emerge. However, convergent evidence is increasingly supportive of the idea, and early clinical studies suggesting the possible efficacy of glutamate-modulating medications are tantalizing. The precise nature of the dysregulation,

however, remains quite unclear. Further work in all of the technical areas here – from genetics to imaging to animal modeling – will be required to clarify these matters.

Ultimately, the value of the 'glutamate hypothesis' of OCD will be whether it can produce pathophysiological insights that lead to clinical advances and benefit our patients. Such benefit could come in several directions. Direct clinical improvement from glutamate-modulating medications would be the most obvious such benefit. Measurements of glutamate-related abnormalities in patients with OCD might also contribute to diagnostic subtyping into biologically meaningful component conditions, which could be valuable in ongoing efforts to make sense of the extreme heterogeneity of patients with OCD. Finally, insights into glutamate physiology in OCD may lead to predictors of treatment response, which would be of immense clinical value.

In sum, the suggestion that glutamate dysregulation contributes to OCD has spurred increasing interest and research efforts. Much more work is needed, and is ongoing; this new neurochemical perspective on the disorder has received increasing attention from clinicians, geneticists, and basic scientists.

ABBREVIATIONS

5-HT	serotonin (5-hydroxytryptamine)
α-KG	α-ketoglutarate
ACC	anterior cingulate cortex
AMPA receptor	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid-type glutamate receptor
CBT	cognitive-behavioral therapy
CSF	cerebrospinal fluid
CSTC	cortico-striato-thalamo-cortical
Cys	cystine
D1 receptor	dopamine receptor type 1
D1CT-7	transgenic mice expressing cholera toxin under the D1 promoter
D2 receptor	dopamine receptor type 2
DCS	D-cycloserine
D-Ser	D-serine
DSM-IV	diagnostic and statistical manual of mental disorders, 4th edition
EAAC1	excitatory amino acid channel 1 (equivalent to EAAT3)
EAAT1–3	excitatory amino acid transporters 1–3
FDA	U.S Food and Drug Administration
GABA	gamma-aminobutyric acid
GAD	generalized anxiety disorder
GAD	glutamic acid dehydrogenase
GAT	GABA transporter
GLAST	glutamate-aspartate transporter (equivalent to EAAT2)

Gln	glutamine
GLT-1	glutamate transporter 1 (equivalent to EAAT1)
Glx	MRS measurement of glutamate, glutamine, and related molecules
Gly	glycine
Gly-T	glycine transporter
GPe	globus pallidus, *pars externa*
GPi	globus pallidus, *pars interna*
GriK	glutamate receptor gene, ionotropic, kainite subtype
GriN2B	glutamate receptor, ionotropic, NMDA, subunit 2B – gene encoding the NR2B subunit
MDD	major depressive disorder
mGluR	metabotropic glutamate receptor
MK-801	an NMDA channel blocking drug
MRS	magnetic resonance spectroscopy
MSN	medium spiny neuron
NAC	N-acetylcysteine
NMDA receptor	N-methyl-D-aspartate-type glutsmate receptor
NR1	obligate subunit of the NMDA receptor
NR2B	2B subunit of the NMDA receptor
OCD	obsessive-compulsive disorder
OFC	orbitofrontal cortex
PET	positron emissio tomography
PSD	postsynaptic density
RNA	ribonucleic acid
SAPAP3	SAP90-PSD-95 associated protein 3
Slc1A1	solute carrier family gene 1A1 (gene encoding EAAT3/EAAC1 protein)
Slitrk5	gene for Slit and Trk-like protein 5
SNc	substantia nigra, *pars compacta*
SNP	single nucleotide polymorphism
SNr	substantia nigra, *pars reticulata*
SSRI	selective serotonin reuptake inhibitor
STN	subthalamic nucleus
Suc	succinate
TCAn	tricarboxylic acid cycle (Krebs cycle)
vGluT	vesicular glutamate transporter

