The role of *N*-methyl-D-aspartate receptors and metabotropic glutamate receptor 5 in the prepulse inhibition paradigms for studying schizophrenia: pharmacology, neurodevelopment, and genetics

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Treatments for the positive and negative symptoms of schizophrenia have been explored for decades, but no completely successful therapy has been found as yet. Metabotropic glutamate receptor 5 (mGluR5), which potentiates *N*-methyl-D-aspartate receptors in brain regions implicated in schizophrenia, has become a novel drug target in the treatment of schizophrenia, especially for the mGluR5-positive allosteric modulators. Individuals with schizophrenia show deficits in prepulse inhibition (PPI), which is an operational measurement of sensorimotor gating. In this review, we focus on pharmacological, neurodevelopmental, and genetic animal models of disrupted PPI, with the aim of showing the potential role of mGluR5 in modulating the activity of *N*-methyl-D-aspartate receptors and their contributions toward the treatment of schizophrenia. As, the impairment of attentional modulation of PPI, but not that of baseline PPI, in individuals with schizophrenia is correlated with their symptom severity, this review also highlights that investigation of attentional modulation of PPI is critical for studying both cognitive impairments and glutamatergic dysfunctions of schizophrenia. *Behavioural Pharmacology* **29:13–27**

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Introduction

Schizophrenia is a complex neuropsychiatric disorder, triggered by a 'domino effect' induced both by genetic and by environmental factors, whereas the actual etiology has not yet been determined (Hennekens *et al.*, 2005). It is characterized by positive symptoms (e.g. hallucinations and delusions) and negative symptoms (e.g. depression and social isolation) as well as other cognitive deficits, such as abnormalities in learning and memory (Lewis and Lieberman, 2000). Animal models are vital tools to investigate the neural mechanism of schizophrenia. In recent decades, many animal models associated with genetics and neurodevelopment have been established; however, their interplay has not been fully elucidated.

The startle reflex is the whole-body response to sudden and intense sensory stimuli (Koch, 1999; Yeomans *et al.*, 2006), acting as an important defense mechanism to avoid danger. This mechanism can also disrupt normal ongoing cognitive and behavioral performance (Hoffman and Overman, 1971; Foss *et al.*, 1989); thus, it is potentially harmful to health. Prepulse inhibition (PPI) is the suppression of this startle reflex when an intense startling stimulus is preceded by a weaker sensory stimulus (the prepulse). It is an operational measure of a sensorimotor gating mechanism (Hoffman and Searle, 1965; Hoffman and Ison, 1980; Braff *et al.*, 2001; Swerdlow *et al.*, 2006). This weak prepulse triggers not only auditory processing of prepulse signals but also the gating mechanism that dampens the disruptive effects of the intense startle (Graham, 1975). Patients with schizophrenia show deficits in PPI (Geyer *et al.*, 2001). Many studies have confirmed deficient PPI in patients with both schizophrenia and schizotypal personality disorder (Braff *et al.*, 1978, 1992, 1999; Cadenhead *et al.*, 2000; Dawson *et al.*, 2000; Swerdlow *et al.*, 2006; Perry, Minassian and Braff, 1994). It should be noted that the reduction of PPI is not specific to schizophrenia. For example, robust deficient PPI has also been found in individuals with obsessive compulsive disorder (Kohl *et al.*, 2013), Tourette syndrome (Swerdlow, 2013), and other psychiatric and neurological disorders (García-Sánchez *et al.*, 2011; Kohl *et al.*, 2013).

