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Glutamate transporters, EAAT1 and EAAT2, are potentially important in the pathophysiology and treatment of schizophrenia and affective disorders

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Abstract

Glutamate is the predominant excitatory neurotransmitter in the human brain and it has been shown that prolonged activation of the glutamatergic system leads to nerve damage and cell death. Following release from the pre-synaptic neuron and synaptic transmission, glutamate is either taken up into the pre-synaptic neuron or neighbouring glia by transmembrane glutamate transporters. Excitatory amino acid transporter (EAAT) 1 and EAAT2 are Na⁺-dependant glutamate transporters expressed predominantly in glia cells of the central nervous system. As the most abundant glutamate transporters, their primary role is to modulate levels of glutamatergic excitability and prevent spill over of glutamate beyond the synapse. This role is facilitated through the binding and transportation of glutamate into astrocytes and microglia. The function of EAAT1 and EAAT2 is heavily regulated at the levels of gene expression, post-transcriptional splicing, glycosylation states and cell-surface trafficking of the protein. Both glutamatergic dysfunction and glial dysfunction have been proposed to be involved in psychiatric disorder. This review will present an overview of the roles that EAAT1 and EAAT2 play in modulating glutamatergic activity in the human brain, and mount an argument that these two transporters could be involved in the aetiologies of schizophrenia and affective disorders as well as represent potential drug targets for novel therapies for those disorders.

Key words: Glia; Excitatory amino acid transporter;

Psychiatry; Affective disorders; Glutamate transporter; Glutamate; Schizophrenia

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Core tip: Following release from the presynaptic neuron, the majority of glutamate within the human cortex is taken up into glia cells where it is converted into glutamine for recycling back into glutamate. Glutamate transporters excitatory amino acid transporter (EAAT) 1 and EAAT2 are predominantly localized in the glial plasma membrane, and are responsible for the majority of glutamate uptake within the human brain. Here we provide a comprehensive review of the unique regulation of EAAT1 and EAAT2 mRNA and protein in health and psychiatric disorder, and in response to medication use.

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GLUTAMATE AND EXCITOTOXICITY

Glutamate has long been recognized as the principal excitatory neurotransmitter of the mammalian brain^[1]. It has been shown that glutamate concentration in the CNS extracellular space (approximately 0.6-2 $\mu\text{mol/L}$)^[2-4] is comparatively lower than levels in cell cytoplasm (approximately 1-10 mmol/L)^[5-7]. It is necessary for the level of extracellular glutamate to be kept low to allow for a high signal-to-noise ratio following the release of glutamate into the synapse and to prevent glutamate-mediated neuronal degeneration^[8-10] as high levels of extracellular glutamate causes excitotoxicity and nerve damage^[10]. The extracellular/intracellular glutamate gradient is at least partly maintained through the activity of Na^+ -dependent excitatory amino acid transporters (EAATs) which are in the membrane of pre-synaptic neurons and glia. Whilst glutamate uptake into astrocytes is also mediated by Na^+ -independent, chloride-dependent antiporters, this family of transporters appears to be responsible for less than 5% overall glutamate uptake^[11]. Thus, this review will focus solely on the Na^+ -dependent EAAT family.

THE EAAT FAMILY: OVERVIEW

The EAAT family of transporters consists of five Na^+ -dependent high-affinity glutamate transporters termed EAAT1 [also known as solute carrier family 1 member 3 (SLC1A3)]^[12,13], EAAT2/SLC1A2^[13,14], EAAT3/SLC1A1^[13,15], EAAT4/SLC1A6^[16] and EAAT5/SLC1A7^[17].

In this review, the accepted nomenclature of "EAAT" will be used in discussing data from both humans and other mammals. These subtypes are quite differentiated - EAAT1, EAAT2 and EAAT3 only share 51%-55% amino acid sequence homology^[18].

THE EAAT FAMILY: FUNCTION

The functionality of the glutamate transporters reflects their coupling to the electrochemical potential gradients of Na^+ , K^+ and H^+/OH^- . Specifically, glutamate is co-transported across the plasma membrane 1:2-3 with Na^+ and 1:1 H^+ (or counter-transport of OH^-) and counter-transported 1:1 with K^+ ^[4,19,20]. This ionic association provides a net positive charge to glutamate transport^[20] however a relatively slow turnover rate of approximately 70 ms makes it unlikely that this electrogenic attribute contributes significantly to the electrochemical gradient of the cell^[21,22]. Furthermore, this slow turnover rate suggests that the transporters act first to buffer glutamate away from the synapse, and transport glutamate into glia at a slower rate. The quantity of charge transferred per molecule of glutamate is highly voltage dependant due to the existence of a thermodynamically uncoupled, transporter substrate-specific movement of chloride ions through the transporter^[16,23]. The ion- and voltage- dependant uptake of glutamate makes this process highly susceptible to changes in the immediate cellular environment and plasma membrane potential.

