Targeting the glutamatergic system to develop novel, improved therapeutics for mood disorders

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Abstract | Mood disorders are common, chronic, recurrent mental illnesses that affect the lives of millions of individuals worldwide. To date, the monoaminergic systems (serotonergic, noradrenergic and dopaminergic) in the brain have received the greatest attention in neurobiological studies of mood disorders, and most therapeutics target these systems. However, there is growing evidence that the glutamatergic system is central to the neurobiology and treatment of these disorders. Here, we review data supporting the involvement of the glutamatergic system in mood-disorder pathophysiology as well as the efficacy of glutamatergic agents in mood disorders. We also discuss exciting new prospects for the development of improved therapeutics for these devastating disorders.

Major depressive disorder (MDD). A chronic mood disorder that is characterized by a long-lasting depressed mood or marked loss of interest or pleasure in all or nearly all activities. MDD often affects mental efficiency, memory, appetite and sleep habits.

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Mood disorders — major depressive disorder (MDD) and bipolar disorder (BPD) — are serious, debilitating, life-shortening illnesses that affect millions of people worldwide. The lifetime risk for any mood disorder in the United States is 20.8%, and onset typically begins in childhood or adolescence[1]. Mood disorders are chronic illnesses characterized by multiple episodes of symptom exacerbation, residual symptoms between episodes and functional impairment[2–4]. The World Health Organization's (WHO) Global Burden of Disease project ranked MDD as the fourth leading cause of disability in 1990, and predicts that by 2020 it will become the second leading cause of disability worldwide[5].

Although most patients with mood disorders receive some benefit from available treatments[6,7], the largest open-label study examining the effectiveness of pharmacological treatment of MDD conducted so far (STAR*D)[7] found that less than one-third of patients achieved remission with an adequate trial of a standard antidepressant after up to 14 weeks of treatment. Furthermore, it was not until the completion of two antidepressant trials and nearly 24 weeks of treatment that half of the patients with MDD in the STAR*D study remitted. Similarly, many patients with BPD do not respond to existing medications[8], particularly during depressive episodes[6,9].

A major obstacle to developing more effective treatments for mood disorders has been our limited understanding of their pathophysiology, and of the mechanisms underlying the efficacy of existing treatments. Mood disorders arise from the complex interaction of multiple genes and environmental factors, and the phenotypic expression of the disease includes not only mood disturbance, but also a range of cognitive, motor, autonomic, endocrine and sleep/wake abnormalities. To date, the monoaminergic (that is, serotonergic, noradrenergic and dopaminergic) systems in the brain have received the greatest attention in neurobiological studies of mood disorders. These systems project widely to limbic, striatal and prefrontal cortical neuronal circuits that are implicated in the behavioural and visceral manifestations of mood disorders (reviewed in REFS 10–12).

However, there are limitations to current monoamine theories related to mood disorders. For example, most antidepressants exert their initial effects by increasing the intrasynaptic levels of serotonin and/or noradrenaline. Nevertheless, meaningful improvement in core depressive symptoms emerges only after several weeks of antidepressant administration, suggesting that downstream neural adaptations rather than the elevation in synaptic monoamine levels itself are responsible for their therapeutic effects. Furthermore, although depletion of monoamines may increase the risk of mood disorders in some individuals under some circumstances, these depletions do not produce widespread clinical depression. Together, these observations suggest that monoaminergic systems do not represent a final common pathway regulating mood, but rather exert a modulatory influence (see REF. 13 for review).

Overall, this focus on monoaminergic systems has not yet greatly advanced our understanding of the biology underlying recurrent mood disorders. Any such understanding must include an explanation for the tendency towards episodic and often profound mood disturbance that can become progressive over time. These observations suggest that although monoaminergic neurotransmitter systems have an important role in the pathophysiology and treatment of mood disorders, other systems that regulate synaptic and neural plasticity are more central to the neurobiology and treatment of these disorders[14,15].

Research on the biological underpinnings of mood disorders has therefore begun to focus less on absolute changes in monoamines and more on the role of neural circuits and synapses, as well as the processes controlling their function. Glutamate is the major mediator of excitatory synaptic transmission in the mammalian brain[16]. Under normal conditions, glutamate has a prominent role in synaptic plasticity, learning and memory, but in pathological conditions it is known to be a potent neuronal excitotoxin, triggering either rapid or delayed neurotoxicity. The potential role of the glutamatergic system in the pathophysiology of, and treatment of, mood disorders has recently been investigated in earnest, and the available evidence suggests that abnormal activity of the glutamatergic system is likely to contribute to the impairments in synaptic and neural plasticity that are observed in patients with severe or recurrent mood disorders. Thus, numerous therapeutic strategies are being explored in an attempt to remedy the presumed impairments of glutamate-mediated plasticity. Indeed, several of these treatments exert robust neurotrophic effects in preclinical paradigms[17]. Testing the efficacy and safety of these glutamatergic treatment strategies in patients with MDD and BPD could yield a better understanding of the neurobiological processes involved in these disorders, and lead to the development of improved treatments.

Physiology of the glutamatergic system

Glutamate can be found throughout the brain. Because tight control over glutamatergic neurotransmission is required to maintain optimal neuronal function and prevent overactivation of the system, multiple levels of regulatory processes have evolved to ensure that glutamatergic excitation is maintained within narrow boundaries (FIG. 1).

In the brain, glutamate can either be synthesized *de novo* from glucose via the Krebs cycle and the transamination of α-oxoglutarate, or it can be recycled through the glutamate/glutamine cycle (see below)[18]. Glutamate is transported into synaptic vesicles by vesicular glutamate transporters (VGLUTs)[19,20], where it is stored at high concentrations, and protected from degradation before being released in a Ca^{2+}-dependent manner into the synaptic cleft by exocytosis.

On release, glutamate binds to and activates specialized ionotropic and metabotropic receptors found throughout the CNS that have wide-ranging effects on neural excitability (BOX 1). The postsynaptic density (PSD), a large supramolecular complex composed of glutamate receptors, anchoring proteins, cytoskeletal proteins and signalling proteins[21], also contributes to the regulation of glutamate signalling. Glutamate receptors bind to several receptor-binding proteins in the PSD, including protein interacting with C kinase 1 (PICK1), stargazin, glutamate receptor-interacting protein (GRIP), membrane-associated guanylate kinases (MAGUKs) and Homer, via regions on their cytoplasmic domains. These proteins can be regulated by both post-translational splicing and phosphorylation events, and are essential for receptor trafficking and for coupling the receptors to other scaffolding and signalling proteins.

