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Glutamate in schizophrenia: Neurodevelopmental perspectives and drug development

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ABSTRACT

Research into the neurobiological processes that may lead to the onset of schizophrenia places growing emphasis on the glutamatergic system and brain development. Preclinical studies have shown that neurodevelopmental, genetic, and environmental factors contribute to glutamatergic dysfunction and schizophrenia-related phenotypes. Clinical research has suggested that altered brain glutamate levels may be present before the onset of psychosis and relate to outcome in those at clinical high risk. After psychosis onset, glutamate dysfunction may also relate to the degree of antipsychotic response and clinical outcome. These findings support ongoing efforts to develop pharmacological interventions that target the glutamate system and could suggest that glutamatergic compounds may be more effective in specific patient subgroups or illness stages. In this review, we consider the updated glutamate hypothesis of schizophrenia, from a neurodevelopmental perspective, by reviewing recent preclinical and clinical evidence, and discuss the potential implications for novel therapeutics.
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1. Introduction

The glutamate hypothesis of schizophrenia, as proposed in the 1990s (Javitt and Zukin, 1991), was based on observations that antagonists of the *N*-methyl-D-aspartate glutamate receptors (NMDAR), such as phencyclidine (PCP) and ketamine, mimic positive, negative, and cognitive symptoms in healthy volunteers and exacerbate these symptoms in patients with schizophrenia (Krystal et al., 2003). In this focused review, we consider updated evidence for the glutamate hypothesis from a neurodevelopmental perspective and discuss what this means for glutamatergic drug development.

Since the 1970s, abnormalities in dopaminergic neurotransmission formed the basis of the neurochemical hypothesis of psychosis (Creese et al., 1976; Seeman and Lee, 1975; Seeman et al., 1976). Previous *in vivo* neuroimaging studies have reported an increase in the presynaptic dopamine synthesis capacity in the striatum in patients with schizophrenia (Howes et al., 2012). However, while dopaminergic abnormalities may be a core feature of psychosis, there are numerous features of psychotic disorders that remain unexplained by dopamine dysfunction alone (Moghaddam and Krystal, 2012; Stone et al., 2007). In many patients, conventional dopamine-blocking antipsychotic medication is only partially effective, and in about a third the overall response is poor (Mailman and Murthy, 2010), even when there is adequate dopamine receptor 2 (D_2) occupancy (Nordstrom et al., 1993). Furthermore, D_2 antagonist antipsychotic drugs have relatively little effect on negative (e.g. poverty of thought, emotional and social withdrawal) and cognitive symptoms (Mailman and Murthy, 2010), which are key drivers of impairments in quality of life and functional outcome. Thus, although striatal dopamine elevation may account for the positive symptoms of psychosis, this may not be the case in all patients. While striatal dopamine elevation is unlikely to explain negative symptoms and cognitive impairment in schizophrenia, abnormalities in cortical dopamine and D_1 receptor activation may contribute to cognitive deficits (Goldman-Rakic et al., 2004). However the suggestion that cognitive deficits and negative symptoms may be better explained by concurrent abnormalities in the glutamatergic system (Javitt, 2010; Moghaddam and Krystal, 2012) has become widely accepted.

1.1. The NMDA receptor hypofunction hypothesis

The initial proposal of a glutamate hypothesis of schizophrenia arose from the subsequently unreplicated finding of lower levels of glutamate in the cerebrospinal fluid (Kim et al., 1980; Korpi et al., 1987; Perry, 1982). Twenty years earlier, observations that PCP produced effects that resembled schizophrenia in healthy volunteers and intensified or reinstated stabilized symptoms when given to participants with schizophrenia (Luby et al., 1959; Rosenbaum et al., 1959), led to the

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withdrawal of PCP from use as an anesthetic. The discovery in 1982 that PCP noncompetitively blocks glutamatergic NMDAR ion channels (Anis et al., 1983), allowed the psychotomimetic effects of PCP to be linked to the glutamatergic system (Berry and Lodge, 1984). This key observation then led to the proposal that schizophrenia may be consequential to NMDAR hypofunction (Olney, 1989).

The NMDAR hypofunction hypothesis has since received extensive scientific exploration, and has made a major contribution to our current biological understanding of schizophrenia (Snyder and Gao, 2013). A principal pathophysiological model, the 'disinhibition model', suggests that hypofunction of NMDARs on fast-spiking γ-aminobutyric acid (GABA)-ergic interneurons in the cortex decreases GABAergic inhibition of glutamatergic pyramidal neurons, leading to excessive glutamate release (Homayoun and Moghaddam, 2007; Lisman et al., 2008; Nakazawa et al., 2012; Olney et al., 1999; Pafundo et al., 2018; Snyder and Gao, 2013). Consistent with the disinhibition hypothesis, acute administration of the NMDA antagonists such as ketamine increases cortical glutamate levels. This is observed in rodents using microdialysis (Liu and Moghaddam, 1995; Lorrain et al., 2003; Moghaddam et al., 1997; Moghaddam and Adams, 1998) and may also be seen in humans using glutamate neuroimaging (Bojesen et al., 2018; Javitt et al., 2018; Rowland et al., 2005; Stone et al., 2012). An important distinction, therefore, is that while NMDARs may be hypofunctional in schizophrenia, glutamate release and signaling through non-NMDAR subtypes appears excessive. Thus, opportunities for the development of drugs targeting the glutamatergic system include both compounds that increase NMDAR activation as well as compounds that decrease glutamate release.