THE EAAT FAMILY: LOCALISATION

Some of the functional properties of the EAATs can be attributed to their differential localisation. EAAT3 and EAAT5 are exclusively neuron-specific^[17,24], with EAAT5 expression restricted to neurons and Müller cells of the retina^[17]. By contrast, EAAT1 and EAAT2 are predominantly localised on astrocytes and are highly expressed in the cerebellum and hippocampus, respectively^[25-27]. EAAT1, EAAT2 and EAAT3 have been reported to make up approximately 20%, 80% and 1% of all cell-surface glutamate transporters in the adult rat hippocampus, respectively^[24]. EAAT4 is found in Purkinje neurons of the cerebellum^[28].

THE EAAT FAMILY: ROLE IN GLIAL METABOLISM OF GLUTAMATE

Glial metabolism of glutamate is now recognised as a major factor in the control of glutamatergic neurotransmission^[9], as, following the release of glutamate from the pre-synaptic neuron, the majority of the neurotransmitter diffuses out of the synaptic cleft where it is taken up into glial cells^[29-31]. This effectively means that the astrocytic EAATs play a significant role in controlling the extent of glutamatergic activation by preventing neurotransmitter spill-over into neighbouring

synapses^[20,22,32].

Once taken up by astrocytes, glutamate is either converted to glutamine by the glia-specific glutamine synthetase (GS)^[33], or converted to α -ketoglutarate (α -KG) (also known as 2-oxoglutarate) through oxidation by glutamate dehydrogenase (GLDH) or transamination by aspartate aminotransferase^[34,35]. α -KG may then be converted to succinate with a by-production of ATP (Figure 1) as part of the tricarboxylic acid cycle^[34,35]. The formation of glutamine - the predominant metabolic pathway for glutamate - is followed by the transport of glutamine to neurons where it undergoes synthesis back into glutamate *via* the enzyme glutaminase^[36] (Figure 1).

It is now acknowledged that glutamate excitotoxicity can potentially lead to problems in CNS functioning^[8]. Significantly, it is now being speculated that glutamatergic excitotoxicity may in part be due to a reduction in glutamate uptake by astrocytic glutamate transporters and subsequent conversion of glutamate to glutamine by GS. Such an hypothesis is supported by research showing that inhibition or antisense oligonucleotide-knockdown of astrocytic glutamate transporters EAAT1 and EAAT2 results in excitotoxic oligodendrocyte death and nerve damage^[37]. Moreover, whilst glutamate is usually taken into astrocytes under physiological conditions, it has been suggested that Ca^{2+} -dependent activation of select signalling molecules, intracellular increase in Na^+ and glutamate, ATP depletion or cell swelling can lead to glutamate release through EAAT transporter reversal/reverse uptake^[11,38]. Such an outcome represents another mechanism that can lead to glutamate excitotoxicity.

THE EAAT FAMILY: A FOCUS ON EAAT1 AND EAAT2

The focus of this review is the potential involvement of glutamate transporters in the aetiology of psychiatric disorders. At present, most evidence implicating glutamate transporters in the aetiologies of psychiatric disorders is from the study of EAAT1 and EAAT2. Hence the remainder of this review will focus on those two forms of glutamate transporters.

EAAT1

The *EAAT1* gene has been localised to human chromosome 5p11-12^[39] and 5p13^[40,41]. *EAAT1* is highly expressed in the glial cells of the cerebellar Purkinje cell layer^[12,13,42] and generally is expressed at higher levels in astrocytes and oligodendrocytes compared to microglia^[43].

The *EAAT1* gene encodes a 59 kDa protein that undergoes glycosylation to produce native 64 kDa and 70 kDa glycoproteins^[44-46]. Post-translational modification of EAAT1 is developmentally regulated, with glycosylated EAAT1 increasing and non-glycosylated EAAT1 decreasing after birth^[47]. Glycosylation does not affect EAAT1 transport activity, however research by

Conradt *et al.*^[46] suggests that the addition of carbohydrates does impact EAAT1 homodimerisation. This is significant because it has been suggested that activation of astrocytes increases homodimerisation of EAAT1 and trafficking of the transporter to the plasma membrane^[48]. In addition to homodimers, EAAT1 protein has shown potential to form homotrimers^[49]. Moreover, it has been reported that cell-surface protein expression of EAAT1 is upregulated by exogenous glutamate^[50-52], a process suggested to be mediated through transporter activity^[51] and/or ionotropic glutamate receptor signalling^[50,52]. EAAT1 protein levels have also been reported as being downregulated by the group I metabotropic glutamate receptor (mGluR) agonist, DHPG, which selectively activates mGluR1 and 5, and upregulated by the group II mGluR agonist, DCG-IV, which activates mGluR 2 and 3^[53]. Further work is therefore required to fully elucidate which glutamate receptors are critical in controlling levels of EAAT1 at the cell surface.