XC-	cystine-glutamate transporter
Y-BOCS	Yale-Brown Obsessive Compulsive Scale

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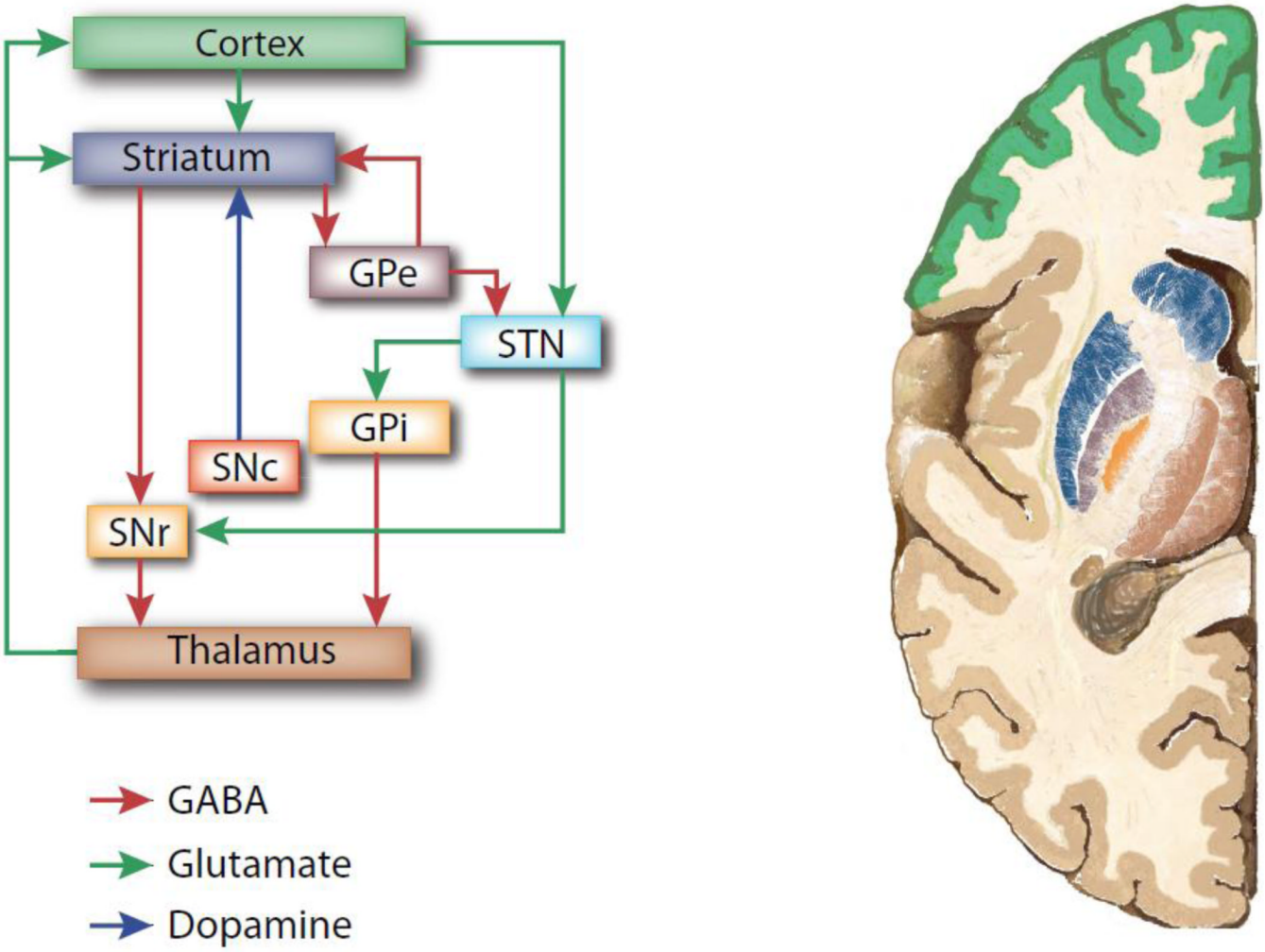

FIGURE 1. The CSTC circuitry implicated in OCD

Convergent evidence from functional and structural neuroimaging suggests that abnormalities in the circuitry interconnecting the cortex, basal ganglia, and thalamus. The canonical connections forming these cortico-striato-thalamo-cortical (CSTC) loops is shown in simplified form here. Projections in this circuit use both the excitatory neurotransmitter glutamate and the inhibitory neurotransmitter GABA, as shown. Modulatory dopamine critically modulates information flow through this circuit. Other important modulatory neurotransmitters, such as acetylcholine, serotonin, and histamine, are excluded for clarity.