1.2. Pharmacological models of NMDA receptor hypofunction

Pharmacological antagonism of NMDAR activity is now commonly used as a preclinical schizophrenia model to investigate potential glutamatergic disease mechanisms and in screening therapeutic compounds (Lodge and Mercier, 2015; Pratt et al., 2012). In rodents, NMDAR antagonists, such as PCP or ketamine, produce behavioral effects that are thought to mimic the positive symptoms of schizophrenia, but also produce social and cognitive deficits, particularly upon repeated administration (Egerton et al., 2008; Jentsch and Roth, 1999; Jones et al., 2011; Neill et al., 2010). Compared with dopaminergic models (e.g. amphetamine administration), animal models involving repeated NMDA administration may arguably better represent elicit social and cognitive deficits. These behavioral changes are accompanied by neurobiological effects relevant to the pathophysiology of schizophrenia, including elevated striatal dopamine release (Abi-Dargham et al., 1998; Jentsch et al., 1998; Laruelle et al., 1996), hypofrontality (Andreasen et al., 1992; Buchsbaum et al., 1990; Cochran et al., 2003; Tamminga et al., 1992; Wolkin et al., 1992), PFC glutamate release (Fattorini et al., 2008), and brain structural damage (Farber et al., 1995; Olney and Farber, 1995; Sharp et al., 2001; Tomitaka et al., 2000). Relevant to the development of therapeutic compounds, some of the effects of NMDA antagonists are reversed by 'typical' D_2 receptor antagonist antipsychotics. However, attenuation of the effects of NMDA antagonists, particularly in assays of social and cognitive deficits, is observed to a greater extent with atypical antipsychotics such as clozapine, olanzapine, and quetiapine (Pratt et al., 2012). This could relate to the contributing effects of $5HT_{2A}$ inverse agonism and actions of these compounds at other 5HT receptors (Meltzer et al., 2011). Efforts to develop glutamate-acting drugs for schizophrenia that facilitate NMDAR activity (e.g. NMDAR glycine site agonists) or reduce presynaptic glutamate release (e.g. mGluR2 agonists) have been supported by positive read-outs in NMDAR antagonist animal models, although ultimately clinical development has not yet been successful. This is discussed further by Dunlop and Brandon, 2015 and Pratt et al., 2012 (Dunlop and Brandon, 2015; Pratt et al., 2012).

Translation of NMDAR antagonist research is greatly facilitated through the availability of acute ketamine challenge as an across-species model (Moghaddam and Krystal, 2012). At subanesthetic doses, acute ketamine administration produces reproducible changes in brain electrophysiology, functional connectivity, task-related activation and frontal glutamate concentration in healthy human volunteers (Frohlich and Van Horn, 2014; Haaf et al., 2018). The ability of antipsychotics and experimental compounds to attenuate these effects of ketamine on neuroimaging biomarkers can be used as an experimental medicine model (Doyle et al., 2013; Gunduz-Bruce et al., 2012; Javitt et al., 2018; Joules et al., 2015; Mehta et al., 2018). However, it is difficult to qualitatively relate ketamine-induced brain functional changes to schizophrenia pathophysiology, in part because in schizophrenia the profiles of altered brain activity and neurochemistry may vary with illness stage, in patient subgroups, with medication or other factors. Interestingly, there is an emerging suggestion that the effects of ketamine, and thereby NMDAR hypofunction, may be more closely akin to those observed in the early stages of schizophrenia/psychosis, rather than the chronic stages of illness (Anticevic et al., 2015; Fleming et al., 2019).

NMDAR antagonist administration to adult animals (or humans) is extremely useful in understanding some aspects of schizophrenia pathophysiology. Nonetheless, a pharmacological challenge will provide only a limited representation of the complex brain alterations that give rise to schizophrenia, as this cannot fully capture the complexity of biological processes that occur during brain development, or the interaction of these processes with environmental factors. While glutamate mechanisms are the focus of this review, it should be emphasized that other neurotransmitters including GABA, dopamine, and serotonin play an important and interacting role, as may inflammatory and other processes. Elevations in striatal dopamine release in schizophrenia may be driven by glutamatergic abnormalities in the frontal cortex and hippocampus (Breier et al., 1998; Howes et al., 2015; Lodge and Grace, 2011; Miller and Abercrombie, 1996), as described in more detail below. Serotonin interacts with both glutamate and dopamine systems to regulate neurotransmission (for review, see de Bartolomeis et al., 2013; de Bartolomeis et al., 2013). For example, modulation of intracellular signaling through the formation of mGluR2/5-HT2A heterodimers (González-Maeso et al., 2008) and D2 / 5-HT2A heterodimers (Łukasiewicz et al., 2010), may have relevance for current and future therapeutic strategies (de Bartolomeis et al., 2013). Healthy cortical function relies on the balance in coordinated activity of excitatory glutamatergic pyramidal neurons and inhibitory GABAergic interneurons. These are tight and complex interrelationships and it is unknown which abnormalities in glutamatergic or GABAergic processes may be primary, secondary, or compensatory (Krajcovic et al., 2019; Nakazawa et al., 2017). Indeed, recent analyses of genetic evidence indicates that schizophrenia may arise from perturbed integration of multiple neurotransmitter receptor signaling pathways at the synapse, extending glutamatergic and GABAergic processes to their broader network interactions (Devor et al., 2017; Fromer et al., 2014; Pocklington et al., 2015; Purcell et al., 2014). These genetic advances expand the NMDAR hypofunction hypothesis of schizophrenia (Olney and Farber, 1995) to implicate a wide range of processes involved in synaptic signaling and in doing so may provide alternative targets for intervention.

1.3. Neurodevelopmental perspectives

Schizophrenia is increasingly recognized as a neurodevelopmental disorder (Insel, 2010; Marenco and Weinberger, 2000; McNeil and Kaij, 1978; Murray et al., 2017; Weinberger, 1987) with 65%–80% heritability (Cardno and Gottesman, 2000; Lichtenstein et al., 2009; Sullivan et al., 2003; Tandon et al., 2008) and associated with genetic polymorphisms and risk loci (Mowry and Gratten, 2013; Psychiatric GWAS Consortium Steering Committee, 2009; Ripke et al., 2013; Stefansson et al., 2009; The International Schizophrenia Consortium,

2009) including those involved in aspects of glutamatergic synaptic signaling (Devor et al., 2017; Harrison and West, 2006; Kirov et al., 2012; Pocklington et al., 2015; Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014; Sundararajan et al., 2018). An important question, particularly for intervention strategies, is the extent to which glutamate dysfunction is present, and can be pharmacologically addressed, at the time of onset of clinically detectable psychotic or prepsychotic symptoms in early adulthood, or whether the key window for intervention occurs earlier in brain development.