At the level of protein localisation, high levels of EAAT1 protein can be observed on rat astrocytic membranes opposed to synaptically dense regions of the CNS and at higher levels on astrocytes facing capillaries, pia mater or stem dendrites^[27]. Although predominantly a glial transporter, EAAT1 protein has also been detected in deep cerebellar rat neurons and transient protein expression of EAAT1 has been observed in cultured rat embryonic hippocampal neurons^[26,54]. Rat neuronal EAAT1 protein expression appears to be restricted to perinuclear localizations, in particular the Golgi apparatus and associated vesicles^[26]. Soluble factors secreted from astrocytes appear to induce the repression of neuronal protein expression of EAAT1^[55], which supports the aforementioned lack of EAAT1 protein at the neuronal cell surface. It is possible that, at least in the adult brain, neuronal EAAT1 is redundant, and may be upregulated where there is an inadequate presence of EAAT1-expressing astroglia.

The *EAAT1* gene is expressed in its full length coding sequence of 10 exons^[39] and as three splice variants which encode shorter protein isoforms known as EAAT1a, EAAT1b and EAAT1c.

EAAT1a lacks exon 3 - which ordinarily encodes the first and second transmembrane domain and the first extracellular loop^[45] - and has been detected in rat brain and retina^[45,56]. Significantly, it has been proposed that the splicing of exon 3 may reverse the orientation of EAAT1a within the membrane, and therefore the direction of glutamate transport^[45]. EAAT1a has been shown to be predominantly expressed within internal vesicles, rather than on the cell membrane, in an osteocyte cell line^[57]. Interestingly, an unglycosylated variant of EAAT1a protein has also been detected in rat brain^[45]; as glycosylation has previously been associated with trafficking of EAAT1 to the cell surface, this may explain the localization of EAAT1a to internal vesicles.

mRNA for EAAT1b, which lacks exon 9^[58], has been

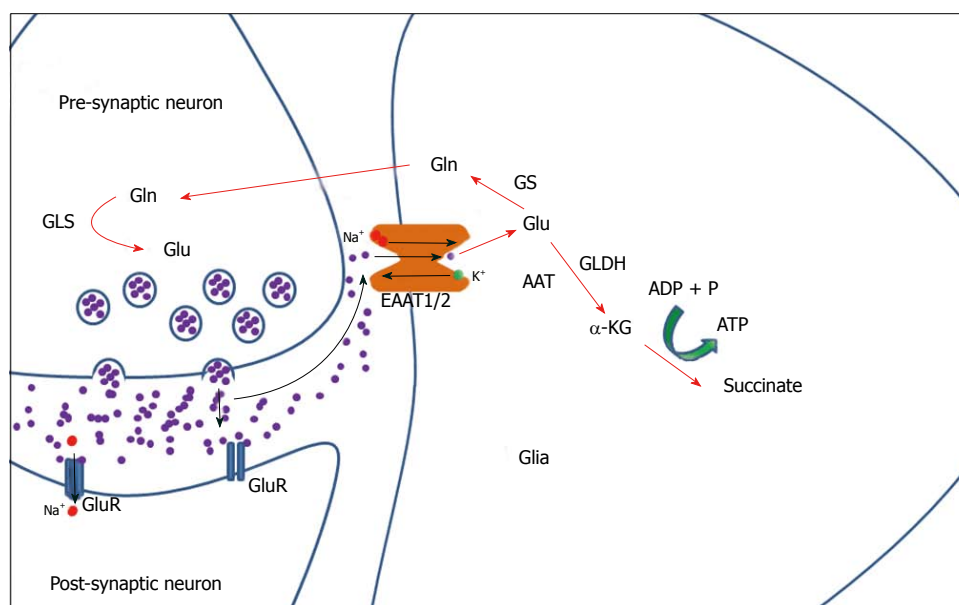


Figure 1 The metabolic fate of glutamate in glia cells. Glutamate is released from the pre-synaptic neuron to induce activation of the post-synaptic neuron via GluR. Spill-over of excess glutamate from the synaptic cleft is prevented through uptake by glial glutamate transporters EAAT1 and EAAT2, following which glutamate is converted to glutamine by GS for recycling back into glutamate, or α -KG for entrance into the tricarboxylic acid cycle. AAT: Aspartate Aminotransferase; α -KG: Alpha ketoglutarate; EAAT1/2: Excitatory amino acid transporter 1 and 2; GLDH: Glutamate dehydrogenase; Gln: Glutamine; GLS: Glutamate synthase; GS: Glutamine synthase; Glu: Glutamate; GluR: Glutamate receptors; Na⁺: Sodium; K⁺: Potassium.

detected in both human grey matter and axonal tracts at levels that are 10%-20% that of the full length EAAT1^[58]. EAAT1b localization has been associated with the endoplasmic reticulum^[58], intracellular inclusions and the plasma membrane^[59], where it appears to have no functional glutamate uptake activity^[58]. Rather, it has been suggested that EAAT1b negatively regulates levels of full-length EAAT1 at the cell surface by preventing the insertion of the latter into the plasma membrane^[58], possibly by interacting directly with full length EAAT1. EAAT1b appears to be particularly localised to cortical neurons^[59] where it is suggested to play a role in preventing ectopic neuronal expression of EAAT1. Immunoperoxidase-labelling of EAAT1b was associated with the plasma membrane for morphologically healthy neurons and in punctate intracellular inclusions of neurons that appeared degenerate^[59]. Furthermore, EAAT1b expression was increased in neuronal populations - and to a lesser extent astrocytes - that were subject to hypoxia, in histologically degenerate brain regions which also displayed a downregulation of glial EAAT1^[60].

