THE ROLE OF GLUTAMATERGIC PATHWAYS IN SCHIZOPHRENIA: FROM ANIMAL MODELS TO HUMAN IMAGING STUDIES

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Abstract

Glutamate, a key excitatory neurotransmitter in the brain is implicated in the pathophysiology of schizophrenia. Animal and human studies have demonstrated that glutamate is involved in patterns of normal connective brain development and its specific receptors such as the N-methyl-D-Aspartate (NMDA) are associated with critical functions such as learning and memory. Therefore, there is a critical need to integrate animal studies of glutamate neurotransmission, human *in vivo* studies of structure and function relevant to the glutamate system, and the computational models of pharmacologic and behavioural processes. Such integrative approaches are needed to develop a clearer understanding of the role of glutamate in schizophrenia pathology. In this review, the authors selectively review relevant findings from the schizophrenia literature, as well as studies in animal and human experimental studies to motivate the need for a translational and integrative framework. Future experimental approaches to understanding glutamatergic neurotransmission in schizophrenia will benefit from considering this diverse collection of experimental literature and such knowledge will sharpen understanding of the precise role of glutamtergic neurotransmission in schizophrenia.

Key Words: Glutamate – Glutamatergic Neurotransmission – Pathophysiology of Schizophrenia

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Different lines of evidence, including animal studies, postmortem findings, and imaging studies suggest that alterations in glutamatergic neurotransmission are central to the pathophysiology of schizophrenia. As an important excitatory neurotransmitter, glutamate is central to the normal connective development of the cortex and its receptors including alpha-**a**mino-3-hydroxy-5-**m**ethyl-4-isoxasole**p**ropionic **a**cid (AMPA) receptor and particularly the N-methyl-D-aspartate (NMDA) are specifically associated with behavioral tasks such as learning that depend on synaptic plasticity. In this integrated manuscript, we selectively review the literature from animal and human experimental work in regard to glutamate transmission in schizophrenia debating possible perspective on this field of research.

Glutamate system and animal models of schizophrenia

Although historically schizophrenia has been correlated with a dysfunction of dopaminergic neurotransmission, a glutamatergic hypothesis has been put forward, suggesting that a deficiency of NMDA receptor-mediated transmission might underlie specific aspects of this mental disorder (Jentsch and Roth 1999, Tsai and Coyle 2002, Stone et al. 2007). This hypothesis was initially developed based on the similarities between schizophrenic symptomatology and the effects produced by the glutamate NMDA receptor antagonist phencyclidine (PCP), a drug of abuse also know as 'angel dust'. Moreover healthy volunteers receiving ketamine, another NMDA receptor antagonist, show

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positive symptoms, in the form of delusions and thought disorder, as well as negative symptoms, characterized by withdrawal and blunted affect (Krystal et al. 1994, Tsai and Coyle 2002).

Further support to this hypothesis came from detailed pharmacological and genetic studies. In rodents, NMDAR antagonists induce a range of acute effects, including locomotor hyperactivity, prepulse inhibition (PPI) deficits, and disruption of working memory, which are highly reminiscent of schizophrenia symptoms. In primates, NMDAR antagonists also produce deficits of working memory and PPI. When compared to acute treatment in humans, prolonged NMDAR blockade, induced by repeated administration of receptor antagonists in rodents or primates, leads to the appearance of hallucinatory-like behavior, enduring cognitive deficits and cortical dopamine dysfunction, suggesting that dysregulation of relevant brain systems may emerge gradually over time (Jentsch et al. 1997, Balla et al. 2001, Javitt 2004).

In line with these results are data obtained in transgenic animal models. In particular Mohn and coworkers developed mice with a knockout of the obligatory NMDA receptor subunit NR-1 (Mohn et al. 1999). These animals, which express only 5% of NR-1, show enhanced locomotor activity, which is normalized by antipsychotic treatment, as well as impaired social interaction and PPI disruption (Mohn et al. 1999, Duncan et al. 2004). A similar phenotype has been observed in knockout mice for the NR-2A subunit.

The involvement of glutamate in schizophrenia has to be considered in the context of neuronal circuitry and its close interaction with other neurotransmitters, including dopamine and GABA. For example, hypofunction of NMDA receptors in prefrontal pyramidal cells can lead to decreased activity in cortical excitatory projections to mesencephalic DA neurons, projecting to dorso-lateral PFC and increased activity of DA cells projecting to the striatum (Lewis and Gonzalez-Burgos 2006).