Glutamate is cleared from the extracellular space via high-affinity excitatory amino-acid transporters (EAATs) in neighbouring glial cells, which convert glutamate into glutamine via the action of glutamine synthetase. Glutamine is then transported back into the glutamatergic neuron where it is hydrolysed by glutaminase back into glutamate (FIG. 1). Owing to the lack of degradative enzymes in the synapse, uptake by the EAATs is the primary mechanism through which the action of extracellular glutamate is terminated. Failure of the EAATs to effectively clear glutamate from the extracellular space results in various forms of cellular damage[22,23] and is thought to be linked with neuropsychiatric disorders[24].

Glutamate pathophysiology in mood disorders

Abnormal function of the glutamatergic system has been implicated in the pathophysiology of many disorders including amyotrophic lateral sclerosis (ALS), Huntington's chorea, epilepsy, Alzheimer's disease, schizophrenia and anxiety disorders. Thus, dysfunction of glutamatergic neurotransmission may be a common pathophysiological mechanism, aspects of which are shared between several disorders. However, it is beyond the scope of this Review to consider this extensive literature, and the reader is referred elsewhere for more information on these other disorders[25–28]. This Review will focus only on the relationship between glutamate neurotransmission and mood disorders.

Changes in glutamate levels. Glutamatergic abnormalities have been reported in plasma[29–31], serum[32], cerebrospinal fluid[33,34] and brain tissue[35] of individuals afflicted with mood disorders. However, these studies are compromised by problems with medication exposure, post-mortem effects on metabolism and the inability to identify the precise source of the glutamate in the peripheral tissue, thus rendering the findings difficult to interpret[36,37]. A recent post-mortem study specifically controlling for the effects of post-mortem interval found increased levels of glutamate in the frontal cortex of patients with BPD and MDD[38].

Fortunately, *in vivo* measures of glutamate content in the brain can now be made with the use of proton magnetic resonance spectroscopy (^{1}H-MRS). Although it remains extremely difficult to assign unequivocal resonance peaks to the individual glutamate resonances, a combined measure termed Glx, which predominantly reflects glutamate content but also contains glutamine

Bipolar disorder
(BPD). A mood disorder whereby affected individuals alternate between states of deep depression and mania. Whereas depression is characterized by persistent and long-term sadness or despair, mania is a mental state that is characterized by great excitement, flight of ideas, a decreased need for sleep, and, sometimes, uncontrollable behaviour, hallucinations or delusions.

Synaptic plasticity
The cellular processes that result in lasting changes in the efficacy of neurotransmission. Changes in neurotransmitter levels, receptor subunit phosphorylation, surface/cellular levels of receptors and conductance changes all regulate the strength of signal transmission at the synapse.

Neural plasticity
Changes in intracellular signalling cascades and gene regulation that lead to modifications of synapse number and strength, variations in neurotransmitter release, remodelling of axonal and dendritic architecture and, in some areas of the CNS, the generation of new neurons. These modifications can be of short duration or long lasting.

Glutamate/glutamine cycle
Process through which most brain glutamate is recycled. Glutamate released by neurons is converted to glutamine in astrocytes. Glutamine is then transported out for re-uptake by neurons, which convert it back into glutamate via the action of glutaminase.