EAAT1c mRNA, which lacks exon 5 and 6 of the full coding sequence, has been detected in astrocytes and oligodendrocytes of the human cortex, retina and optic nerve, as well as pig forebrain, midbrain, hindbrain and cerebellum^[61]. The approximately 47 kDa glia-specific EAAT1c protein has been shown to have an intracellular perinuclear localization, with rapid redistribution to the cell surface following astrocytic stimulation^[61]. Furthermore, EAAT1c does not undergo glycosylation^[61]. Unfortunately the only study to examine EAAT1c was not able to determine its function, with the two most

likely (default) candidates remaining as a regulator of full length EAAT1 cell surface expression, or as a *bona fide* transporter trafficked to the cell surface under appropriate conditions.

EAAT2

The EAAT2 gene is localized within human cytogenetic bands 11p12-13^[62], and is responsible for the majority of glutamate uptake within the EAAT family (see^[63] for review). EAAT2 expression appears to be restricted to the brain and placenta in humans^[13] and has also been detected in cultured hippocampal neurons from rat embryo^[64]. The mRNA expression of EAAT2 was found to be greater in cultured rat oligodendrocytes than astrocytes or microglia^[43].

While EAAT2 protein expression has an overall homogenous brain distribution, it predominates across the forebrain with a particular focus in the hippocampus^[26,65,66]. EAAT2 appears to be a predominantly glial glutamate transporter, with up to 80% of EAAT2 protein detected in glia plasma membrane, 6% localized to plasma membrane of pre-synaptic neurons and 8% to the axonal plasma membrane in the stratum radiatum of the rat hippocampal subregion CA1^[67]. In line with the detection of EAAT2 mRNA^[64], EAAT2 protein expression has similarly been recorded in cultured rat embryonic hippocampal neurons^[54,64]. Like EAAT1, EAAT2 protein undergoes glycosylation, which produces a 5-15 kDa shift in molecular weight^[48,68] and mediates its cell surface expression^[68]. EAAT2 also exists in the plasma membrane as a multimer, with the potential to form dimers and trimers^[49,69].

EAAT2 would seem to have a complex role in devel-

opment as it is transiently detected in neurons throughout ovine forebrain and cerebellum at 71 d gestation, and lost by 136 d gestation^[70]. In addition, EAAT2 and glial fibrillary acidic protein (GFAP) have been reported to not be expressed by the same cells at 71 d ovine gestation but showed region-specific colocalization by 136 d gestation^[70]. A similar transition from prenatal axonal pathways to astrocytic EAAT2 protein expression was also seen in rat^[47]. Interestingly, it appears as if neuronal soluble factors may be required for proper expression of EAAT2 in neighbouring astrocytes^[53,71] with EAAT2 protein levels quantitatively higher in the synaptically dense regions of glial cells^[27].

The human *EAAT2* gene consists of 11 exons^[72]. Two functional splice variants of EAAT2, termed EAAT2b and EAAT2c, contain unique C-terminal domains and have been detected in rat brain (EAAT2b) and retina (EAAT2c)^[73,74]. Additional splice variants which share the C-terminals of EAAT2 and EAAT2b, but have a unique N-terminal domain, have also been detected in mouse and rat liver and referred to as mGLT-1A/rGLT-1A and mGLT-1B, respectively^[75] (see^[74] for a comparison of amino acid terminal sequences). While the unique N-terminals has been proposed to regulate tissue-specific expression, the function of the differing C-terminal of mGLT-1A and mGLT-1B is less clear - the authors propose that it may be related to the retention time of the transporter in the plasma membrane^[75]. As mGLT-1A/rGLT-1A and mGLT-1B are localized to the liver^[75], they will not be discussed further in this review. Rather, further evidence for the role of the C-terminus can be presented using data on rat EAAT2b, which will be discussed in the following paragraph.

Full length EAAT2 (commonly referred to as EAAT2a) expression is about 25-fold and 10-fold higher than EAAT2b in human and rat brain, respectively^[76]. EAAT2b protein is similarly found in glia, localized close to or within the plasma membrane^[77-79], however transcript and protein have also been detected in neurons^[78]. While EAAT2 is constitutively trafficked to the cell surface membrane, localization of EAAT2b is mediated through its C-terminal, which is predicted to interact with the postsynaptic density-95/Discs large/zona occludens-1 (PDZ) domain-containing protein disks large homolog-1 (DLG1)^[80]. The interaction between EAAT2b and DLG1 is itself regulated through AMPA-associated intracellular calcium levels, with exogenous glutamate resulting in dissociation of EAAT2b and DLG1 and subsequent internalization of EAAT2b^[80]. EAAT2b also coimmunoprecipitates with the excitatory postsynaptic density scaffolding protein, PSD-95, as well as the ionotropic N-methyl-D-aspartate receptor (NMDAR), both found within the postsynaptic neuron^[81]. Significantly, EAAT2 has also been detected in these protein complexes, through the indirect formation of a hetero-oligomer with EAAT2b^[81]. This suggests that EAAT2b may assist in conditional neuronal cell-surface expression of EAAT2. EAAT2b represented 6%

of total rat hippocampal EAAT2 variants at 8 wk of age, compared to EAAT2 at 90%, whereas the equally functional EAAT2c sits at just 1%^[77].