Important support for the role of glutamate in the disease has also come from investigations of susceptibility genes for schizophrenia. Indeed genes encoding for dysbindin-1, neuregulin-1 (NRG1), D-amino acid oxidase (DAO), its activator DAOA and regulator of G protein signalling-4 (RGS4) are not only important for synaptic plasticity and neuronal development, but share the ability to directly or indirectly modulate the function of glutamatergic synapses and, more specifically, NMDA receptor mediated transmission (Harrison and Weinberger 2005, Chen et al. 2006, O'Tuathaigh et al. 2007).

One gene of particular interest is NRG1 that is expressed in different isoforms and has a remarkably complex biology. NRG1 has a wide range of functional effects on neuronal and glial cells since it regulates development, neurotransmission and synaptic plasticity (Corfas et al. 2004, Harrison and Law 2006). Within the context of glutamate function in schizophrenia, NRG1 may modulate the expression of glutamate receptor subunits and is thought to regulate its kinetic properties through the phosphorylation of NR2 subunits (Stefansson et al. 2002, Moghaddam 2003). The identification of vulnerability genes for schizophrenia has prompted the development of novel animal mutants that might provide novel insight for the neurobiology of schizophrenia (Chen et al. 2006). Heterozygous NRG1 knockout mice lacking the trans-membrane domain of the gene show hyperlocomotor activity (that is sensitive to attenuation by antipsychotic treatment), impaired PPI as well as decreased expression of NMDA receptors (Stefansson et al. 2002). A similar phenotype has been observed in mice lacking ErbB4, the NRG1 receptor. Despite these data, the link between NGR-1, NMDA receptors and schizophrenia is far from being fully understood. In fact, different single nucleotide polymorphism (SNP) have been described in NRG1 genes (Law et al. 2006), but their functional consequences remain unknown (Harrison and Law 2006). According to postmortem studies the mRNA levels for NRG1 type I isoforms are increased in schizophrenia, which is in line with the observation that NRG1 induced activation of ErbB4 is increased in the prefrontal cortex of schizophrenic patients (Hahn et al. 2006). Moreover since NRG1 stimulation may suppress NMDA receptor activation, the enhanced NRG1 signaling could contribute to NMDA hypofunction in schizophrenia (Gu et al. 2005, Hahn et al. 2006). This example highlights the difficulty in translating clinical data into animal models, especially for genes, such as NRG1, which are important for development as well as for the modulation of synaptic plasticity at adulthood (Chen et al. 2006).

Nevertheless, these recent data suggest that there is a strong link between susceptibility genes to schizophrenia and the glutamate system, in particular the NMDA receptor complex. It is expected that the vulnerability to the disease might arise from proteins that are important for the selective and activity-dependent changes in the function of NMDA receptors as opposed to gross abnormalities in this receptor complex. Herein, although structural abnormalities can be observed in the schizophrenic brain (Kristiansen et al. 2007), available evidences support the idea that schizophrenia is a 'functional' disease of the synapse and of cell-cell communication (Moghaddam 2003).

On this basis, it must be emphasized that effective pharmacological treatments should be able to correct the abnormalities in glutamatergic function. Although currently used antipsychotics can regulate different components of glutamatergic synapses (Tascedda et al. 2001, Heresco-Levy 2003), more direct interventions are under development and might prove useful for the amelioration of core symptoms of schizophrenia that are strongly related to glutamate dysfunction (Tuominen et al. 2006, Arai and Kessler 2007, Javitt 2008).

The relevance of glutamate to the pathophysiology of schizophrenia

In vivo studies of structure and neurochemistry, provide evidence for alterations in hippocampal structure and quantitated glutamate. Hippocampal volume deficits have been documented in at-risk, prodromal and chronic schizophrenia patients suggesting a plausible loss of gray matter neuropil (Velakoulis et al. 2001, Keshavan et al. 2002). Neurochemical imaging studies suggest reduced expression of the subunits for the three ionotropic