Throughout pre- and postnatal development, extensive and complex process of structural and neurochemical alterations in inhibitory and excitatory cortical neurons contribute to the maturation of prefrontal cortical circuitry (Beneyto and Lewis, 2011; Hoftman et al., 2017; Snyder and Gao, 2013). Disruptions in NMDA function during different temporal windows in brain development may contribute to schizophrenia risk (Nakazawa et al., 2017). Preclinical studies of NMDAR hypofunction have demonstrated the link between dysregulation occurring during the early stages of postnatal development and schizophrenia-like behaviors in adulthood. This is most clearly seen though studies showing schizophrenia-relevant phenotypes in mice with genetic alterations that reduce NMDAR function (Belforte et al., 2010; Born et al., 2015; Carlen et al., 2012; Labrie et al., 2008; Mohn et al., 1999; Rompala et al., 2013; Yasuda et al., 2017). For example, postnatal reduction in NMDA NR1 subunit expression is associated with hyperlocomotion, social, and cognitive deficits as mice reach adolescence (Belforte et al., 2010). Expression of genes associated with the GABAergic system is also important, for example in early development mutations in neuregulin 1 and its receptor ErbB4 may lead to suboptimal GABAergic interneuron differentiation and inhibitory synapse formation (Fazzari et al., 2010). Such early genetic influences on synaptic signaling will evoke compensatory mechanisms, in an attempt to normalize neurotransmission and brain function during development, and NMDAR are dynamically regulated throughout the lifespan by key processes such as phosphorylation, trafficking, stabilization, or removal from the synaptic membrane (Mao et al., 2009; Nong et al., 2004; Snyder and Gao, 2013). However, if compensatory mechanisms are inadequate, the consequences of NMDA hypofunction in early postnatal development could increase the risk of glutamatergic–GABAergic imbalance emerging in adolescence (Nakazawa et al., 2017).

While it is only partially understood how NMDAR hypofunction may arise during development and interact with environmental factors to increase risk of schizophrenia in adulthood, aberrant epigenetic regulation of NMDAR subunit expression may play an important role (Snyder and Gao, 2013). The expression and localization of NMDAR subunits is age-dependent, and impacts NMDAR kinetics, pharmacological sensitivity, synaptic plasticity, and learning (Paoletti et al., 2013). The developmental switch in NMDAR subunit composition (NR2B to NR2A, and NR3A to NR3B) marks the transition to adult neural processing (Dumas, 2005; Snyder and Gao, 2019; Snyder and Gao, 2013) and is regulated by epigenetic mechanisms (Rodenas-Ruano et al., 2012; Stadler et al., 2005). This switch may explain the temporal dependency of the effects of NMDAR antagonist administration during development on both the pattern and extent of the resulting neuronal damage (Farber et al., 1995; Ikonomidou et al., 1999; Olney and Farber, 1995). As NR2B subunits are replaced by NR2A subunits, NMDAR on fast-spiking GABAergic neurons in the PFC undergo considerable changes (Wang and Gao, 2009; Xi et al., 2009). Relative to NR2B subunits, the presence of NR2A decreases the affinity for glycine site co-agonists, decreases calcium conductance and reduces vulnerability to excitotoxicity (Jantzie et al., 2015). Thus, this subunit switch may render NMDAR and fast-spiking GABAergic interneurons especially vulnerable to genetic or environmental risks (Snyder and Gao, 2019; Snyder and Gao, 2013). For example, maternal deprivation during early postnatal development disrupts epigenetic activation and the switch to the mature NMDA subunit phenotype (Rodenas-Ruano et al., 2012). Thus, adverse experiences and stress during childhood may impact on gene expression and NMDAR function during critical stages of development, which could lead to progressive synaptic and neural circuit dysfunction and cumulate in the expression of schizophrenia symptoms in early adulthood.

1.4. Neurodevelopmental models of schizophrenia

The gestational methylazoxymethanol acetate (MAM) model is a developmental disruption model of schizophrenia that involves the administration of MAM to pregnant female rats, on gestational Day 17, which results in neurochemical, behavioral, and anatomical deficits in adult rats that are consistent with those observed in patients with schizophrenia (Lodge and Grace, 2011). These include: a reduction in cortical and subcortical volume; increased neuronal cell density in prefrontal/cingulate and insular/perirhinal areas; decreases in the thickness of the PFC, ventral perirhinal cortex, and hippocampus; impairment of pre-pulse inhibition of startle, executive function, and reversal learning; and increased response to amphetamine and PCP-increased locomotion in adult, but not prepubertal rats (Moore et al., 2006).

In the MAM model, NMDAR dysfunction appears to arise during the period of heightened epigenetic vulnerability (Gulchina et al., 2017; Zhu et al., 2017). Epigenetically mediated alterations in NMDAR subunit composition are observed in the prelimbic cortex of juvenile MAM-exposed animals (Gulchina et al., 2017). These alterations occur before the emergence of dopaminergic hypersensitivity (Flagstad et al., 2004) and cognitive deficits (Moore et al., 2006) in young adulthood. Thus, developmental animal models, such as the gestational MAM model, can be used to test the extent to which deficits resulting from postnatal glutamatergic manipulations may be rescued by antipsychotic drugs or experimental compounds or environmental interventions at different periods during brain development and in adult animals. Furthermore, it may also be possible to determine from these models whether, theoretically, glutamate activity might be rescued pharmacologically in people showing early signs of psychosis in young adulthood (Boerner et al., 2017; Grannan et al., 2016).