EAAT2c is made up of exons 1-10 from the EAAT2 transcript plus a unique eleventh exon and C-terminus spliced from intron 10 - thereby losing the original eleventh exon from EAAT2 - similarly contains a PDZ-binding domain and is pre-synaptically expressed in the rat and human retina^[74].

Aberrant EAAT2 splice variants which skip exons have also been discovered: In particular, EAAT2 exon7skipping and EAAT2 exon9skipping lack glutamate transport functionality and must form multimers with functional EAAT2 or EAAT2b (see^[82] for review). These splice variants add another layer of complexity to what has been considered a predominantly astrocytic glutamate transporter.

EAAT1 vs EAAT2: A summary

Despite belonging to the same family of transporters, sharing 52% amino acid identity^[18] and being localized within the same astrocytic plasma membrane^[49], EAAT1 and EAAT2 display many differences in their functionality. EAAT1 protein levels have been shown to function approximately 6 times slower than EAAT2, and be expressed at a level approximately 6 times higher in the adult rat cerebellar molecular layer^[21,65]. On the other hand, EAAT2 protein levels are upwards of 4 times higher than EAAT1 in the adult murine hippocampus^[65]. Furthermore, unlike EAAT1, cell-surface protein expression of EAAT2 appears unaffected by exogenous glutamate levels but rather, is regulated by neuronal soluble factors^[50-52]. Finally, within the EAAT family, only EAAT2 can be competitively inhibited by kainic acid (KA) and dihydrokainic acid (DHK)^[13]. Conversely, KA has been shown to increase EAAT1 protein levels^[50]. It is possible that this increase in EAAT1 protein in response to KA is a homeostatic mechanism, counterbalancing for the inhibition of EAAT2.

The fact that EAAT1 and EAAT2, and their functionally distinct splice variants, may be differentially regulated by internal and external factors presents us with two distinct transporters that are part of a system that is highly responsive to cellular physiology. In the following paragraphs, we will present the current knowledge surrounding EAAT1 and EAAT2 in psychiatric illness, as well as their responsiveness to medication and potential as drug targets (refer to Table 1 for a summary).

EAATS IN PSYCHIATRIC ILLNESS

Glial dysfunction has been implicated in a range of psychiatric illnesses, including major depressive disorders (MDD)^[83,84], schizophrenia^[85], bipolar disorders (BD)^[86] and post-traumatic stress disorder (PTSD)^[87]. Glia dysfunction has also been associated with suicide completion^[88,89]. The association between the glutamatergic

Table 1 The role of EAAT 1 and 2 in psychiatric disorder and medication use

EAAT1	Genetic studies	BD	SNP rs2731880 T/T genotype associated with worse working memory and selective attention during a depressive episode ^[102]
		Scz	SNP rs2731880 T/T genotype increased negative fMRI BOLD coupling between the amygdala and AnCg ^[103] SNP rs2731880 T/T genotype associated with worse executive function, verbal fluency and verbal memory ^[104] No association between EAAT1 SNPs rs1428973, rs2033267, rs426040, rs4869684, rs1544795, rs3776585, rs962686, rs2303716, rs3776586, rs1049524, rs1529461 and Scz ^[112]
	mRNA studies	MDD	↓Lower levels in the DLPFC ^[83] , AnCg ^[83] , locus coeruleus ^[105] and hippocampus ^[106] ↑Higher cortical levels in suicide completers with a MDD diagnosis compared to those without a diagnosis ^[118]
		Scz	↑Higher mRNA in the cerebellar vermis ^[113] , AnCg ^[114] , thalamus ^[115] and prefrontal cortex ^[116] →No change in the DLPFC or primary visual cortex ^[76,114] ↓Lower levels in the prefrontal cortex of subjects who completed suicide compared to those who did not ^[117]
	Medication use		↑Haloperidol has been associated with an increase in EAAT1 mRNA in the thalamic medial dorsal nucleus ^[121] ↑Chronic sodium valproate resulted in an upregulation of EAAT1 mRNA in chick cerebellar BGC culture ^[110]
	Protein studies	Scz	↓Decreased in the prefrontal cortex ^[114] ↓N-glycosylation of EAAT1 monomer was decreased in the AnCg ^[114, 119]
		PTSD	↓Hippocampal EAAT1 protein was lower in a single prolonged stress (SPS) rat model of PTSD ^[108]
	Medication use		→Clozapine did not affect EAAT1 protein levels in rat ^[113,122] ↑Chronic sodium valproate resulted in an upregulation of EAAT1 protein in rat hippocampus and chick cerebellar BGC culture ^[109,110]
	Genetic studies	Scz	SNP rs4354668 G/G associated with poorer working memory performance ^[104,138] and a reduction in frontal grey matter ^[139]
		MDD	↓Lower levels in DLPFC and AnCg ^[83] ↑Higher levels in subjects who had completed suicide without a diagnosis of MDD compared to those with a diagnosis ^[118,127]
	Scz		↓Lower levels in the hippocampus, cerebral cortex and striatum of a rat model of depression ^[128, 129] ↓Lower levels in the parahippocampal gyrus ^[140] and prefrontal cortex ^[141] ↑Higher levels in the thalamus ^[115] and prefrontal cortex ^[142] →No change in EAAT2 or EAAT2b mRNA in the DLPFC or primary visual cortex ^[76]
		Medication use	↓Clozapine decreased levels in hippocampal CA1, parietal temporal, frontal and cingulate cortical ^[144] , and striatal ^[145] brain regions of male Sprague-Dawley rats ↓Haloperidol decreased frontal and cingulate cortical ^[144] , as well as striatal ^[145] , EAAT2 expression in rat ↓Levels were higher in untreated subjects with Scz than in those prescribed typical or atypical antipsychotics ^[142] ↓Increased levels caused by chronic stress were normalised by tianeptine treatment in rat ^[130] ↓Increased hippocampal levels caused by stress were normalised by lithium administration in rat ^[137] ↑Fluoxetine increased rat hippocampal and cortical levels ^[136] ↑Tranylcypromine increased levels in rat amygdala ^[136]