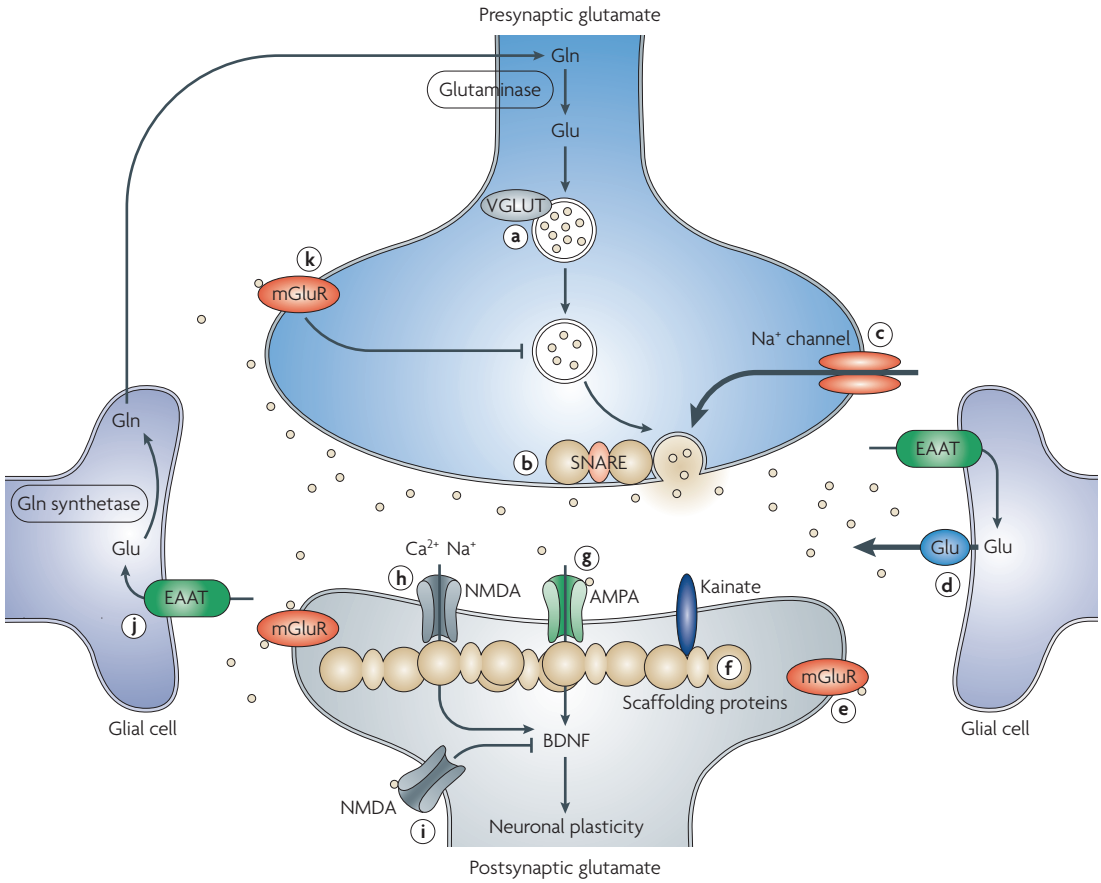

Figure 1 | **Glutamatergic neurotransmission and potential targets for drug development.** Tight physiological control is maintained over glutamatergic neurotransmission. Glutamine (Gln) is converted to glutamate (Glu) by glutaminase, although it can also be derived from the tricarboxylic acid cycle (not shown). Glu is packaged into presynaptic vesicles by the vesicular Glu transporters (VGLUTs) and released from the neuron in an activity-dependent manner through interactions with soluble *N*-ethylmaleimide-sensitive factor attachment receptor (SNARE) proteins. Glu is cleared from the extracellular space by excitatory amino-acid transporters (EAATs) present predominantly on glial cells. In glial cells Glu is converted to Gln by Gln synthetase. Various Glu receptors are present on presynaptic and postsynaptic neurons as well as on glial cells. These include both ionotropic receptors — AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid), NMDA (*N*-methyl-D-aspartate) and kainate receptors — as well as metabotropic Glu receptors (mGluRs). The effect of Glu is determined by the receptor subtype, localization and interactions with various scaffolding and signalling proteins in the postsynaptic density (PSD). Activation of Glu receptors results not only in rapid ionotropic effects, but also in long-term synaptic plasticity. Potential targets for drug development are highlighted in the figure: modulation of presynaptic vesicular loading of Glu (**a**); modulation of presynaptic vesicular Glu release (**b**); voltage-dependent Na^+ channel modulation that regulates Glu release (**c**); modulation of extrasynaptic Glu release (**d**); Group I mGluR modulation (**e**); PSD proteins (theoretically, it is possible that agents capable of modifying the expression or function of PSD proteins could be used to treat mood disorders) (**f**); AMPA receptor modulation (**g**); synaptic NMDA receptor modulation (**h**); extrasynaptic NMDA receptor modulation (**i**); facilitation of Glu clearance by EAATs (**j**); Group II mGluR modulation (mGluR2/mGluR3 antagonists have demonstrated antidepressant activity, mGluR2/mGluR3 agonists have demonstrated anxiolytic activity) (**k**). BDNF, brain-derived neurotrophic factor.

and GABA (γ-aminobutyric acid) components, has now been adopted by several groups. A growing collection of ^{1}H-MRS brain imaging studies suggests that abnormalities do exist within the glutamatergic system of patients with mood disorders. However, the extent and direction of the changes are still to be determined, with reports of elevated glutamate levels in the occipital cortex of depressed patients, and decreased glutamate levels in the anterior cingulate cortex and possibly other frontal regions. In addition, there are reports of increased glutamate content in several brain regions of individuals with BPD. Although it remains difficult to draw any specific conclusions regarding the pathophysiological significance or aetiology of the post-mortem and imaging findings related to glutamate content to date, the studies do suggest that the glutamatergic system is altered in several brain regions in association with mood disorders. Newer ^{13}C-MRS studies capable of measuring the rate of glutamate/glutamine cycling should provide greater detail on the changes in glutamatergic function that are associated with mood disorders[39].

Box 1 | **Glutamate receptors**

There are two major subtypes of glutamatergic receptors in the CNS: ionotropic and metabotropic. Metabotropic glutamate receptors (mGluRs) are G-protein-coupled receptors. Eight types have been cloned and they can be organized into three subgroups based on the signalling transduction pathways that they activate. Group I (mGluR1a–d, mGluR5a,b) act primarily through phospholipase Cβ and the activation of the inositol triphosphate and diacylglycerol second messenger systems[154]. Group II (mGluR2 and mGluR3) and group III (mGluR4, mGluR6–8) receptors are negatively coupled to adenylyl cyclase. Ionotropic glutamate receptors are ligand-gated ion channels that open when activated by the binding of an agonist. There are three subgroups:

AMPA receptors. AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptors mediate the fast, rapidly desensitizing excitation at most synapses, and are responsible for the initial reaction to glutamate in the synapse. Their activation opens the pore allowing the inward flow of Na^+, resulting in the depolarization of the neuronal membrane. The AMPA receptors comprise a homo- or heteromeric complex of four subunits (GLUR1–4). Because of differences in individual subunit expression, post-transcriptional modifications and alternative splicing modifications they are functionally diverse. At mature synapses, AMPA receptors are usually co-expressed with NMDA (*N*-methyl-D-aspartate) receptors.

Kainate receptors. Kainate (KA) receptors are coded by two gene families coding for the low-affinity GLUR5–7 subunits and the high-affinity KA1 and KA2 subunits. These subunits are also subject to extensive post-transcriptional and post-translational modification. Like AMPA receptors, KA receptors are associated with voltage-dependent channels that primarily allow for the influx of Na^+ ions that mediate fast excitatory neurotransmission, but they appear to have a distinct distribution.

NMDA receptors. NMDA receptors (NRs) are thought to exist primarily as tetrameric complexes comprising two obligatory NR1 subunits and two NR2 subunits. There are at least eight splice variants of the NR1 subunit, four NR2 genes (*NR2A–D*); and two NR3 subunits (NR3A and NR3B). The binding site for glutamate has been found in the NR2 subunit and the site for the co-agonist glycine has been localized to the NR1 subunit.

NRs are normally blocked under resting conditions by the obstructing effects of Mg^{2+} ions. However, once the surrounding membrane is depolarized, these receptors may be activated by the combined binding of two molecules of glutamate and two molecules of glycine or D-serine[155]. Thus, NR activation serves as a functional marker of converging excitatory input and produces excitation over longer periods of time. Synaptic NRs activate mitogen-activated protein kinase (MAPK) and the transcription factor cyclic AMP-Ca^{2+} response element-binding protein (CREB); induce expression of the gene that encodes brain-derived neurotrophic factor (BDNF); and promote neuronal survival, whereas extrasynaptic NRs propagate opposing signals that promote cell death[156,157].