In the MAM model, increased excitatory input from the hippocampus to the nucleus accumbens reduces inhibition of the ventral pallidum and leads to increased population activity of dopaminergic neurons projecting to the striatum (Fig. 1) (Lodge and Grace, 2011). In this psychosis model, striatal dopaminergic hyperfunction is driven by the hippocampus and glutamate is critical in this process (Bossong et al., 2018; Schobel et al., 2013; Stone et al., 2010). MAM rats show a reduction in parvalbumin (PV) interneuron density throughout the medial PFC (mPFC) and the ventral hippocampus that impacts gamma oscillations during task performance (Lodge et al., 2009). In people at clinical high risk (CHR) for psychosis, resting blood flow and activity in the hippocampus are also increased (Allen et al., 2015; Modinos et al., 2015), and may be related to mPFC GABA levels (Modinos et al., 2018). Schobel et al., observed that hypermetabolism in the CA1 sub region of the hippocampus spread to the subiculum after psychosis onset in patients at CHR and predicted hippocampal atrophy (Schobel et al., 2013). As acute ketamine produced similar pattern of hypermetabolism in mice, these findings may be linked to NMDAR hypofunction (Schobel et al., 2013). Postmortem studies in schizophrenia describe a selective loss of GABAergic PV interneurons in the hippocampus and frontal cortex (Zhang and Reynolds, 2002), and a corresponding deficit in GABAergic signaling may also contribute to hyperactivity within the hippocampus (Lodge et al., 2009; Modinos et al., 2018).

The use of multiple genetic or neurodevelopmental models may provide the greatest opportunity for identifying changes precipitating the development of schizophrenia (Snyder and Gao, 2013). These models are valuable for detecting the neurons that express altered glutamate receptor subtypes (Snyder and Gao, 2013). They are also important to help determine if there is a point during development where brain circuitry is sufficiently altered to the point that no interventions will halt disease progression (Snyder and Gao, 2019; Snyder and Gao, 2013).

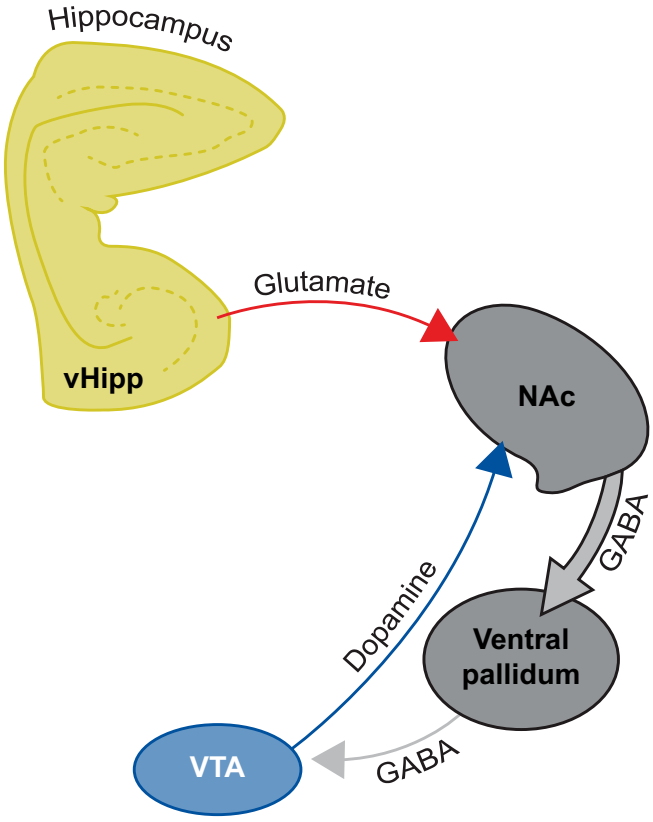

Fig. 1. A schematic to show the regulation of dopamine neuron activity by the ventral hippocampus. GABA, γ-aminobutyric acid; NAc, nucleus accumbens; vHipp, ventral hippocampus; VTA, ventral tegmental area.

For example, in a rat developmental model, administration of a glutamate modulating compound (a metabotropic glutamate-5 receptor [mGluR5] positive allosteric modulator [PAM]) reversed adult-onset deficits when administered during adolescence and prevented the emergence of cognitive impairment (Clifton et al., 2013). A more recent study also showed that juvenile administration of an mGluR2/3 agonist prevented the learning and memory deficits and restored the dendritic spine loss that are observed in MAM-treated rats in adulthood (Xing et al., 2018).

1.5. The role of stress

Interactions between genetic and environmental risk factors such as stress may be particularly important during neurodevelopment. Stressful stimuli may exacerbate positive and negative symptoms in schizophrenia (Lysaker and Salyers, 2007), and converging evidence from clinical and preclinical studies suggest that an inability to regulate stress early in life can lead to pathological changes, particularly in the hippocampus (Zimmerman et al., 2013). In the MAM model, rats show increased prepubertal anxiety and response to stress on the elevated plus maze, a measure of anxiety (Du and Grace, 2013; Du and Grace, 2016). MAM rats also show longer and more intense vocalizations and more freezing behavior (Zimmerman et al., 2013), as well as significantly faster amygdala firing (Du and Grace, 2016). Similarly, in rats stress exposure in the prepubertal, peripubertal, and adolescent stages causes the hippocampus to become hyperactive post stress through to adulthood, and causes a loss of PV interneurons in the hippocampus (Zimmerman et al., 2013). This suggests that major stress alone during this critical prepubertal period could lead to PV interneuron loss and induce a psychosis-like state (Gomes and Grace, 2017). Pretreatment with diazepam has been shown to prevent the emergence of these changes, which suggests that MAM is facilitating the impact of stress rather than causing the disorder (Du and Grace, 2016). This may also indicate that a main impact of genetic risk is to increase vulnerability to the impact of stressful life events (Du and Grace, 2016). The susceptibility to stress is critically dependent on its timing in adolescence (Gomes and Grace, 2017).

Glutamatergic interactions between the mPFC, hippocampus, amygdala, and ventral striatum mediate effects of stress. In control rats, mPFC lesions are sufficient to induce anxiety at the prepubertal stage (Gomes and Grace, 2017). Increased stress responsivity may therefore be mediated by a failure of the mPFC to limit the impact of stress exposure, leading to abnormally high amygdala-hippocampal drive (Gomes and Grace, 2017), and could potentially be modulated by glutamate-acting therapeutics. Therapeutic approaches based on normalizing hippocampal activity, rather than blocking the downstream effects of dopamine elevation with a D_2 antagonist antipsychotic, may show greater efficacy and potentially less side effects (Gill et al., 2014). Of potential importance to translational drug development, dopamine supersensitivity, resulting from previous D_2 antipsychotic exposure, may interfere with the ability of novel therapeutic compounds to reduce striatal dopamine hyperactivity (Gill et al., 2014; Sonnenschein and Grace, 2020). This could suggest that such therapeutics would have more observable efficacy in individuals prior to the onset of psychosis or early in illness, before D_2 antipsychotic treatment (Sonnenschein and Grace, 2020).