There are a growing number of studies showing homology between PPI performances in animals and humans, which makes PPI a reliable cross-species measure of the

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sensorimotor gating process (Braff *et al.*, 2001; Geyer *et al.*, 2002; Swerdlow *et al.*, 2006). In healthy humans, selective attention to the prepulse can enhance PPI (Li *et al.*, 2009). For example, actively attending to the prepulse leads to an enhancement in PPI compared with ignoring the prepulse (Filion and Poje, 2003). Moreover, PPI could be enhanced when the prepulse is perceived as emotionally salient rather than a neutral stimulus (De la Casa *et al.*, 2012) or when electrical shock following the prepulse is anticipated (Grillon and Davis, 1997). More importantly, impairment of attentional modulation of PPI, rather than baseline PPI, is correlated with the symptom severity of schizophrenia (Hazlett *et al.*, 2007). In recent years, the attentional modulation of PPI paradigm has been established to investigate the attentional impairments in individuals with schizophrenia and in animal models (Li *et al.*, 2009).

The glutamate hypothesis of schizophrenia posits that noncompetitive *N*-methyl-D-aspartate receptor (NMDAR) antagonists, such as phencyclidine (PCP), ketamine, and MK-801, induce schizophrenia-like symptoms in healthy humans (Luby *et al.*, 1959). To be specific, dysfunctions of NMDAR activity on inhibitory neurons result in disinhibition of glutamate neurons, which increases extracellular glutamate levels in the synaptic cleft, especially in the prefrontal cortex (PFC) (Moghaddam and Javitt, 2012). In previous postmortem studies on patients with schizophrenia, both morphological changes in glutamatergic neurons and changes in the synthesis and expression of glutamine in the cerebral cortex have been detected (Hu *et al.*, 2015). Thus, normalization of excess extracellular glutamate is achieved by mGluR agonists (e.g. mGluR2/3, mGluR5) and can be used for the therapy of schizophrenia (Marek *et al.*, 2010). Both metabotropic glutamate receptors agonists and glycine uptake inhibitors have been suggested to be useful for treating schizophrenia (Zink and Correll, 2015; Wierońska *et al.*, 2016). In recent years, several clinical trials have found that both glycine inhibitors (Javitt, 2009; Bejczy *et al.*, 2014) and glutamate ligands (Maksymetz *et al.*, 2017) were unsuccessful, although this does not preclude their potential in the future for the treatment of mental disorders. Particularly, some novel groups of mGluR-related drugs have been designed, such as metabotropic glutamate receptor 5 (mGluR5) agonists, which focus more on multiple receptors and are expected to have better therapeutic effects (Wierońska *et al.*, 2016).

On the basis of the glutamatergic hypothesis, the association between NMDARs and mGluR5 has become the focus in the treatment for schizophrenia. The distribution of NMDARs and mGluR5 overlaps in many brain regions, including the hippocampus, striatum, neocortex, and PFC (Luccini *et al.*, 2007). The mGluR5 and NMDARs are also physically linked by scaffolding proteins, such as Homer (through Preso1), SH3 and multiple ankyrin repeat domains (SHANK), guanylate-kinase-associated protein (GKAP, also known as SAPAP), and postsynaptic density 95 (Spooren *et al.*, 2003). Physical links between the two receptors lay the foundation for both the relevant signaling pathways and their biological interactions. Induced by intracellular Ca^{2+} release, glutamate potentiates mGluR5 by phosphorylation and initiates the activation of protein-kinase C (PKC), which continues to signal downstream and finally activates brain-derived neurotrophic factor. Through feedback, PKC potentiates NMDARs through the Src protein (Vinson and Conn, 2012). As a result of Ca^{2+} influx through NMDARs, glutamate activates calcineurin (also known as Ca^{2+}-dependent protein phosphatase 2B), which in return dephosphorylates mGluR5 (Alagarsamy *et al.*, 2005). This interaction between the two receptors confirms their mutual influence. A large body of evidence suggests that activation of mGluR5 enhances NMDAR function. The mGluR5 agonist potentiates NMDARs in the hippocampus (Doherty *et al.*, 1997), spinal cord (Ugolini *et al.*, 1999), subthalamic nucleus (Awad *et al.*, 2000), and medium spiny striatal neurons (Pisani *et al.*, 2001). Meanwhile, NMDARs affect mGluR5 function reciprocally, for example, activation of NMDARs reverses the desensitization of mGluR5 (Gereau and Heinemann, 1998; Alagarsamy *et al.*, 1999). Pharmacological studies further indicate that mGluR5 undergoes a rapid agonist-induced desensitization that is mediated by the activation of PKC (Gereau and Heinemann, 1998). However, activation of NMDARs reverses this desensitization effect and phosphatase inhibitors (such as sodium orthovanadate and cypermethrin) completely block this reversal (Alagarsamy *et al.*, 1999). The shared signaling pathways and relevant biological interaction between the two receptors provide a suitable explanation for the modulating role of mGluR5 in the activation of NMDARs.