Glutamate receptor alterations. Several studies have found differences related to NMDA (*N*-methyl-D-aspartate)-receptor expression and binding affinities between individuals with and without mood disorders. An initial report demonstrated differences in the allosteric modulation of glutamate binding through the glycine binding site on the NMDA receptor in the frontal cortex of age-matched and post-mortem, interval-matched suicide victims[40]. Later studies reported decreased binding of glutamate receptor antagonists in the hippocampus of eight subjects with BPD[41]. Because these compounds bind to the glutamate binding site and open the ion channel of the NMDA receptor, respectively, these data suggest that there is a decrease in the number of open ion channels associated with no significant change in the density of NMDA receptors in regions of the hippocampus from subjects with BPD. Using the same hippocampal tissue, McCullumsmith and colleagues recently demonstrated a coexistent decrease in NMDA receptor 1 (NR1) and NR2A transcript expression, but no difference in NR2B expression in BPD subjects[42]. This finding is consistent with an earlier report of reduced hippocampal NR1 transcript expression in individuals with mood disorders[43]. A similar reduction in NMDA receptor binding and NR1 subunit expression was also reported in the superior temporal cortex of individuals with MDD and BPD[44]. Together, these studies point to a differential expression of the various NMDA receptor subunits in individuals with mood disorders.

At the genetic level, two polymorphisms of the *GRIN1* gene coding for the NR1 subunit have been associated with BPD through a linkage disequilibrium study[45]. Two polymorphisms in the *GRIN2B* gene coding for NR2B were also recently reported to be associated with BPD, especially if psychotic features were present, but no coexistent change in *NR2B* mRNA expression could be associated with the polymorphism in the region of the dorsolateral prefrontal cortex (DLPFC)[46]. In a related study, the density of GABA interneurons that express the NR2A subunit appeared to be decreased in the anterior cingulate cortex of subjects with BPD[47].

Fewer post-mortem studies have explored the association between AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) and kainate receptors in mood disorders. There is a single report of increased AMPA binding associated with a decreased glutamate receptor 1 (GLUR1) subunit expression in the striatum in BPD[48]. Although no differences in AMPA or kainate binding were detected in the hippocampus or in the DLPFC, decreased levels of GLUR2 were found in the DLPFC of individuals with BPD, and GLUR2 and GLUR3 in individuals with MDD[41,49].

Recent post-mortem studies have begun to explore whether alterations in the expression of intracellular anchoring and trafficking proteins associated with the PSD are altered in mood disorders. Decreased expression of SAP102 (a synapse-associated protein that primarily interacts with the NR2B subunit) coincided with a decrease in NR1 and NR2A subunit expression in the hippocampus of subjects with BPD[42], and has also been observed in the striatum[50] and thalamus[51] of subjects with MDD and BPD. Additional decreases in neurofilament-L and PSD95 transcripts were observed only in subjects with BPD. PSD95 immunoreactivity was also decreased in the hippocampal dentate in patients with BPD, but not in patients with MDD or in the orbital frontal cortex or hippocampal hilus in patients with either MDD or BPD[52]. Furthermore, no differences in the expression of AMPA receptor trafficking and signalling molecules (NSF, PICK1, stargazin and syntenin) could be found in the DLPFC of individuals with mood disorders[49]. The key findings are noted in TABLE 1.

Evidence of glial-cell pathology. Recent work has highlighted the importance of glial cells in the function and regulation of the glutamatergic neurotransmitter system. Although some evidence suggests that glial abnormalities are predominantly due to reduced numbers of oligodendrocytes[53], other glial cells involved in glutamate neurotransmission are also likely to be involved in glial pathology[54]. Decreased glial cell number and density have been found in several brain regions in individuals

Table 1 | **Evidence for alterations in NMDA and AMPA/KA receptor function in mood disorders***

Target receptor	Mood disorder	Brain region	Effect	Refs
NMDA	MDD	Frontal cortex	Reduced [^{3}H]CGP-39653 binding	75
NMDA	MDD	Superior temporal cortex	NMDA receptor binding and NR1 subunit expression	44
NMDA	BPD	Hippocampus	Reduced CGP-39653 and MK-801 binding and reduced levels of NR1 and NR2A transcript	41–43
NMDA	BPD	Superior temporal cortex	NMDA receptor binding and NR1 subunit expression	44
NMDA	BPD	Anterior cingulate cortex	NR2A subunit decreased in GABA interneurons	47
NMDA	BPD	Dorsolateral prefrontal cortex	Polymorphisms in genes coding NR2B, no differences in mRNA expression	46
AMPA	MDD	Dorsolateral prefrontal cortex	Decreased levels of GLUR2 and GLUR3	41
AMPA	MDD	Thalamus and striatum	Decreased expression of SAP102	50,51
AMPA	BPD	Striatum	Increased AMPA binding is associated with decreased GLUR1 subunit expression	48
AMPA	BPD	Dorsolateral prefrontal cortex	Decreased levels of GLUR2	49
AMPA	BPD	Thalamus and striatum	Decreased expression of SAP102	50,51
NMDA and AMPA	BPD	Hippocampus	Decrease in PSD95 immunoreactivity	52

*Reviewed in REFS 65,66,81. AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; KA, kainate; BPD, bipolar disorder; GABA, γ-aminobutyric acid; GLUR1/2/3, glutamate receptor 1/2/3 (also known as GRIA1/2/3); MDD, major depressive disorder; NMDA, *N*-methyl-D-aspartate; NR1, NMDA receptor 1 (also known as GRIN1); NR2A/B, NMDA receptor subtype 2A/B (also known as GRIN2A/B); PSD95, postsynaptic density protein 95 (also known as DLG4); SAP102, synapse-associated protein 102 (also known as DLG3).

with mood disorders[53,55–62]. Reduced expression of EAAT1, EAAT2 and glutamine synthetase has been found in two frontal brain regions in post-mortem brain samples from individuals with MDD[63]. Also, decreased levels of *EAAT3* and *EAAT4* mRNA expression were found in the striatum of subjects with mood disorders[64] (reviewed in REFS 65–67). The reduced levels of glial cell number and density in the brains of patients with mood disorders are one of the most consistent pathological findings in psychiatric research. If this represents a true decrease in glial-cell function it could help to explain the altered glutamate content observed in several brain regions of these patients.