receptors of the glutamatergic system (NMDA, AMPA, and kainate) in the hippocampus (Harrison et al. 2003), related to the expression of vulnerability genes including DISC1 and GRM3 that have been associated with schizophrenia (Harrison and Weinberger 2005). The mechanisms that relate reduced NMDAR sensitivity to psychosis are obscure, but putative reductions may have cascading effects including tonic reduction in glutamatergic transmission (Keshavan 1999), its ultimate expression in selective behavioral deficits on fronto-temporal lobe tasks (Greene 2001) or excitatory glutamatergic neurotoxicity (Konradi and Heckers 2003). Neurochemical studies of the hippocampus and other structures in schizophrenia are consistent with this idea. *In vivo* spectroscopy indicate systematic patterns of pathology in the hippocampus, including reduced N-acetyl-aspartate (NAA; an intra-neuronal marker of integrity) (Nasrallah et al. 1994, Bertolino et al. 1996, Deicken et al. 1998). These findings are not restricted to the hippocampus alone. Post mortem studies have shown changes in glutamate receptor binding (Konradi and Heckers 2003), reduced expression of the NMDA subunit (NMDAR1) (Meador-Woodruff and Healy 2000) and reduced glutamate (Ohrmann et al. 2007) in the prefrontal cortex as well.

As previously noted, direct experimental modulations of the glutamatergic system with NMDA antagonists such as ketamine have been intriguing. Sub anesthetic doses of ketamine in controls induce schizophrenia like symptoms, including thought disorder and working memory disruption (Adler et al. 1998). Recent work suggests specific deficits in versions of the Morris water maze task administered to humans (Rowland et al. 2005). In patients, ketamine exposure briefly exacerbates psychosis-related symptoms and leads to an increase in memory-related impairments (Malhotra et al. 1997). NMDA antagonists also negatively affect recruitment of pathways of associative memory retrieval including the hippocampus and prefrontal cortex (Honey et al. 2005). In mice, repeated post-training exposure to ketamine, leads to selective impairment in the consolidation of spatial associative memories that are hippocampal in their bases (Best et al. 2001), with little effect on passive avoidance paradigms. Finally, NMDA or glutamate *agonists* induce short term increases in synaptic transmission in the hippocampus (Kauer et al. 1988). Thus, impairment in N-methyl-D-aspartate (NMDA) function related to physical loss of NMDA synapses in the hippocampal and prefrontal regions may be central and proximate to the pathophysiology of schizophrenia (Moghaddam 2003, MacDonald and Chafee 2006).

The role of NMDA in associative memory as gleaned from animal studies provides unique synergy with the schizophrenia findings to demonstrate why glutamate function is implicated in the illness.

Glutamate, NMDA and Associative Learning in the Brain

Associative learning and memory rely on the consolidation and retrieval of associations between diverse memoranda, sensory inputs and streams of neural activity (Friston 2003), particularly by hippocampal and medial temporal lobe neurons (Wirth et al. 2003). This detection and consolidation of correlated spatio-temporal patterns of neuronal activity was proposed in classic neuroscience as a centerpiece of learning and memory (Hebb 1949). The idea is that coincidence detection (Konorski 1948) between two contemporaneously active synapses results in a consolidation of linkage between these cells thereby forming the building blocks for the localization of memories. This basic idea is central to almost all theories of neural encoding including long term potentiation (Bliss and Collingridge 1993), neuronal population selection (Edelman 1993), and coherence (Singer 1994).

N-methyl-D-aspartate (NMDA) receptors are synaptic coherence detectors, and modulation of detection sensitivity enhances or inhibit tasks of associative learning/memory that rely on synaptic coincidence. For instance, transgenic mice with an over expression of NMDA 2-B receptors in their forebrain show *increased* performance on tasks such as the water maze task (Tang et al. 1999). Such performance enhancement results from an increase in activation of NMDA receptors that results in increased synaptic potentiation. Converse effects have been documented. Selective ablation of NMDA receptor genes in CA3 pyramidal cells of the hippocampus in adult mice, results in marked impairment in the recall of associations learned during the water maze task under partially cued conditions (Nakazawa et al. 2002). This suggests dependence of associative recall on NMDA receptor sensitivity and the CA3 sub-region of the hippocampus. Clearly, enhanced activation of NMDA receptors leads to increased synaptic potentiation and consequently increased performance on tasks such as the water maze, that rely on associative memory for learning and may facilitate other systems such as working memory (Compte et al. 2000). Further synergy with these findings is provided by *in vivo* studies of memory systems in the human brain.

fMRI studies of associative memory

In vivo fMRI studies of paired-associate memory and learning have identified correlates of the BOLD (Blood Oxygen Level Difference) response with learning. Using an object-location paired-associated learning task, Buchel and colleagues (Buchel et al. 1999) demonstrated increased effective connectivity between heteromodal cortical regions, the hippocampus and the prefrontal cortex. These studies and others (Law et al. 2005, Ranganath et al. 2005) emphasize the crucial role played by the hippocampus in the formation and consolidation of new memories (Fries et al. 2003).