All research refers to human studies unless explicitly stated otherwise. References numbered as they are in the Reference section. ↑: Increase; ↓: Decrease; →: No change; AnCg: Anterior cingulate cortex; BGC: Bergmann glia cell; DLPFC: Dorsolateral prefrontal cortex; BD: Bipolar disorders; BOLD: Blood-oxygen dependent contrast imaging; fMRI: Functional magnetic resonance imaging; MDD: Major depressive disorders; PTSD: Post-traumatic stress disorder; Scz: Schizophrenia.

neurotransmitter system and psychiatric illness is not new^[90,91]; originally based on the observation that phenylcyclidine (PCP), and later ketamine - both NMDA receptor antagonists - could induce schizophrenia-like positive and negative symptoms, as well as cognitive impairment^[92-94]. While glutamatergic dysfunction is also hypothesized to be involved in other neurodevelopmental disorders such as autism^[95] and attention deficit hyperactivity disorder^[96,97], neurodegenerative disorders such

as dementia^[98,99], substance abuse/addiction^[100] and chronic pain^[101] (the latter two referenced reviews are written with a focus on EAATs), these topics are outside the scope of the current review.

EAAT1 in psychiatric illness

The rs2731880 (C/T) single nucleotide polymorphism (SNP) of *EAAT1* has been associated with deficits in working memory and selective attention in patients with

Type 1 bipolar disorder during a depressive episode, with T/T homozygotes displaying significantly worse performance^[102]. Furthermore, bipolar disorder patients with the rs2731880 T/T genotype have displayed an overall negative correlation between amygdala and subgenual anterior cingulate cortex (AnCg) functional magnetic resonance imaging (fMRI) blood-oxygen-level dependent (BOLD) contrast imaging during a task which involved the processing of emotional or neutral faces, whereas in carriers of the C allele the coupling was absent^[103]. SNP rs2731880 is a putative functional polymorphism within the promoter region of *EAAT1*, with the T/T genotype proposed to be associated with lower expression^[104]. In support of the hypothesis that lower *EAAT1* expression is associated with affective disorders, lower levels of *EAAT1* mRNA have been reported in the human dorsolateral prefrontal cortex (DLPFC)^[83], AnCg^[83], locus coeruleus^[105] and hippocampus^[106] from subjects with MDD. Interestingly, Group II mGluR receptors - the agonists of which have been shown to upregulate *EAAT1* protein levels^[53] - are also decreased in MDD^[107].

Furthermore, Feng *et al.*^[108] detected an increase in CSF glutamate levels and decrease in hippocampal *EAAT1* protein levels in the single prolonged stress (SPS) rat model for PTSD. Interestingly, administration of fibroblast growth factor 2 (FGF2) alleviated the SPS-induced PTSD-like behaviour, promoted glutamate uptake and increased *EAAT1* protein expression, thereby suggesting that astrocyte activation (and *EAAT1* upregulation) may be advantageous in the treatment of PTSD^[108].

Short-term sodium valproate treatment augmented *EAAT1* translocation to the cell membrane, whereas prolonged or chronic sodium valproate treatment resulted in an upregulation of *EAAT1* mRNA and protein levels, as well as glutamate transport and production of glutamine^[109,110]. The ability of sodium valproate treatment to increase *EAAT1* mRNA and protein levels, which are downregulated in affective disorders, contributes *EAAT1* dynamics to an understanding of the medication's effectiveness^[111]. This is not surprising, given that sodium valproate is used to treat both epilepsy - a disorder of excitotoxicity - and bipolar disorders.