Effects of mood-disorder therapeutics

Antidepressants. Pursuant to their initial finding showing that NMDA antagonists have antidepressant properties[68], seminal studies by the Skolnick laboratory demonstrated that chronic antidepressant administration (monoaminergic-based antidepressants, tricyclic antidepressants[69,70] and electroconvulsive therapy) regulates NMDA receptor expression and function[71–75]. *In situ* hybridization studies[76,77] have revealed that repeated electroconvulsive shock in rats produced an increase in expression of mRNA for GLUR1, a subunit of the AMPA receptor in the dentate gyrus, and in the CA1 and CA3 cell fields of the hippocampus — areas that are thought to be critical for normal affective functioning.

Data also suggest that antidepressants upregulate AMPA receptor function by stimulating AMPA receptor subunit phosphorylation. Acute treatment with fluoxetine increases the phosphorylation of GLUR1 at Ser831 and Ser845, whereas chronic dosing (19 days) with fluoxetine selectively increases the phosphorylation of GLUR1 at Ser845 (REF. 78). Interactions of GLUR1 and GLUR2/3 with proteins implicated in AMPA receptor trafficking and with scaffolding proteins appear to account for the enhanced membrane expression of AMPA receptors in the hippocampus after antidepressant treatment[79]. Barbon and colleagues examined the mRNA expression of all subunits of AMPA receptors after antidepressant treatment and found that chronic treatment with fluoxetine and desipramine exerted moderate but selective effects on glutamate receptor mRNA expression and RNA editing[80].

In summary, growing evidence supports the idea that antidepressants, via a cascade of time-dependent signalling changes, ultimately converge to regulate AMPA-mediated and NMDA-mediated synaptic plasticity. Taken together, these preclinical studies suggest that reductions in NMDA receptor function are a consequence of treatment with known antidepressant medications and that antidepressants and mood stabilizers regulate AMPA receptor phosphorylation and trafficking (reviewed in REF. 81). The evidence supporting these hypotheses is briefly presented in TABLE 2.

Mood stabilizers. Patients with BPD are generally treated with a class of medications known as mood stabilizers. Mood stabilizers have antimanic effects, exert prophylactic effects in preventing recurrent manic or depressive episodes, and may also have some antidepressant properties. The prototypical agent of this class is lithium,

RNA editing
Molecular processes in which the information content is altered in a RNA molecule through a chemical change in the base make-up.

Table 2 | **Effects of antidepressants on the glutamatergic system**

Effect	Drug	Brain region	Refs
Reduced depolarization-stimulated glutamate release and overflow	Several classes of antidepressants	Hippocampus and prefrontal cortex	144,159
Reduced expression or function of NMDA receptors	Several classes of antidepressants	Several brain regions	69,70,72–75, 160,161
Altered expression and activation of AMPA receptors	Several classes of antidepressants	Prefrontal cortex and hippocampus	78–80, 114,162,163
Increased expression of the vesicular glutamate transporter	Several SSRI and TCA agents	Cerebral cortex	164,165

AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; NMDA, *N*-methyl-D-aspartate; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

a seemingly simple monovalent cation. Various anticonvulsant agents, most notably valproic acid (valproate, a substituted pentanoic acid), are also used as mood-stabilizing agents[82].

In view of the evidence that excessive synaptic glutamate may contribute to neuronal atrophy and loss, it is notable that chronic treatment with lithium has been shown to upregulate synaptosomal uptake of glutamate in mice[83]. Furthermore, chronic treatment with therapeutically relevant concentrations of lithium in cultured rat cerebellar, cortical and hippocampal neurons protected against glutamate-induced excitotoxicity[84]. The investigators report that the protection could be attributed, at least in part, to inhibition of NMDA-receptor-mediated Ca^{2+} influx[84,85]. Chronic administration of valproate led to a dose-dependent increase in hippocampal glutamate uptake capacity, as measured by uptake of [^{3}H]glutamate into proteoliposomes, by increasing the levels of the glutamate transporters EAAT1 and EAAT2 in the hippocampus. Overall, chronic treatment with valproate or lithium is likely to decrease intrasynaptic glutamate levels through various mechanisms.

In view of the crucial role of AMPA receptor trafficking in regulating various forms of plasticity, recent studies have sought to determine whether these two structurally highly dissimilar antimanic agents — lithium and valproate — affect AMPA receptor trafficking. Both have the common effect of downregulating AMPA GLUR1 synaptic expression in hippocampus after prolonged treatment with therapeutically relevant concentrations, both *in vitro* and *in vivo*[86]. The key findings are highlighted in TABLE 3.

Additional support for the therapeutic relevance of these data is provided by recent studies indicating that AMPA receptor antagonists attenuate several manic-like behaviours produced by amphetamine administration[87].

Lamotrigine is an anticonvulsant that also has mood-stabilizing properties in patients with BPD. Of all the medications currently used in the treatment of mood disorders, lamotrigine probably has the most direct effects on the glutamate system. There is evidence that it inhibits the release of glutamate in the hippocampus of rats[88] and that it increases AMPA subunit receptor expression[89].

Montgomery–Asberg Depression Rating Scale
An 11-item clinician-administered questionnaire that is used to rate the severity of a patient's depression.

Hamilton Depression Rating Scale
A 21-item, clinician-administered questionnaire that is used to rate the severity of a patient's depression.

Glutamatergic agents in mood disorders

Several therapeutic agents that act on the glutamatergic system can be explored as potential treatments for mood disorders.

Inhibitors of glutamate release. In addition to lamotrigine, the US Food and Drug Administration-approved drug riluzole (2-amino-6-(trifluoromethoxy) benzothiazole), which is used for the treatment of ALS, has also been shown to inhibit glutamate release. However, riluzole exerts a range of effects on the glutamatergic system, including an increase in AMPA receptor trafficking[89], stimulation of neurotrophic factor synthesis[90] and enhancement of glutamate re-uptake[91]. It does not appear to directly affect NMDA or kainate receptors[92]. Riluzole has also been found to strongly attenuate the electrically evoked release of dopamine and noradrenaline but not serotonin; as mentioned previously, such neurotransmitters have long been implicated in the mechanism of antidepressant action[93].