A majority of published fMRI and PET studies in schizophrenia have assessed hippocampal activity during tasks of episodic or declarative memory and recollection (Heckers et al. 1998, Jessen et al. 2003, Leube et al. 2003). These studies suggest that the conscious recollection of episodic memories (such as memories for events or words previously learned in word lists), leads to impaired recruitment of the hippocampus. This pattern suggests general memory-related dysfunction of this structure. More recent studies have suggested slightly more complex patterns of

functional impairment. In particularly, hippocampal activity is not impaired when patients encode semantically related item pairs but is impaired during the encoding of arbitrary item pairs (Achim et al. 2007). These studies are not strong demonstrations of impaired hippocampal function during memory dynamics. Nevertheless they suggest that the hippocampal response during memory tasks is impaired in schizophrenia, providing convergence with *in vivo* structural and neurochemical studies and animal studies on the role of NMDA and memory.

In summary, deficits of the glutamatergic system and the NMDA receptor system are central to the pathophysiology of schizophrenia (Konradi and Heckers 2003, Coyle 2004, Lewis and Moghaddam 2006), and impairments in the structure and function of both the medial temporal lobe (Harrison 2004) and the prefrontal cortex (Lewis et al. 1999) are widely associated with the illness and NMDA function in the hippocampus is critical to associative memory and learning. This convergence of findings highlights the importance of translational and integrative neuroscience in understanding the role of glutamate in schizophrenia pathology.

Glutamatergic neurotransmission disturbances and cortical disconnection in schizophrenia

The brain levels of glutamatergic metabolites can be detected by ^{1}H magnetic resonance spectroscopy (MRS). This non-invasive method allows *in vivo* measurements of the brain concentration of important neurochemicals, including glutamate, glutamine, N-acetylaspartate (NAA), and N-acetylaspartate-glutamate (NAAG) (Stanley et al. 1996, 2000; Brambilla et al. 2002, 2004). Glutamatergic neurotransmission is linked to GABAergic and monoaminergic brain neurotransmitter systems. Indeed, glutamate, which is the most abundant excitatory amino acid in the human brain, is a precursor of GABA and stimulates GABA metabolic activity (Brambilla et al. 2003). It is released from neuronal terminals, subsequently taken up by glial cells, and returns to nerve terminals as glutamine, playing a key role in synaptic plasticity, learning, and memory. Specifically, the enzyme glutaminase forms glutamate from glutamine in presynaptic nerve terminals, and glutamine synthetase forms glutamine from glutamate in the glia cells. NAA is the second most abundant brain amino acid after glutamate in the human brain and is the second most prominent peak in the proton spectrum after water. It accounts for approximately 85% of the proton signal of the N-acetyl group, whereas NAAG accounts for the remaining 15% (Pouwels et al. 1998). NAAG is an endogenous peptide binding as an agonist to NMDA receptors and to a group II metabotropic glutamate receptors (i.e. mGluR3) (Trombley et al. 1990, Sekiguchi et al. 2007). NAA is found in high concentrations in all neurons, with highest concentrations in pyramidal glutamatergic neurons, whereas it is absent in glia cells (Simmons et al. 1991, Urenjak et al. 1993). Therefore, it is thought to be a marker of neuronal integrity, density, viability, or activity. However, its specific neuronal function is still unclear. Nevertheless, there are several putative roles for NAA, including involvement in de novo synthesis of fatty acids, initiation of protein synthesis, NAAG metabolism, and aspartate storage (Tsai and Coyle 1995). Also, NAA may act via the NMDA receptor to elevate intracellular calcium, and its concentrations may vary as a correlate of neuronal glutamatergic activity (Rubin et al. 1995). NAA is synthesized in the mithocondria by L-aspartate N-acetyl transferase that uses glutamate as a precursor for aspartate and either pyruvate or 3-hydroxybutyrate as substrates. It is also formed by cleavage from N-acetyl aspartyl glutamate (NAAG), which yields to glutamate, by N-acylated a-linked L-amino dipeptidase (NAALADase), and is catabolized to acetate and aspartate by N-acetyl aspartate amino hydrolase (amino acylase II) (Baslow et al. 2000).