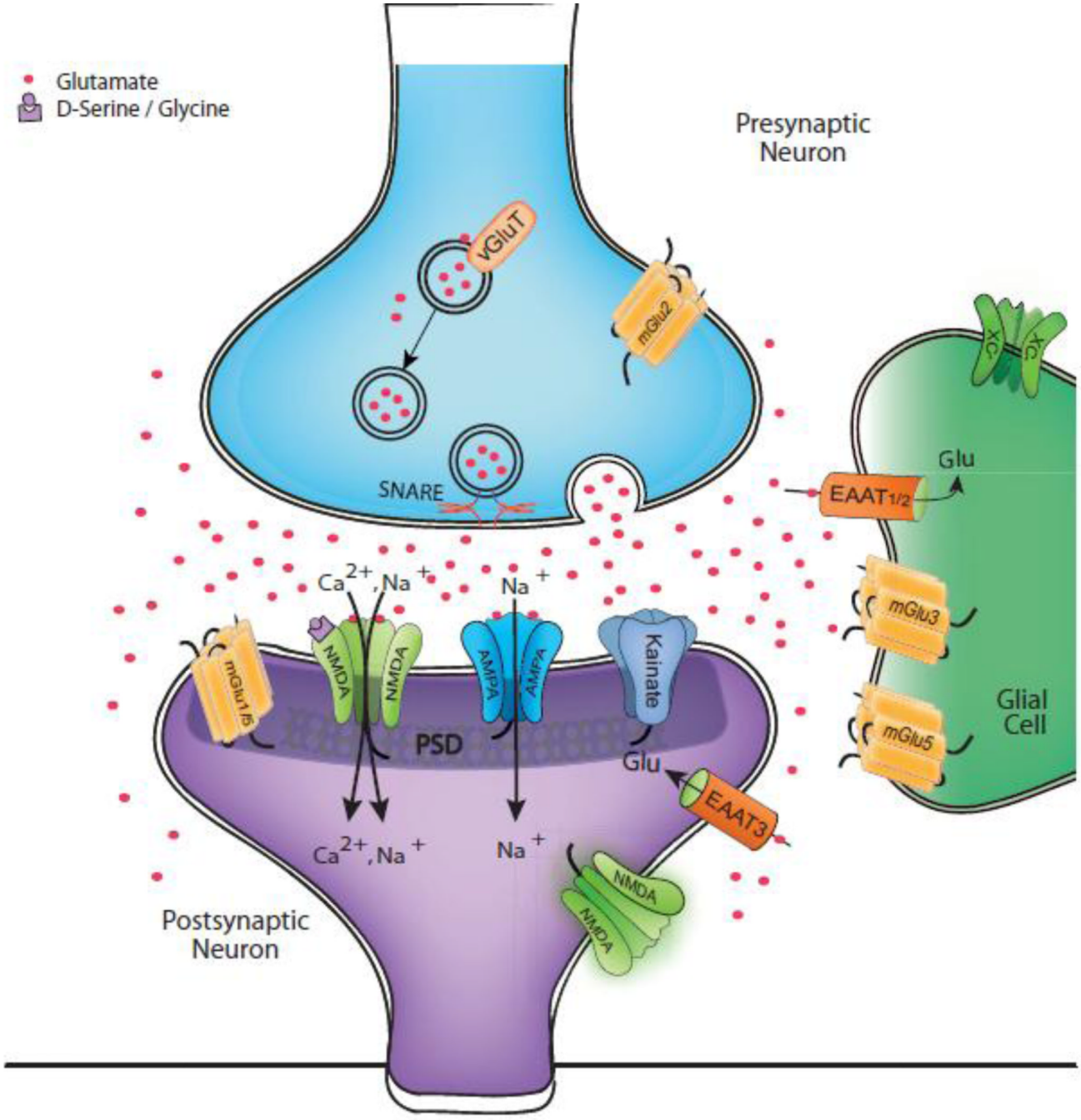

FIGURE 2. The principle components of the glutamate synapse

Glutamate is the primary excitatory neurotransmitter in the adult brain. It is packaged into vesicles in axon terminals by the vesicular glutamate transporter, **vGluT**. Glutamate binds to both ionotropic receptors (**NMDA, AMPA**, and **kainate**) and metabotropic receptors (mGluRs), postsynaptically, extrasynaptically, and presynaptically. Glial cells, principally astrocytes, play a major role in glutamate reuptake through the transportwea **EAAT1** and **EAAT2**, terminating the glutamate synaptic signal; the neuronal transporter **EAAT3** plays a quantitatively minor role in this process. Steady-state extrasynaptic glutamate levels are also regulated by the glial cystine-glutamate antiporter (**XC-**). See text for further discussion.