Both preclinical and clinical studies indicate that riluzole has antidepressant properties[94–96]. The first open-label study, undertaken in depressed patients who had failed to respond to adequate trials of at least two antidepressants, found that riluzole had significant antidepressant effects, with 46% of trial completers meeting response criteria[94]. In a subsequent study of patients with BPD, augmentation of lithium with open-label riluzole for 8 weeks significantly improved depressive symptoms with the average total Montgomery–Asberg Depression Rating Scale scores dropping by more than 15 points by the eighth week of the study[95]. Finally, in another open-label study in which riluzole was added to ongoing antidepressant therapy in patients with treatment-resistant MDD, patients experienced a significant improvement in depressive symptoms reflected by a nearly 10-point reduction in Hamilton Depression Rating Scale scores after 6–12 weeks[96]. Overall, riluzole was well-tolerated in these trials and, interestingly, the patients who responded to riluzole tended to be in remission (that is, almost symptom-free), suggesting that there may be a subgroup of patients for whom glutamatergic strategies have considerable therapeutic value.

Although the mechanisms of lamotrigine and riluzole appear to be similar, preliminary data have also shown that patients who had previously failed to respond to lamotrigine subsequently responded to riluzole. This may be due in part to riluzole's additional effects on glutamate neurotransmission, such as enhanced glutamate uptake, that are not seen with lamotrigine[91]. The studies that highlight riluzole's efficacy in subjects who were previously medication-resistant are encouraging, especially because these patients usually have markedly reduced rates of response to medication. However, it will be important to confirm these findings in randomized placebo-controlled trials before any firm conclusions can be drawn about the true efficacy of riluzole in the treatment of MDD.

Partial NMDA receptor agonists. D-Cycloserine (4-amino-isoxazolidin-3) is a broad-spectrum antibiotic with some antidepressant properties in rodent models of depression. Early reports based on clinical observation indicated that

Table 3 | **Effects of lithium or valproate on the glutamatergic system***

Drug	Effect	Refs
Lithium	Alters VGLUT1 expression and presynaptic glutamate release	83,164,166
Lithium	Alters glutamate uptake	167
Lithium	Alters glutamate receptor expression and function	84,85,153,168,169
Valproate	Alters VGLUT1 expression and presynaptic glutamate release	170,171
Valproate	Increases EAAT expression	172,173
Valproate	Alters glutamate receptor expression and function	89,153,174–179

*Reviewed in REFS 65,81,114,153,164,180. EAAT, excitatory amino-acid transporter; VGLUT1, vesicular glutamate transporter 1 (also known as SLC17A7).

D-cycloserine had positive effects on mood, insomnia and appetite in depressed patients with tuberculosis[97,98]. A subsequent double-blind, placebo-controlled, 6-week crossover study involving 22 patients with treatment-resistant MDD found the addition of D-cycloserine at 250 mg per day to other antidepressants to be ineffective[99]. However, it is possible that the doses studied were too low. It was not until 1997 that it was shown that doses higher than 500 mg per day of D-cycloserine are required to elicit a neuroendocrine response (measured as an increase in plasma levels of luteinizing hormone); such a response is indicative of NMDA antagonism[100,101]. Interestingly, based on animal work showing that D-cycloserine facilitated extinction of fear when given either before or shortly after exposure to fearful cues[102], recent clinical studies have shown that lower doses of D-cycloserine are effective in enhancing the efficacy of exposure-based therapies for anxiety disorders; no significant effect was seen when the higher dose of 500 mg per day was used[103–105].

NMDA antagonists. Memantine (1-amino-3, 5-dimethyl-adamantane) is a derivative of amantadine, a low-affinity, uncompetitive, open-channel NMDA antagonist. Memantine is well tolerated[106], and is approved for the treatment of moderate to severe Alzheimer's disease, in which it has been shown to enhance cognition and minimize clinical deterioration in patients with Alzheimer's disease, vascular dementia or mixed dementia[107].

Preclinical studies have described a dose-dependent decrease in immobility time in the forced-swim test in rats following administration of memantine. A synergistic effect was seen when imipramine and fluoxetine were given jointly with memantine in the forced-swim test (reviewed in REFS 65,81). One recent paper reported that two patients with treatment-resistant BPD had improved cognition and mood stabilization with memantine[108], but an 8-week, double-blind, placebo-controlled trial of memantine in 32 patients with MDD found no significant antidepressant or anti-anxiety effects[181]. It is possible, however, that antidepressant effects might have occurred with much higher doses of memantine, as suggested by another recent open-label flexible dosing study of memantine in subjects with MDD[110]. Another possibility is that memantine might evince antidepressant properties by augmenting the effects of other agents.

Ketamine (DL-2-(o-chlorophenyl)-2-(methylamino) cyclohexanone hydrochloride) is another NMDA antagonist[111] and a derivative of phencyclidine. Its use in humans is associated with psychotomimetic and cognitive effects that possibly preclude its chronic use in treatment[112].

Ketamine's primary mechanism of action is blocking the NMDA receptor at the phencyclidine site within the ionotropic channel. Simultaneously, ketamine, presumably by producing a disinhibition of GABAergic inputs and thereby enhancing the firing rate of glutamatergic neurons, increases the presynaptic release of glutamate, resulting in increased extracellular levels of glutamate[113]. This increase in glutamate release preferentially favours AMPA receptors over NMDA receptors, because the latter are blocked by ketamine; thus, the net effect of ketamine's antidepressant effect on a cellular level is an increased glutamatergic throughput of AMPA relative to NMDA. The ability to block ketamine's antidepressant-like effects with an AMPA antagonist suggests that enhanced AMPA throughput might be crucial in producing these effects[114].

Clinically, ketamine is a popular agent for emergency department procedural sedation in children, with ample evidence to support its safety and efficacy[115]. Although its psychotomimetic side effects have led to its misuse and abuse, there is no evidence that ketamine causes physical dependence in humans[116]. In addition, recent studies found no evidence that repeated, albeit limited (typically less than four exposures), exposure to ketamine increases the risk of more severe or more protracted psychosis, perceptual changes resembling dissociation, severe emotional distress or euphoria in healthy subjects[117] or in patient populations[118].

Ketamine and related NMDA antagonists have been shown to have anxiolytic and antidepressant effects in animal models of anxiety and depression (reviewed in REFS 65,81) as well as antidepressant effects in humans[109,119]. One study found that seven subjects with treatment-resistant MDD showed significant improvement in depressive symptoms within 72 hours of treatment with ketamine[119]. Furthermore, a double-blind placebo-controlled crossover study found that a single intravenous dose of ketamine (0.5 mg per kg over 40 minutes) resulted in rapid and significant antidepressant effects in patients with treatment-resistant MDD within 2 hours, an effect that remained significant for 7 days. Seventy-one percent of subjects met response criteria, and 29% achieved remission 24 hours following the infusion of ketamine. Thirty-five percent of subjects maintained response to ketamine for at least 1 week; two of these maintained response at least 2 weeks. By contrast, no subject on placebo responded at 1 or 7 days. Mild perceptual disturbances occurred in most patients, but in all cases lasted less than 1 hour. No serious adverse events occurred[109].