A hyperglutamatergic state in specific brain regions, such as prefrontal cortex, anterior cingulate, thalamus and cortical white matter, has been reported in patients with schizophrenia as well as in high risk subjects (Théberge et al. 2002, Tibbo et al. 2004, Chang et al. 2007, Olbrich et al. 2007, Purdon et al. 2008). Decreased gene expression for glutamic acid decarboxylase (GAD), the key enzyme transforming glutamate in GABA, has been shown in the prefrontal cortex and striatum of subjects suffering from schizophrenia (Akbarian et al. 1995, Bird et al. 1977, Straub et al. 2007). Deficits of other glutamatergic markers, such as specific receptor subtypes (GluR AMPA/Kainate, NMDA), transporters (EAAT3, VGluT1), and peptides (GAP-43) have been found in schizophrenia, particularly in prefrontal cortex, hippocampus, and caudate (Breese et al. 1995, Kerwin et al. 1990, Porter et al. 1997, Law et al. 2001, Weickert et al. 2001, Scarr et al. 2005, Nudmamud-Thanoi et al. 2007). Furthermore, abnormal activity of glutamate carboxypeptidase II (GCP II), an enzyme that forms NAA and glutamate from NAAG, has been detected in prefrontal cortex and hippocampus of patients with schizophrenia (Ghose et al. 2004). Taken together, these findings provide further evidence that glutamate neurotransmission is implicated in the pathophysiology of schizophrenia (Tsai 2005). One possible explanation for these abnormalities is that reduced glutamate uptake could account for a hyperglutamatergic state. That may be due to impaired functionality of glutamate transporters, such as the glial glutamate-aspartate transporter (GLAST), and glutamate transporter-1 (GLT-1), or the neuronal excitatory amino acids carrier-1 (EAAC1). Abnormally increased levels of extracellular glutamate are a known cause of excitotoxicity, which leads to neuronal death (Greene and Greenamyre 1996). Also, glutamate uptake in the glia, which is operated by glial glutamate transporters, stimulates glucose uptake into astrocytes (Pellerin and Magistretti 1994). In conclusion, it is possible that impaired glutamate/glutamine transport into nerve terminals, or impaired glutamate/glutamine cycle, possibly due to an enzymatic block (i.e. glutaminase synthetase, or glutaminase), may lead to abnormal accumulation of glutamate/glutamine. In order to further clarify the mechanisms potentially involved, future studies should couple the investigation of glutamatergic neurotransmission with examination of enzyme activity, and glutamate transporter function, to

attempt to determine the potential altered step in the glutamate/glutamine neuronal cycle in schizophrenia. However, there are no currently available methods that would allow study of these specific enzymatic activities in the *in vivo* human brain. Alternatively, since the glutamate/glutamine cycle accounts for 80% of glucose oxidation in the resting human brain (Pellerin and Magistretti 1994, Shen et al. 1999), a reduction of glutamate uptake could diminish the oxidative glucose metabolism. Moreover, reduced glycolisis diminishes the energy needed for the conversion of glutamate to glutamine and vice-versa, potentially leading to a block in the glutamate/glutamine cycle, and to accumulation of glutamate.

Future ^{1}H MRS studies with larger patient samples and longitudinal designs will be needed to further investigate the possible role of abnormalities in glutamatergic neurotransmission in schizophrenia. However, there is evidence suggesting that glutamatergic pathways are impaired in schizophrenia, particularly the cortico-thalamic-striatal connection. In this regard, white matter disruption may represent the microstructure basis of such impairment, being possibly associated with altered synaptic plasticity (Stephan et al. 2006). For instance, it has been suggested that NMDA receptor subtypes may be implicated in white matter impairments (Paoletti and Neyton 2007). One example of such disconnection may involve reduced integrity of cortico-cortical white matter (Brambilla and Tansella 2007). To this extent, impairments of cortical white matter integrity have been found in patients with schizophrenia by several prior diffusion imaging reports (Kubicki et al. 2005a for a review; Andreone et al. 2007a,b), particularly in frontal and temporal lobes. Abnormalities in cortical white matter may lead to misconnection, which may ultimately be relevant for glutamatergic disturbances reported in schizophrenia. This may be due to reduced axonal density or myelination. Indeed, oligodendrocytes, which have the potential to influence myelination and synaptic transmission, have been found to be functionally abnormal in schizophrenia (Hof et al. 2002, Davis et al. 2003, Bartzokis and Altshuler 2005). Also, reduced expression of myelin and oligodendrocyte-related genes and proteins have been shown in schizophrenia, suggesting oligodendrocyte dysfunction (Flynn et al. 2003, Hof et al. 2003, Tkachev et al. 2003, Chambers and Perrone-Bizzozero 2004). Therefore, given the central role of glutamate in excitatory neurotransmission, and in turn cortical connectivity (Konradi and Heckers 2003), it will be important to further understand white matter impairments in schizophrenia within the framework of glutamatergic dysfunction.