2. Levels of glutamate in the human brain

It is possible to measure glutamate concentrations in the human brain *in vivo* using proton magnetic resonance spectroscopy (^{1}H-MRS). The most common approach is to estimate the total concentration of glutamate in a prespecified voxel of interest over around 10 minutes while the participant lies at rest in a magnetic resonance imaging (MRI) scanner. There are now more than 60 published ^{1}H-MRS studies of glutamate metabolites in individuals with established psychosis or schizophrenia, or at risk for developing the disorder. Overall, meta-analysis ^{1}H-MRS studies found evidence of glutamatergic elevations in schizophrenia (Merritt et al., 2016), as would be predicted by the NMDA receptor hypofunction/disinhibition model. The majority of ^{1}H-MRS studies examining NMDAR hypofunction produced by ketamine infusion have also found increases in cortical glutamate (Bojesen et al., 2018; Javitt et al., 2018; Rowland et al., 2005; Stone et al., 2012). Nonetheless, the results of individual ^{1}H-MRS studies in schizophrenia have been mixed. This could reflect clinical differences between the samples as well as methodological factors. Questions for translational research include the extent to which ^{1}H-MRS glutamate measures may predict the onset (Bossong et al., 2016; Bossong et al., 2019) and clinical course of psychosis (Egerton et al., 2018), and whether they may provide biomarkers for glutamate-targeted drug development in schizophrenia (Javitt et al., 2018).

In individuals at risk for developing psychosis, ^{1}H-MRS studies have investigated whether glutamatergic differences are present prior to the onset of clinical symptoms. While an initial meta-analysis found that medial frontal Glx (glutamate plus glutamine) was elevated in individuals at high risk for psychosis (Merritt et al., 2016), a more recent meta-analysis found no overall difference compared with controls (Wenneberg et al., 2019). However, as the majority of high-risk individuals will not develop schizophrenia, it may be difficult to detect differences in this group as a whole. Potential differences in brain glutamate will be most marked in those at-risk individuals who go on to transition to psychosis. Two longitudinal studies have reported that at-risk individuals who later transition to psychosis appear to have elevated glutamate levels in the striatum (de la Fuente-Sandoval et al., 2013) and in the hippocampus (Bossong et al., 2019) compared with healthy volunteers and at-risk participants who do not transition during the study observation period. While replication is required, these studies are challenging as low transition rates mean that large baseline samples are required, and the clinical follow-up period can be several years.

^{1}H-MRS studies in samples at risk for psychosis have also compared subgroups according to functional outcome, or whether or not they still met 'at-risk' criteria for attenuated psychotic-like symptoms at follow-up. In the study of Bossong et al., hippocampal glutamate levels were also elevated in at-risk individuals with a 'poor' compared with a 'good' functional outcome as defined using the global assessment of functioning scale (Bossong et al., 2019). When examining the relationship between glutamate levels in the thalamus and outcome, we observed that lower levels of thalamic glutamate were associated with the continued presence of attenuated symptoms at follow-up (Egerton et al., 2014). While further research is required, these initial studies may suggest that regionally specific glutamatergic changes might occur during the prodromal period.

The level of ^{1}H-MRS-determined brain glutamate may also be related to clinical outcome under antipsychotic treatment in patients with established psychosis or schizophrenia. Cross-sectional studies have found glutamate or Glx elevation in the anterior cingulate cortex (ACC) in patients with non-remission of symptoms, antipsychotic treatment resistance, or clozapine resistance compared with those who have responded well to medication (Demjaha et al., 2014; Egerton et al., 2012; Iwata et al., 2019; Mouchlianitis et al., 2016; Tarumi et al., 2020); although this has not been observed in all studies (Goldstein et al., 2015). A recent longitudinal study in first-episode psychosis showed that higher ACC glutamate levels at illness onset are associated with a higher likelihood of non-remission of symptoms following subsequent antipsychotic treatment (Egerton et al., 2018). A longer-term follow-up of a subgroup of the same cohort found that non-remission was associated with increases in Glx in the thalamus over 9 months (Merritt et al., 2019). Together, these findings may suggest that there may be a subgroup of patients with schizophrenia with higher brain glutamate levels who are less likely to respond to antipsychotic treatment, and by extension that glutamate-reducing therapeutics may have particular benefit in this group.

One question from these studies is whether measurement of brain glutamate levels may accurately predict clinical outcome, in both individuals at CHR and in established psychosis. Accurate prediction of outcome could enable glutamate-based interventions to be targeted to patient subgroups who are most likely to benefit. In our study predicting remission in first-episode psychosis, ACC glutamate levels correctly classified 69% cases overall, and the predictive accuracy increased to 75% when age and baseline symptom severity score were included in the model (Egerton et al., 2018). While these results were significant, they are not accurate enough to inform clinical decision-making. Therefore, there is a requirement to improve predictive accuracy, which might be achieved by combining ^{1}H-MRS glutamate levels with other predictive factors in a multivariate model.

A further consideration is whether technological advances may improve the accuracy and reliability of glutamate measurement. The majority of the studies described above applied ^{1}H-MRS on 3 Tesla MRI systems. This technology is widely available and suitable for most participants, but does not fully separate resonances from glutamate and glutamine. It also provides an overall measure of glutamate in the voxel rather than glutamate involved in neurotransmission specifically. Some factors associated with accuracy of glutamate metabolite concentration estimation may be improved by scanning at ultra-high field strengths (Godlewska et al., 2017). An alternative approach is provided by emerging developments in functional ^{1}H-MRS (^{1}H-fMRS), which measures dynamic changes in glutamate occurring in response to a stimulus or psychological challenge and may more closely relate to glutamate release during neurotransmission (Jelen et al., 2018; Mullins, 2018; Rowland et al., 2005).