Emerging promise of novel therapeutics

AMPA potentiators. Positive modulators of AMPA receptors do not activate AMPA receptors themselves but slow the rate of receptor desensitization and/or deactivation in the presence of an agonist (see REFS 120,121 for reviews).

Psychotomimetic
Refers to a drug or substance that produces psychological or behavioural changes that resemble those of a psychotic state.

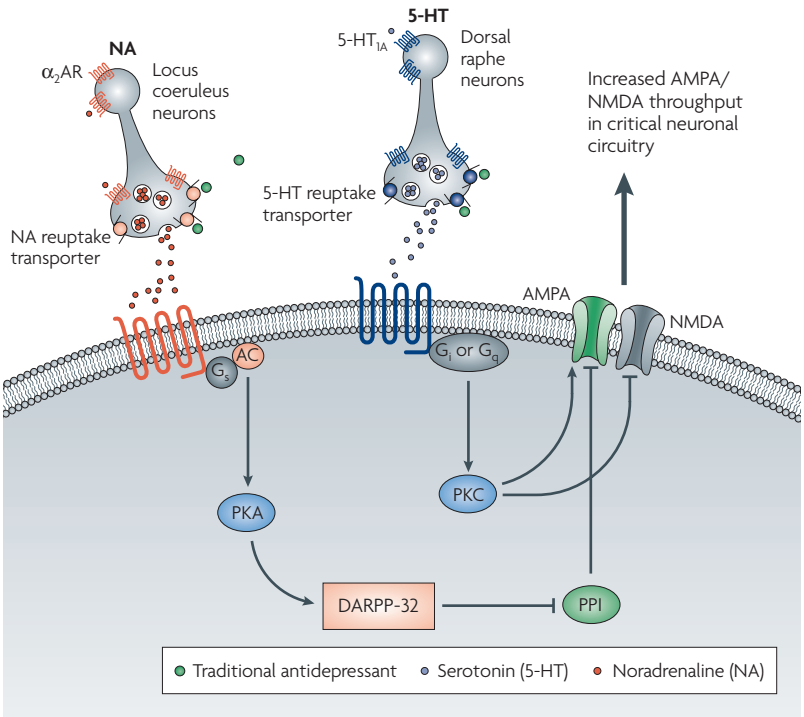

Figure 2 | **Antidepressants converge to regulate AMPA- and NMDA-mediated synaptic plasticity in critical neuronal circuits.** This figure depicts the complex, time-dependent regulation of intracellular signalling cascades by traditional antidepressants (green). Through their initial effects on intrasynaptic serotonin (5-hydroxytryptamine; 5-HT) and/or noradrenaline (NA), these agents ultimately converge to regulate AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) and NMDA (*N*-methyl-D-aspartate) receptor trafficking, synaptic plasticity and information processing in critical circuits. Targeting AMPA/NMDA-mediated synaptic throughput more directly might result in improved and faster-acting antidepressants. α_2-AR, α_2-adrenergic autoreceptor; AC, adenylyl cyclase; DARPP-32, dopamine and cyclic AMP-regulated phosphoprotein of 32 kD; G_i or G_q, G proteins coupled to phosphoinositide turnover; G_s, G-protein stimulating adenylyl cyclase; PKA/C, protein kinase A/C; PP1, protein phosphatase 1. This figure is modified from *Nature Reviews Drug Discovery* REF. 158 © (2007) Macmillan Publishers Ltd.

Several modulators from various structural classes have been synthesized, including benzothiazides (for example, cyclothiazide); the benzoyliperidines (for example, ampalex); and the birylpropylsulphonamides (for example, LY392098). They are being studied in cognition, anxiety, stroke, Parkinson's disease and MDD (reviewed in REF. 122). In preclinical studies, aniracetam[122], Ampalex[123], LY392098 (REFS 124), LY451616 (REFS 124,125) and S18986 (REFS126,127) have all been found to have some antidepressant properties, such as reduction of submissive behaviour. Some of these compounds have entered clinical trials but proof of their antidepressant efficacy is pending.

Subunit-selective NR2B antagonists. The first-generation NMDA receptor complex antagonists include ketamine, MK-801 and phencyclidine. These blockers are potent neuroprotectants *in vitro* and *in vivo*, but are likely to produce psychotomimetic effects when used acutely. However, other more selective NMDA antagonists, especially those that act on the NR2B receptor subtype (for example, ifenprodil), appear to have a low liability for this outcome, particularly when used at lower doses. Unfortunately, some of these compounds also have a high affinity to α_1-adrenoreceptors and other ion channels.

More recently, a series of oral, brain-penetrant NR2B antagonists with more selective effects are being developed. These include indole-2-carboxamides, HON0001 and benzimidazole-2-carboxamides[128–130]. A recent double-blind, randomized, placebo-controlled study indicated that CP-101-606, another NR2B-specific NMDA antagonist, had statistically significant antidepressant effects in patients with treatment-resistant MDD[131]. The average reduction in symptom severity was approximately two-times greater in active versus placebo-treated patients. Dissociative symptoms produced by the active infusion were generally modest and resolved within 8 hours.

Glial glutamate transporter enhancers. Recently, there has been considerable enthusiasm in the scientific community for studying the effects of β-lactam antibiotics in neurodegenerative diseases because, unlike other classes of antibiotics, they selectively induce transcription of the gene encoding the EAAT2 glutamate transporter[132–134]. One of the β-lactam antibiotics — ceftriaxone — was found to increase expression of the gene encoding for EAAT2 within a few days of its administration, and therefore might selectively modulate the glutamatergic system. Ceftriaxone has been found to have antidepressant-like effects in several animal models of depression[135]. The data from this study are also consistent with the hypothesis that excessive glutamate transmission might be involved in the pathophysiology of MDD.