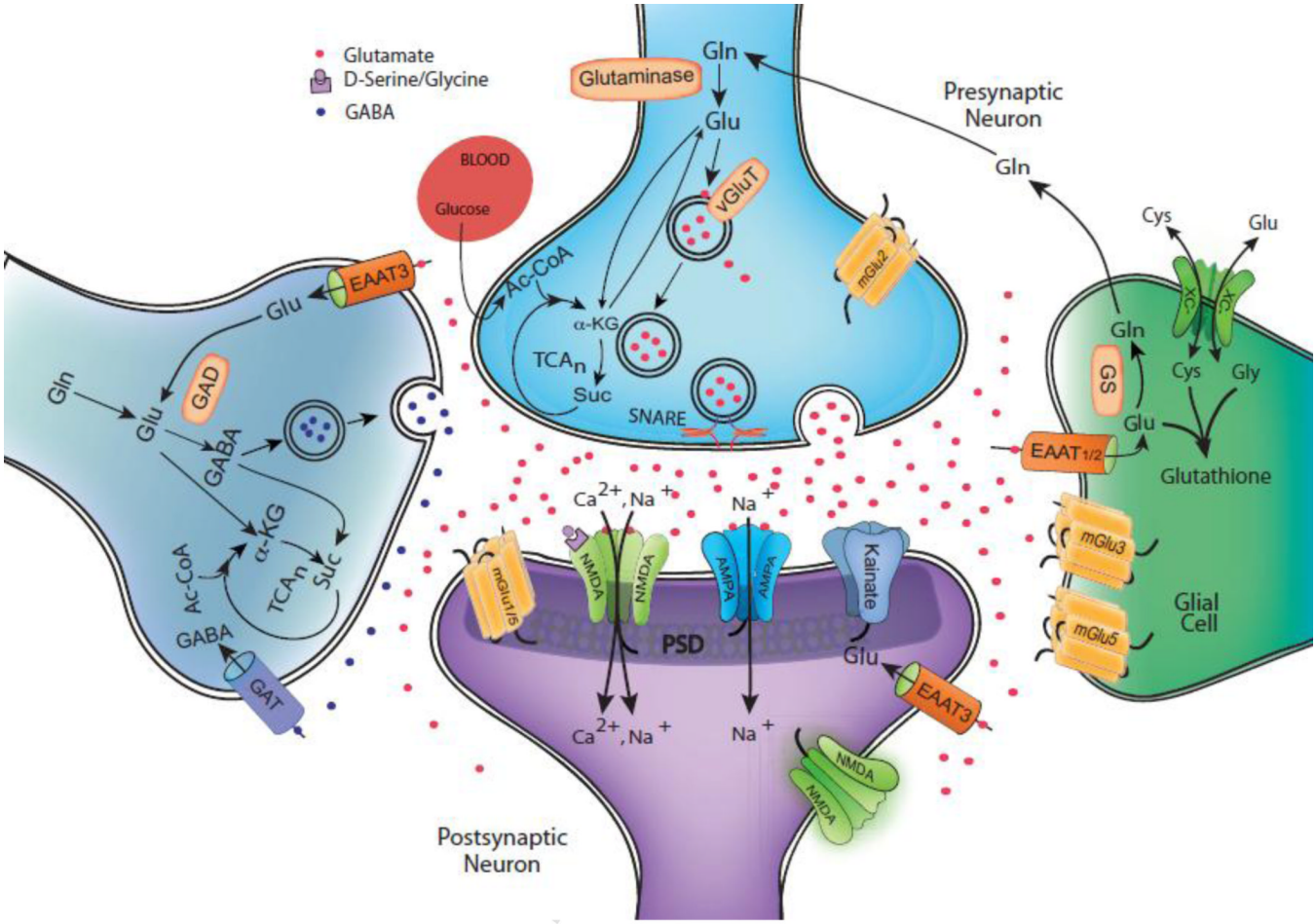

FIGURE 3. Glutamate participates in multiple metabolic processes in different cell types

Whole-tissue glutamate, as measured by techniques such as MRS, reflects many sources of glutamate beyond synaptic neurotransmitter glutamate. In glial cells, glutamate enters through the transporters **EAAT1** and **EAAT2**, and via the cystine-glutamate antiporter, **XC-**. Some is converted to **glutathione**, the brain principle antioxidant; this represents a link between glutamate homeostasis and redox state. Biosynthesis of glutathione, the details of which are not shown, also can include cystine (**Cys**) and glycine (**Gly**). Much glutamate taken up by glial cells is converted into glutamine (**Gln**), which passively diffuses back into neurons and is converted back into glutamate by the enzyme glutaminase. Neurotransmitter glutamate is packaged into vesicles by the vesicular glutamate transporter (**vGluT**). Vesicle fusion and glutamate release upon action potential invasion of the axon terminal through a calcium-dependent mechanism involving the **SNARE** proteins.

In the synaptic cleft, released glutamate binds to postsynaptic receptors. Activation of the **NMDA** receptor also requires binding by coagonist **Gly** or D-serine (**D-Ser**) at a distinct site. Glycine levels are regulated by the glycine transporter, **GlyT** (not shown). Glutamate diffuses out of the synaptic cleft; most is taken up by the **EAAT** glutamate transporters, but some binds to extrasynaptic receptors, both postsynaptically and presynaptically.

Glutamate is also closely tied to basic energy metabolism and the tricarboxylic acid (**TCA_n**) cycle, in all cells; it is interconvertable with the intermediate α-ketoglutarate (**α-KG**); other components of the TCA cycle shown here are succinate (**Suc**) and acetyl-coenzyme (**Ac-CoA**), which enters from the bloodstream and is the principle source of energy for neurons.

Glutamate also enters inhibitory GABAergic neurons, shown on the left, where it is converted to neurotransmitter **GABA** by the enzyme glutamic acid dehydrogenase (**GAD**). Levels of glutamate and GABA are thus metabolically coupled. GABA is released from these neurons and binds postsynaptic and presynaptic inhibitory receptors (not shown). Synaptic GABA is taken up by the transporter **GAT**.