One of the authors recently conducted a preliminary study to determine whether ^{1}H-fMRS at 3 Tesla is sensitive enough to detect dynamic changes in ACC glutamate, and to assess any differences in these changes between healthy volunteers and patients with schizophrenia using an *n*-back task, a continuous-recognition measure (Kane et al., 2007). A total of 14 patients with schizophrenia, 15 patients with bipolar II disorder, and 14 healthy volunteers underwent a 15-minute *n*-back (0-back, 1-back, 2-back, and 3-back) task in a 48-second block design during fMRS acquisition. The significant increase in Glx/Cr and Glu/Cr that was observed in healthy controls with increasing task difficulty (between the averaged last spectra of the 0-back and the first of the 2-back task conditions) was absent in patients with schizophrenia or bipolar disorder. In contrast, during the relatively easy task condition (0-back) Glx levels were increased in the schizophrenia compared with healthy control group (Jelen et al., 2019). These findings are similar to those of the previous study that applied ^{1}H-fMRS to measure task-related changes in dynamic glutamatergic concentrations in schizophrenia, which acquired data in the ACC during the performance of a color-word Stroop task at a field strength of 7 Tesla (Taylor et al., 2015). This study additionally included a sample with major depressive disorder (MDD) and healthy volunteers. While in healthy volunteers glutamate was increased during the initial period of the Stroop task, this response was lacking in the schizophrenia and MDD groups (Taylor et al., 2015). Together with the results of Jelen et al. (2019) these studies suggest that schizophrenia may be associated with blunted activation of dynamic glutamate responses in the ACC to task requirements.

3. The glutamatergic hypothesis and drug development

3.1. Typical and atypical antipsychotics

Rodent studies have shown that some, but not all, antipsychotics can attenuate increases in glutamate efflux that arise on NMDA antagonist administration (Abekawa et al., 2007; Carli et al., 2011; López-Gil et al., 2009; López-Gil et al., 2007; Roenker et al., 2011), which could relate to antagonism at $5HT_{2A}$ receptors (Ceglia et al., 2004; López-Gil et al., 2009). We recently performed a systematic review of longitudinal ^{1}H-MRS studies that have examined the effects of antipsychotic treatment on glutamate or Glx levels in patients with schizophrenia (Egerton et al., 2017). This review found that the majority of studies reported a numerical reduction in glutamate metabolites during antipsychotic treatment, and there was some evidence that reductions in glutamate metabolites may correlate with symptomatic improvement. As glutamate levels, particularly in the ACC, may remain elevated in patients who do not respond adequately to antipsychotic treatment, together this could suggest that standard antipsychotics are ineffective in modulating glutamate level in this subgroup. Interestingly, there is some suggestion that the additional efficacy of clozapine, an antipsychotic reserved for otherwise antipsychotic-resistant schizophrenia, may arise from its ability to reduce cortical glutamate levels or facilitate NMDAR activation (Abekawa et al., 2006; Amitai et al., 2012; Fukuyama et al., 2019; Javitt et al., 2005; López-Gil et al., 2007; Melone et al., 2001; Williams et al., 2004). Nonetheless, currently available antipsychotics, including clozapine, are not effective in reducing positive symptoms in all patients and also do not adequately address negative symptoms and cognitive impairment. It is hoped that glutamate-acting drugs may have potential as future therapeutic compounds.

3.2. Glycine transporter 1 inhibitors

Initial clinical trials targeting glutamatergic neurotransmission were aimed at increasing NMDAR activation through increasing occupancy at the glycine co-agonist site, by administering glycine, D-serine or d-cycloserine. While smaller studies indicated beneficial effects, larger trials did not detect separation from placebo (Girgis et al., 2018). These interventions are also limited by tolerability. More recently, strategies have focused on reducing glycine reuptake, via inhibition of glycine transporter 1 (GlyT1), a key regulator of synaptic glycine levels (Supplisson and Bergman, 1997). Various GlyT1 inhibitors have been trialed; however, bitopertin is the only compound to have reached

Phase III clinical trials (Singer et al., 2015) and, due to lack of signals of efficacy, is no longer being developed for use as an antipsychotic (Bugarski-Kirola et al., 2017; Kantrowitz et al., 2017).

3.3. D-Amino acid oxidase inhibitors

A further approach is to manipulate the metabolism of D-serine, an endogenous ligand of the NMDA modulatory site, which is degraded in the brain by D-amino acid oxidase (DAAO) (Sershen et al., 2016). DAAO inhibitors may therefore be novel treatments to increase NMDA activity via the elevation of endogenous D-serine concentrations (Sershen et al., 2016). Indeed, a previous study with the DAAO inhibitor 5-chloro-benzo[d]isoxazol-3-ol (CBIO) found that co-administration of CBIO with D-serine significantly attenuated pre-pulse inhibition deficits instigated by administration of dizocilpine, an NMDAR antagonist (Hashimoto et al., 2009). In another study, acute administration of CBIO had no effect on PCP-induced locomotor activity when administered alone, but led to reductions when co-administered with D-serine (Sershen et al., 2016). However, this effect was also observed when the vehicle was tested with D-serine, indicating that the decrease in locomotor activity was potentially unrelated to DAAO inhibition. It was concluded from this study that the precise mechanisms of DAAO inhibitors are yet to be determined, but that, together with existing findings, continued glutamatergic drug development is supported (Sershen et al., 2016). None of the identified human DAAO inhibitors have yet been approved for the treatment of schizophrenia. The primary limitations of these agents include poor bioavailability, high clearance rate, and poor ability to cross the blood–brain barrier (Molla, 2017).

3.4. mGluR agonists

mGluRs are an alternative target and pharmacological advancements have allowed for the attainment of subtype specificity of mGluRs through the development of allosteric modulators (Stansley and Conn, 2018). PAMs operate to potentiate endogenous glutamate signaling, whereas negative allosteric modulators reduce receptor responsiveness to glutamate (Conn et al., 2009). Drug discovery efforts in the field of CNS have clarified the beneficial modes of action for allosteric modulators that target the various subtypes of mGluRs (Stansley and Conn, 2018). Group I mGluRs, which are coupled to signaling proteins, consist of mGluR1 and mGluR5 (Stansley and Conn, 2018). The mGluR5 receptor subtype has been considered an attractive therapeutic target due to its interaction with NMDARs through structural connections with scaffolding proteins (Tu et al., 1999). In addition, positive allosteric modulation of mGluR5s has been reported to enhance long-term synaptic plasticity in the hippocampus and has beneficial cognitive effects in rodents (Ayala et al., 2009). mGluR5 therefore presents a target that could be efficacious for positive, negative, and cognitive symptoms of schizophrenia, although this will be dependent on the possibility to develop mGluR5 PAMs that do not cause adverse events (Stansley and Conn, 2018).