Carriers of the rs2731880 SNP T/T genotype with a diagnosis of schizophrenia performed worse in tests of executive function, verbal fluency and verbal memory than the C carrier group^[104]. This association has overlap with cognitive performance of subjects with bipolar disorder I^[102]. Furthermore, Deng *et al.*^[112] analysed 11 *EAAT1* SNPs - exclusive of rs2731880 - in a Japanese population and found no association between *EAAT1* genotype and schizophrenia. These genotypic association studies suggest that while there may exist a relationship between *EAAT1* genotype and cognition, particularly within the context of psychiatric disorder, it is not a susceptibility locus specific to either schizophrenia or bipolar disorders.

Levels of *EAAT1* mRNA have been reported as higher in the cerebellar vermis^[113], AnCg^[114], thalam-

us^[115] and prefrontal cortex^[116] of subjects with schizophrenia. In comparison, other studies have found no changes in *EAAT1* expression in the DLPFC^[76,114] or primary visual cortex^[76] of subjects with schizophrenia. However, lower levels of *EAAT1* mRNA were found in the prefrontal cortices of subjects with schizophrenia who completed suicide relative to those who did not^[117], a confounding factor that many studies have not taken into consideration. Conversely, it has also been reported that *EAAT1* mRNA levels were higher in the cortex of suicide completers without a prior diagnosis of MDD but not those with the diagnosis^[118]. These data suggest complex expression x diagnoses x suicide factors that need to be considered when contemplating the role of *EAAT1* in psychiatric disorders. Finally, monomeric *EAAT1* protein expression was decreased in the DLPFC of elderly subjects with schizophrenia^[114], while N-glycosylation of *EAAT1* protein monomer was decreased in the AnCg^[119]. Animal models have shown that *EAAT1* knock-out mice displayed locomotor hyperactivity in response to a novel environment which was exacerbated by NMDAR antagonists - two phenotypes considered to be relevant models for the positive symptoms of schizophrenia^[120].

Interestingly, the locomotor hyperactivity in *EAAT1* knock-out mice could be normalised by treatment with haloperidol or the mGluR 2/3 agonist LY379268^[120]. As *EAAT1* protein levels have previously been shown to increase with administration of the mGluR 2/3 agonist DCG-IV^[53], the data in *EAAT1* knockout mice suggests that activation of mGluR 2/3 may impact on a function downstream of glial glutamate uptake. Haloperidol has similarly been associated with an increase in *EAAT1* RNA in the thalamic medial dorsal nucleus in subjects with schizophrenia^[121]. On the other hand, administration of clozapine did not appear to affect *EAAT1* protein levels in treated Sprague-Dawley rats^[113,122], possibly due to the fact that clozapine, but not haloperidol, increases NMDAR-mediated neurotransmission through synaptobrevin-associated glial release of glutamate and D-serine^[123]. If clozapine administration induces glutamate release from glia, it seems unlikely that glia would simultaneously increase a means to re-uptake glutamate. In conclusion, it appears that while the actions of haloperidol indirectly affect *EAAT1* expression, clozapine seems to act through an alternative mechanism that is unrelated to *EAAT1*.

In summary, current data suggest an overall decrease in *EAAT1* mRNA in affective disorders, while an increase in *EAAT1* mRNA and decrease in *EAAT1* protein is associated with schizophrenia; results which are further complicated by suicide completion and medication use. These factors must be taken into consideration when studying *EAAT1*, and the glutamatergic system as a whole, in terms of treatment for psychiatric illness.

EAAT2 in psychiatric illness

EAAT2 translation may be regulated by a large range

of molecules, including the stress-related glucocorticoids^[124-126], creating a putative link between EAAT2 protein levels and stress-induced biological responses. To date, one study has recorded a lower levels of EAAT2 mRNA in the DLPFC and AnCg of subjects with MDD^[83]. Interestingly, as with EAAT1, levels of EAAT2 mRNA were higher in the cortex of subjects who had completed suicide without a history of MDD, but not in those with a prior diagnosis^[118,127]. EAAT2 mRNA was also lower in the hippocampus and cerebral cortex of learned helplessness rats – an established animal model of depression^[128] and in the hippocampus, striatum, and frontal cortex of prenatally, restraint- stressed juvenile rats displaying increased behavioural despair^[129].

Hippocampal EAAT2 protein levels were also observed to be lower in a SPS rat model of PTSD, which, like EAAT1 protein levels, could be alleviated by treatment with FGF2^[108]. Interestingly, a rat model of chronic stress produced upregulated EAAT2 mRNA and protein levels in the hippocampus^[130], suggesting that EAAT2 regulation may respond differently to the type, duration and severity of stress stimuli. Finally, amygdala specific DHK-inhibition of EAAT2 activity in rat resulted in reduced social interaction – a behavioural phenotype that could be blocked by the NMDA receptor antagonist, AP5^[131].