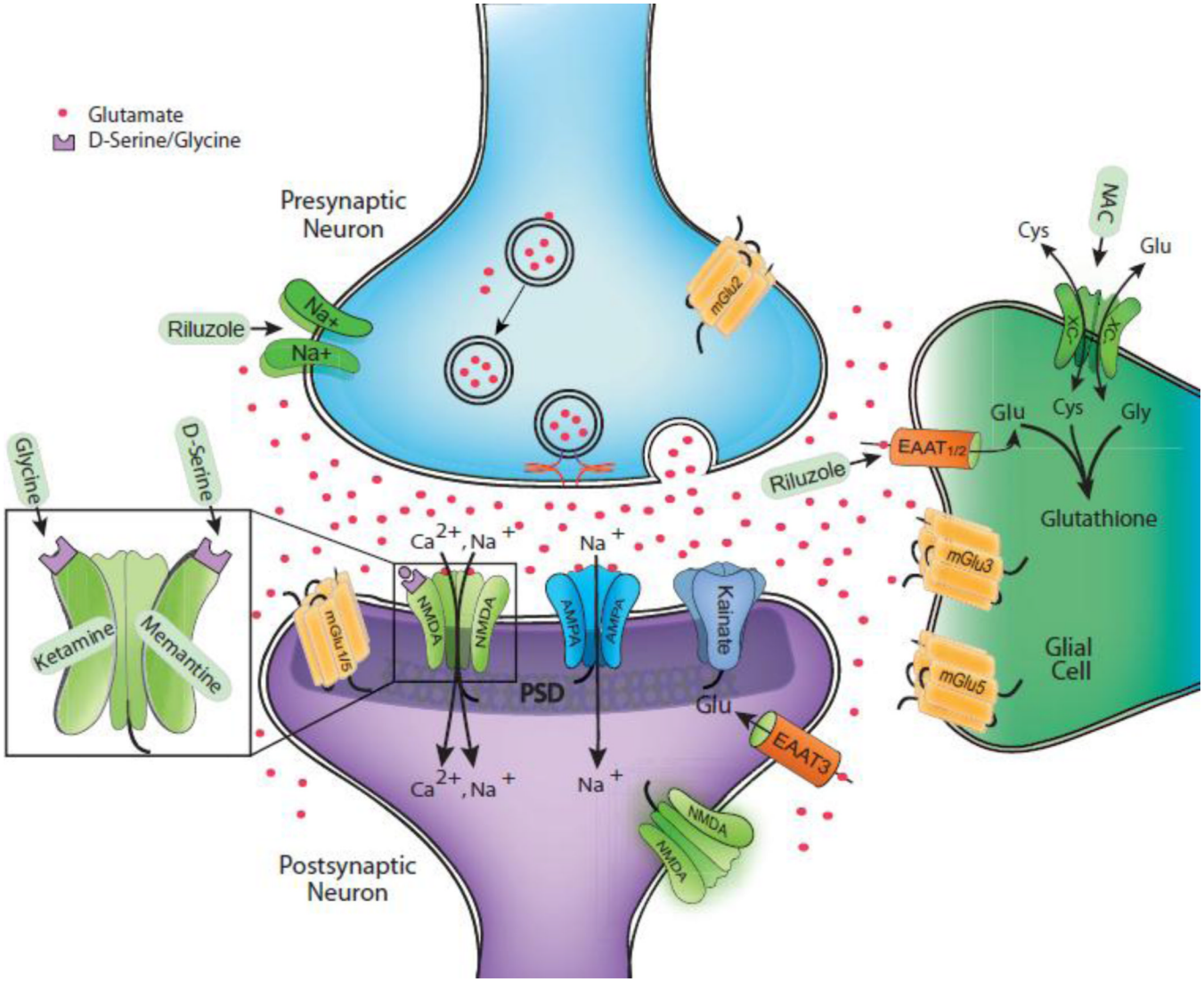

FIGURE 4. Major sites of action of glutamate-modulating drugs

The glutamate modulator **riluzole** acts (i) by inhibiting axonal voltage-gated sodium channels (**Na^+**) – a mechanism shared with the antiepileptic agent **lamotrigine** – thereby limiting glutamate release; and (ii) by enhancing glial uptake of extrasynaptic glutamate. The antioxidant **N-acetylcysteine (NAC)** also modulates extrasynaptic glutamate; it is converted into cystine and drives the extrusion of glutamate from astrocytes via the cystine-glutamate antiporter. The NMDA blockers **memantine** and **ketamine** block the pore of the NMDA receptor, preventing cation influx. **Glycine, D-serine**, and **D-cycloserine (D-CS)**, in contrast, bind to the NMDA receptor coagonist site and potentiate activation of the receptor. **Sarcosine** (not shown) inhibits the glycine receptor Gly-T, increasing the endogenous levels of glycine. See Figures 2 & 3 for abbreviations of components of the glutamatergic synapse, and main text for more details.