Myelin and schizophrenia

Several observations have recently suggested a potential role of myelin proteins, white matter and oligodendrocytes in the pathogenesis of schizophrenia. For instance, in cerebral post-mortem tissues of schizophrenia patients, oligodendrocyte- and myelin-related genes, like for instance 2',3'-cyclic nucleotide 3'-phosphodiesterase (*CNP*), SRY (sex determining region Y)-box 10 (*SOX10*), myelin-associated glycoprotein (*MAG*), peripheral myelin protein 22 (*PMP22*) are down-regulated (Dracheva et al. 2006, McCullumsmith et al. 2007, Karoutzou et al. 2008). MAG knockout mice show changes in dendritic branching patterns of pyramidal cells in layer III of the prefrontal cortex, which might be especially relevant for schizophrenia dysfunction (Haroutunian 2007) significant down regulation is also observed for glial gene quaking (*QKI*) (McInnes and Lauriat 2006, McCullumsmith et al. 2007). This gene encodes for a RNA binding protein responsible of splicing and stabilization of mRNA transcript that plays a role in myelination. Accordingly mutant mice in which the 5' promoter region of this gene is disrupted show abnormal compaction of myelin and dysregulation of cytoplasmic loop formation (Hardy 1998) and behavioral abnormalities. Interestingly, these alterations show some similarities to myelin structure observed within prefrontal cortex and caudate nucleus of schizophrenic subjects (Uranova et al. 2001, 2004). Moreover, *QKI* encodes also for proteins able to control oligodendrocyte differentiation, such as QKI-5, 6 and 7 (McInnes & Lauriat 2006). Other genes controlling the differentiation and function of oligodendrocytes have been associated with schizophrenia. For instance, a role for oligodendrocyte lineage transcription factor 2 (*OLIG2*), which encodes for a transcription factor central to oligodendrocyte development and which is reduced in post-mortem schizophrenic brain, has been recently proposed (Georgieva et al. 2006). In addition, evidences have been accumulated implicating neuroregulin 1 (NRG1) and its receptor erbB4. For instance, transgenic mice in which erbB signaling is blocked in oligodendrocytes show reduction in myelin sheath thickness, slow conduction velocity in CNS axons and changes in oligodendrocyte number and morphology (Roy et al. 2007). Interestingly, these animals also show behavioral alterations, such as reduced locomotor activity and exploration in novel open space, elevated plus maze and abnormal social behaviour, which are also associated with schizophrenia (Roy et al. 2007). Indeed, a systematic direct gene analysis has indicated an interaction between variants in *NRG1, erbB4* and that this interaction is associated with increased risk of schizophrenia (Norton et al. 2006). These findings, together with other observations obtained by an electron microscopic study in the prefrontal cortex of schizophrenia patients, which showed a significant decrease in the density of oligodendrocytes (Uranova et al. 2004), suggest that alterations in myelin synthesis as well as in differentiation and oligodendrocyte function may contribute to the altered connectivity observed in schizophrenia. Abnormalities of NGR1 and erbB4 might also represent an important link between glutamate and oligodendrocyte dysfunction in schizophrenia.

Deficit of myelin in schizophrenia probably arises from a failure occurring during late adolescence and early adulthood and this might also affect the age of onset of the disorder (Dwork 2007). Myelin and oligondendrocyte abnormalities, together with abnormal function at neurotransmitter level might contribute to functional disconnectivity that represents a central aspect of schizophrenia.

Conclusions

There is strong evidence from animal and human studies that glutmatergic pathways are impaired in schizophrenia. In particular, disrupted NMDA receptor sensitivity and learning may be critical to understanding the functional expression of the altered glutamatergic transmission in schizophrenia. However, whereas experimental approaches abound, there is a critical need to integrate animal studies of glutamate neurotransmission, human *in vivo* studies of structure and function relevant to the glutamate system, and computational models of pharmacologic and behavioral processes. Such integrative (as opposed to only translational) approaches are needed to develop a clearer understanding of molecular, neural and behavioral disruptions in schizophrenia.

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