The mGluR1 receptor subtype has received less attention; however, it has been reported that mutations associated with schizophrenia lead to a reduction in mGluR1 signaling *in vitro* (Cho et al., 2014). Furthermore, a range of highly selective mGluR1 receptor PAMs can potentiate responses to activation of these mutant receptors (Cho et al., 2014). This may suggest that mGluR1 PAMs could reverse deficits in mGluR1 signaling in patients with schizophrenia who carry these mutations (Stansley and Conn, 2018).

Group II mGluRs, which couple to G-protein subunits that inhibit adenylate-cyclase activity, consist of mGluR2 and mGluR3 (Stansley and Conn, 2018). Early studies in rodents with the mGluR2/3 agonist LY354740 revealed an improvement in deficits in stereotypy, locomotion, spatial working memory, and cortical glutamate efflux caused by the NMDAR antagonist PCP (Moghaddam and Adams, 1998). Activation of mGluR2/3 receptors has since been shown to enhance NMDAR function (Tyszkiewicz et al., 2004), regulate long-term depression and long-term potentiation in the PFC and hippocampus, respectively (Walker et al., 2017; Walker et al., 2015), and reduces excessive activity at glutamatergic synapses in the PFC (Homayoun et al., 2005). Inhumans, these findings were supported by the demonstration that mGluR2/3 agonist administration can attenuate the disruptions in working memory that are produced by the NMDAR antagonist ketamine (Krystal et al., 2005). However, although the mGluR2/3 agonist, pomaglumetad methionil showed beneficial effects on both positive and negative symptoms in early clinical trials, subsequent Phase III trials were disappointing (Caraci et al., 2017). Interestingly, a *post hoc* analysis of trial data suggested that pomaglumetad methionil may be selective in subgroups of patients, and particularly those who are in the earlier phases of illness, or who had been previously treated with a predominantly D_2 antagonist over $5HT_{2A}$ antagonist antipsychotic (Kinon et al., 2015). This may relate to the level of glutamatergic tone as glutamate level may vary with illness stage or treatment response (Egerton et al., 2018; Merritt et al., 2016). One possibility is therefore that mGluR2/3 agonists may be effective if applied earlier in illness, and potentially even before the onset of psychosis. This is suggested by studies in the MAM rodent model showing that NMDAR hypofunction and cognitive deficits were prevented by mGluR2 agonist administration in juvenile but not adult rats (Li et al., 2017; Li et al., 2015; Xing et al., 2018). Furthermore, the potential lack of efficacy of pomaglumetad methionil in patients previously treated with 'atypical' antipsychotics may be explained by downregulation frontal cortical mGluR2 receptors, occurring via decreased histone acetylation following $5HT_{2A}$ antagonism (Kurita et al., 2012). This might indicate that histone deacetylase (HDAC) inhibitors could have therapeutic benefit via modulation of expression of genes encoding mGluR2 and other proteins (Fischer et al., 2010).

3.5. Phosphodiesterase inhibitors

Phosphodiesterase (PDE) enzymes play a key role in regulating the activity of signaling pathways downstream of both glutamate and dopamine receptors (Snyder and Vanover, 2017). The human PDE family contains 11 subfamilies, each displaying a unique pattern of tissue-specific distribution (Heckman et al., 2018). Preclinical evidence suggests that at least four PDE subfamilies (PDE4, PDE9, PDE10, and PDE11) play a role in glutamatergic neurotransmission. Rolipram, an inhibitor of the PDE4 subfamily, blocks hyperlocomotion in both the PCP and amphetamine models of schizophrenia (Kanes et al., 2007; Snyder and Vanover, 2017). BI 409306 has been shown to be a potent and selective PDE9A inhibitor in rodents, which induced a dose-dependent increase in cGMP levels in the PFC and CSF (Rosenbrock et al., 2015). In a first-in-human trial, single doses of BI 409306 showed an acceptable safety and tolerability profile for young, healthy males (Moschetti et al., 2016). Inhibition of PDE10 appears to be beneficial against both positive and negative symptoms in the PCP model (Grauer et al., 2009). The PDE11A isoform, meanwhile, is thought to support glutamatergic neurotransmission in regions of the hippocampus and extended amygdala that may be related to social dysfunction in schizophrenia (Snyder and Vanover, 2017). To date, the clinical effects of PDE4, PDE9, and PDE11 inhibition in schizophrenia remains unreported. PDE10 inhibitors have been the subject of intense and ongoing neuropsychiatric research but clinical development has been hindered by associations with extrapyramidal side effects, such as akathisia and dystonia (Heckman et al., 2018).

3.6. α7 nicotinic acetylcholine receptor agonists

The α7 nicotinic acetylcholine receptor (α7-nAChR) is a cation channel-linked receptor subtype (Taly et al., 2009). α7-nAChRs are commonly expressed on the pre- and postsynaptic elements of the hippocampus and cerebral cortex where they facilitate release of various key neurotransmitters, including glutamate, dopamine, and GABA

(Beinat et al., 2015; Taly et al., 2009). In preclinical models, low levels of α7-nAChRs correlate with the poor sensory gating associated with inattention in schizophrenia (Taly et al., 2009). The PFC of patients with schizophrenia also show low levels of α7-nAChRs, and patients with schizophrenia show improved sensory gating in response to nicotine or the atypical antipsychotic clozapine, with effects thought to be mediated by α7-nAChRs (Taly et al., 2009). Agonists of α7-nAChRs have been assessed as adjunct therapy to antipsychotics in clinical trials of patients with schizophrenia. However, results to date have generally been disappointing, with a recent meta-analysis showing no statistically significant effects against cognitive impairment or negative symptoms compared with placebo (Jin et al., 2017). On the other hand, α7 modulators that do not act as direct agonists may show a better pharmacotherapeutic profile, based on preclinical evidence (Neves and Grace, 2018).