Group I metabotropic receptor modulators. As noted above, the group I metabotropic receptors (mGluRs) have a major role in regulating postsynaptic excitability through interactions with NMDA receptors. mGluR5 is an attractive target for modulating glutamate neurotransmission because, in addition to being present on postsynaptic neurons, it is also present on glial cells where it appears to regulate the release of excitatory transmitters from glia. This, in turn, leads to selective stimulation of extrasynaptic NMDA receptors[136–138]. Group I mGluR-modulating agents, especially mGluR1/mGluR5 antagonists such as 2-methyl-6-(phenylethynyl) pyridine and 3-[(2-Methyl-1,3-thiazol-4-ylethynyl]pyridine, have strong anxiolytic effects in preclinical animal models. More recent studies suggest that they may also have antidepressant-like properties (see REFS 139,140); however, to date, there are no published clinical studies demonstrating the effectiveness of this class of drug.

Group II mGluRs (mGluR2 and mGluR3) are largely present on presynaptic membranes and on glial cells where they are thought to modulate glutamatergic neurotransmission by sensing glutamate spillover and regulating transmitter release. The function of these mGluR2/mGluR3 receptors in modulating glutamate neurotransmission make them extremely interesting targets for antidepressant drug development, and there is evidence suggesting that mGluR2/mGluR3-targeted drugs have both antidepressant and anxiolytic properties (see REFS 139,140 for reviews).

However, whereas mGluR2/mGluR3 antagonists (for example, LY341495 and MSG0039) appear to have antidepressant-like properties, mGluR2/mGluR3 agonists (that is, LY404039 and LY354740) have a profile consistent with anxiolytic and antipsychotic drugs. As with the NMDA antagonists, many of the antidepressant-like effects of the mGluR2/mGluR3 antagonists can be prevented by co-administration of an AMPA receptor antagonist[141], suggesting that activation of synaptic AMPA receptors may be a common pathway through which the antidepressant effects are transduced. No clinical studies have yet been conducted to explore the antidepressant efficacy of mGluR2/mGluR3 antagonists[139,140].

Early phase clinical trials have recently supported the efficacy of mGluR2/mGluR3 agonists in the treatment of schizophrenia[142], although some safety concerns for this class of drugs have been raised[143]. If replicated in larger clinical trials, mGluR2/mGluR3 agonists would represent a completely novel class of therapeutics for schizophrenia.

Presynaptic packaging and glutamate-release inhibitors. Increasing evidence suggests that chronic antidepressant treatment results in modulation of presynaptic glutamate release[144]. Some evidence suggests this is the result of effects on the soluble *N*-ethylmaleimide-sensitive factor attachment receptor (SNARE) complex that controls the structural and biochemical aspects of synaptic vesicle exocytosis[145]. Therefore, targeting the expression and function of these proteins has been suggested as a useful tool in the development of novel biomarkers and therapies for neuropsychiatric disorders[146].

As mentioned previously, an essential step in glutamate neurotransmission is the concentration of glutamate into synaptic vesicles before release from the presynaptic terminal. As a result, a series of inhibitors of VGLUT are being developed, and include amino acids and amino-acid analogues, fatty acids, azo dyes, quinolines and alkaloids. The potency with which these agents inhibit VGLUT varies considerably[147].

Recent studies have also shown the importance of the cystine–glutamate antiporter in controlling extracellular glutamate content[148] and vesicular glutamate release[149]. *N*-Acetyl cystine, an agent known to modulate the function of the cystine–glutamate antiporter has recently gained attention as a potential treatment for various neuropsychiatric disorders[150,151], and several clinical trials are currently underway.

Conclusions

A considerable body of evidence supports the role of the glutamate system in mediating synaptic plasticity as well as long-term cell growth and atrophy. Mounting evidence now also suggests that disturbances of brain and synaptic plasticity contribute to the pathological processes associated with mood disorders[152], thus providing a potential link between the glutamatergic neurotransmitter system and the pathophysiology of mood disorders. The data reviewed here suggest that mood disorders are in fact associated with abnormal function and regulation of the glutamatergic neurotransmitter system. Furthermore, emerging studies suggest that targeting glutamate-mediated synaptic plasticity could be an effective strategy for treating these devastating disorders.

There has, unfortunately, been little progress in developing truly novel medications for mood disorders. Although a relationship between the glutamatergic system and mood disorders was originally proposed nearly two decades ago[68], interest in the field has grown rapidly in recent years. Today, several therapies targeting this system show substantial promise for the treatment of mood disorders. Most notably, ketamine and riluzole merit continued study as putative archetypes for improved therapeutics. Ketamine is of particular interest because it has been shown to bring about rapid and relatively sustained antidepressant effects. Its rapid, robust and consistently reproducible antidepressant effects offer a unique opportunity to better delineate the precise cellular mechanisms involved[114].

AMPA receptor stimulation appears to mediate the antidepressant-like effects of both ketamine and the group II mGluR antagonist MGS0039 (REF. 141), suggesting that enhanced transmission through glutamatergic AMPA receptors may provide a common mechanism of antidepressant action. In agreement with this hypothesis, chronic administration of antidepressants also enhances AMPA receptor levels[89,153], and AMPA potentiators have shown antidepressant-like effects in animal models[124]. We postulate that the therapeutic effects of both monoaminergic antidepressants and glutamatergic agents may be mediated by increased AMPA to NMDA throughput in critical neuronal circuits (FIG. 2).

Although the results obtained with riluzole-like or ketamine-like drugs are still preliminary, they provide incentive for further studying of the role of glutamate in mood disorders. Continued exploration of the antidepressant-like effects of glutamatergic drugs holds considerable promise for the development of new treatments for mood disorders. The fact that currently available antidepressants take weeks to achieve their full effects leaves patients particularly vulnerable to devastating symptoms and elevated risk of self-harm. Thus, any pharmacological strategy that could exert a rapid and sustained antidepressant effect within hours or even days could have a substantial beneficial impact on patients' quality of life as well as public health.

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Competing interests statement

The authors declare competing financial interests: see web version for details.

DATABASES

Entrez Gene:
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene
GRIN1 | *GRIN2B*
OMIM:
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM
Alzheimer's disease | amyotrophic lateral sclerosis | bipolar disorder | Huntington's chorea | major depressive disorder | schizophrenia
UniProtKB: http://ca.expasy.org/sprot
EAAT1 | EAAT2 | EAAT3 | EAAT4 | GLUR1 | GLUR2 | GLUR3 | mGluR1 | mGluR2 | mGluR3 | mGluR5

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