Cerebrospinal fluid glutamate levels have been reported as higher in patients with obsessive compulsive disorder (OCD)^[132,133]. To date however, an association between OCD and the glutamate transporters has only been proposed for the neuronal EAAT3, which is significantly less involved in glutamate uptake when compared to EAAT1 and EAAT2^[134]. That said, astrocyte-specific inducible knockout of EAAT2 in adolescent - but not prenatal or adult - mice has been shown to result in glutamatergic hyperexcitability-related pathological repetitive self-grooming and tic-like head shakes^[135]. Interestingly, these mice did not present with increased anxiety or social impairments^[135].

It seems that the lower EAAT2 expression associated with depression and learned helplessness can be rescued by mood stabilizers. Chronic sodium valproate treatment increased EAAT2 protein levels in the rat hippocampus, but not other brain regions^[109]. The antidepressant fluoxetine (class: SSRI) also produced rat hippocampal and cortical increases in EAAT2 expression, while tranylcypromine (class: monoamine oxidase inhibitor) resulted in an amygdala-specific increase^[136]. In contrast to a depressive state, increases in EAAT2 mRNA and protein caused by chronic stress could be normalised by the antidepressant tianeptine in rat^[130]. Interestingly, EAAT2b protein, but not mRNA, was also increased by chronic stress, however remained unaffected by tianeptine treatment^[130]. A similar stress-induced increase in hippocampal EAAT2 mRNA expression was countered by food-based administration of lithium in rat^[137]. This increase in EAAT2 expression in response to chronic stress lies in stark contrast to the previously mentioned decreases in EAAT2 expression

associated with depression and learned helplessness, and suggests that EAAT2 is highly responsive to, or correlated with, different mood states.

EAAT2 SNP rs4354668 (T/G), located in the gene promoter region and associated with lower transport activity, has been correlated to cognitive dysfunction in schizophrenia, with the lower activity G allele linked to poorer working memory performance^[104,138] and a reduction in frontal grey matter^[139]. EAAT2 mRNA levels have been reported as lower in the parahippocampal gyrus -but not other hippocampal regions^[140] and prefrontal cortex^[141], and higher in the thalamus of subjects with schizophrenia^[115]. In contrast, Matute *et al.*^[142] found an increase in EAAT2 expression in the prefrontal cortex. Finally, Lauriat *et al.*^[76] found no change in EAAT2 or EAAT2b mRNA in the DLPFC or primary visual cortex of subjects with schizophrenia, however the authors acknowledge the potential masking effect of antipsychotics on their results. N-glycosylation of the EAAT2 multimer was reduced in the DLPFC from subjects with schizophrenia^[119], which may be associated with ER retention and reduced trafficking of EAAT2 to the plasma membrane^[68]. The splice variant EAAT2b was increased in extra-synaptic membrane/cytosol post-mortem fractions from the DLPFC of subjects with schizophrenia^[143]. As EAAT2b cell-surface expression is internalised in response to increases in intracellular calcium^[80], it is possible that the elevated cytosolic localization of EAAT2b is a countermeasure to excitotoxicity.

Clozapine treatment has been reported to decrease EAAT2 expression in hippocampal CA1, parietal temporal, frontal and cingulate cortical^[144], and striatal^[145] brain regions of male Sprague-Dawley rats. EAAT2 protein levels and glutamate uptake were similarly reduced in the cerebral cortex of clozapine-treated adult rats with an accompanying increase in extracellular glutamate^[146]. Clozapine also induced a decrease in EAAT2 protein in astrocyte culture, which was accompanied by a reduction in glutamate uptake^[147]. This response to clozapine, which contrasts with the lack of effect that clozapine had on EAAT1 expression (discussed earlier in this review), suggests once again that the two EAAT subtypes are intrinsically different. Haloperidol similarly decreased frontal and cingulate cortical^[144], as well as striatal^[145], EAAT2 expression in rat. Matute and colleagues have provided support to the argument that antipsychotic drug treatment can affect EAAT2 expression by showing the higher levels of EAAT2 mRNA in the prefrontal cortex of untreated subjects with schizophrenia were not detectable in those with the disorder who had received typical or atypical antipsychotics^[142].

CONCLUSION

Given the differential expression of EAAT1 and EAAT2 throughout brain development^[47] and their importance in normal brain development^[148], it is not surprisingly

that abnormal levels of these glutamate transporters have been found in the pathophysiology of psychiatric illness. It is imperative, however, that the subtype splice variants and glycosylation states be taken into consideration when researching the EAATs, as their unique attributes make them just as susceptible to disorder. The ability to analysis EAAT dynamics in a pre-mortem setting will assist in understanding the cause for their dysregulation and through that, the glutamatergic role in psychiatric disorder. Such information will allow for the prescription of medication with an understanding of how it may, or may not, affect the glutamatergic system. This review concludes with the contention that the EAAT family is dynamically regulated by a range of internal and external factors and offer a viable means to region-specific, subtype-specific therapeutic targets with the potential to respond to the immediate environment. However, a better understanding of the dynamic regulation of EAATs within the convoluted context of psychiatric disorder will be advantageous in advancing drug discovery.

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