3.7. N-acetylcysteine

N-acetylcysteine (NAC) is a L-cysteine derivative, which may modulate extracellular glutamate concentrations through the glial cysteine-glutamate antiporter (Bridges et al., 2012), to reduce presynaptic glutamate release via mGluR2/3 activation (Baker et al., 2002). NAC also increases biosynthesis of the antioxidant glutathione, which may increase NMDA receptor activity (Steullet et al., 2006; Willborn et al., 2019) NAC has been evaluated for therapeutic efficacy in schizophrenia as well as other psychiatric disorders (Berk et al., 2013). An initial study assessing the efficacy of NAC as an adjunct to standard treatment for schizophrenia reported significant improvements in Positive and Negative Syndrome Scale and the Clinical Global Impression-Severity Scale (Berk et al., 2008). NAC was also well tolerated, with no significant adverse events reported in the group of patients treated with NAC (Berk et al., 2008). Improvements in negative symptoms were subsequently reported when NAC was administered as an adjunct to risperidone (Farokhnia et al., 2013). A recent study evaluated the effect of NAC on symptoms and neurocognition in early psychosis (Conus et al., 2018). Although NAC did not improve negative symptoms, there was some improvement in neurocognition as well as an increase in brain glutathione levels, indicating target engagement (Conus et al., 2018). Recent meta-analysis of seven randomized controlled trials of adjunctive NAC in schizophrenia found improvements in positive, negative symptoms, and working memory, and suggested that these effects may be most apparent after longer treatment periods (Yolland et al., 2019). Furthermore, blood glutathione peroxidase activity (as redox peripheral index is associated with glutathione levels), may help identify a subgroup of patients whose positive symptoms improve with NAC, which could represent a step towards biomarker-guided treatment (Conus et al., 2018). A further trial, for which data collection is planned to continue until mid-2019, is underway to determine the clinical value of NAC as an adjunctive therapy in patients who are only partly responsive to clozapine (Rossell et al., 2016).

3.8. GABA agonists

Due concept of functional imbalance between excitatory (glutamatergic) and inhibitory (GABAergic) neurotransmission in schizophrenia, GABA-acting compounds have also been investigated for therapeutic potential, so far with little clinical success (Xu and Wong, 2018). As described above, the MAM developmental model indicates that striatal dopaminergic hyperactivity results from over-active signaling between the medial temporal lobe and the striatum (Modinos et al., 2015) due to a selective loss of GABAergic PV interneurons in the hippocampus and frontal cortex (Zhang and Reynolds, 2002). In turn, this stimulates GABAergic neurons that project from the striatum to the ventral pallidum, thus increasing inhibition of ventral pallidum GABAergic neurons (Modinos et al., 2015). Potentially, the use of adjunctive GABA agonists may help to restore this imbalance (Gill et al., 2014; Wassef et al., 2003), although this may be more successful in the absence of previous antipsychotic exposure (Gill et al., 2014). While non-selective $GABA_A$ modulators such as benzodiazepines may not be effective in improving positive symptoms (Volz et al., 2007), compounds with greater subunit selectivity, particularly at α5 could have therapeutic potential (Lodge and Grace, 2011).

4. Conclusions and future perspectives

Since its conception, the NMDAR hypofunction theory of schizophrenia has received intense research interest across the spectrum of preclinical to clinical science. While the tenet of NMDAR hypofunction remains central, what has emerged is an extreme neurobiological complexity and an emphasis on interacting environmental factors and developmental processes. These studies raise many further questions, as well as identifying numerous potential targets for intervention. Nevertheless, the development of glutamatergic drugs for schizophrenia has proved to be extremely challenging and, as yet, unsuccessful. There may be several reasons for this, including a lack of suitable biomarkers for target engagement and dose selection (Javitt et al., 2018), indications of inverted U-shape dose–response relationships for glutamatergic compounds (Kinon et al., 2015; Spiros et al., 2014; Umbricht et al., 2014) and factors associated with clinical trial design such as high placebo response rates. The glutamatergic system is also under tight homeostatic control, so pharmacological perturbation is likely to evoke compensatory mechanisms to restore the healthy or pathophysiological 'state' of the system.

One exciting area of research is the identification of biomarkers for target engagement in early-stage clinical trials in healthy participants. A recent study evaluated three potential neuroimaging biomarkers of functional target engagement using ketamine administration in healthy volunteers, namely the functional MRI (fMRI) blood oxygen level-dependent (pharmaco-BOLD) response, ^{1}H-MRS, and task-based fMRI (Javitt et al., 2018). The primary objective was to compare both the magnitude of response and feasibility of implementation of imaging-based biomarkers for glutamate-targeted drug development (Javitt et al., 2018), with pharmaco-BOLD showing the most encouraging results. Such biomarkers will be useful in identifying promising compounds for patient studies, and guiding dose selection. For example, reductions in the ketamine BOLD-response can be observed following single dose administration of the higher, but not lower, tested doses of mGluR2/3 and mGluR2 agonist compounds in healthy volunteers, indicating the most pharmacologically active doses (Mehta et al., 2018). A second question is whether glutamate biomarkers, such as ^{1}H-MRS or ^{1}H-fMRS glutamate measures or glutamate genetic/epigenetic markers, can be used to preselect patients with a 'greater degree' of glutamate dysfunction who may be more likely to respond to a glutamate drug, in a stratified approach. Here, glutamate brain imaging approaches could also be applied to monitor glutamate function during an intervention trial.

Finally, the question as to 'when' in the course of illness glutamate manipulation may be most effective may be extremely important. This is related to the emerging clinical evidence that glutamate levels may be highest and predictive of outcome at or before the onset of psychosis (Bossong et al., 2019; de la Fuente-Sandoval et al., 2013; Egerton et al., 2018; Marsman et al., 2013; Merritt et al., 2016). Animal genetic and neurodevelopmental models may have utility in providing platforms against which experimental glutamatergic compounds may be tested for efficacy during different stages of development and in different environmental contexts.

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