Here, we focus on the effects of both NMDARs and mGluR5 in the behavioral paradigm of PPI and attentional modulation of PPI in animal models of schizophrenia. The recent pharmacological, developmental, and genetic animal models are first reviewed to provide a context for the overall discussions. More importantly, we propose that the attentional modulation of PPI paradigm is essential for establishing animal models to investigate cognitive function (particularly attention) in schizophrenia.

Pharmacological models of prepulse inhibition deficits

Pharmacological studies assume the fact that brain neurotransmitter pathways and systems are affected by drugs that are effective in targeting symptoms of disease (Joober *et al.*, 2002). Chemical imbalance in the brain is hypothesized to induce schizophrenic symptoms (Sedvall and Farde, 1995). By binding to neurotransmitter receptors and altering neuronal activities, pharmacological agents represent a new therapeutic method for the treatment of schizophrenia.

N-methyl-D-aspartate receptors-mediated prepulse inhibition deficits

The hypofunction of NMDARs in the brain is involved in the pathophysiology of schizophrenia. Some NMDAR antagonists, such as PCP, mimic positive symptoms

(e.g. delusions and hallucinations) and some negative symptoms (e.g. progressive withdrawal and poverty of speech) of schizophrenia in healthy humans (Luby *et al.*, 1959). By inducing several symptoms in humans relevant to those in schizophrenia, these pharmacological rodent models of schizophrenia show good face validity. On the basis of their pharmacology and pharmacokinetics, several positive NMDAR modulators, such as D-serine, cycloserine (Heresco-Levy *et al.*, 2002), and glycine (Javitt *et al.*, 1994), have been designed as novel therapies for the treatment of schizophrenia. The cognitive impairments induced by NMDAR antagonists are attenuated by atypical antipsychotics (Abdul-Monim *et al.*, 2006), which indicate their potential for alleviating some symptoms of schizophrenia.

PPI deficits in animals caused by systemic administration of NMDAR antagonists have been found in many studies (Bakshi *et al.*, 1999; Geyer *et al.*, 2001). Mansbach and Geyer (1989) first reported disruptive effects on PPI by acute administration of PCP or MK-801 in rats (Mansbach and Geyer, 1989). They also found that ketamine disrupted PPI in animals at appropriate doses (Mansbach and Geyer, 1991). Martinez *et al.* (1999) reported disrupted PPI after subchronic exposure to PCP in rats by either mini-pump or intraperitoneal administration (Martinez *et al.*, 1999). Although rodents showed deficits in PPI similar to those found in patients with schizophrenia (Linn *et al.*, 2007), NMDAR antagonists have different effects on PPI in human patients. For example, the effects of ketamine on PPI in humans are inconsistent (Duncan *et al.*, 2001; Abel *et al.*, 2003). The divergent effects of ketamine on PPI between human studies and animal models may partially be attributed to experimental parameters (Mansbach and Geyer, 1991). For example, Abel *et al.* (2003) found that ketamine (at dose of 0.5 mg/kg) enhanced PPI in healthy individuals, but these results were not reported by Duncan *et al.* (2001) using the same doses. In these two studies, the different prepulse types and prepulse-pulse intervals may have contributed toward the different findings.

In addition, NMDARs participate in the regulation of PPI at different developmental stages. For example, neonatal exposure to MK-801 disrupted PPI in adolescence and early adulthood in Wistar rats, but had limited effects on PPI when the rats became adults (Uehara *et al.*, 2009). More recent studies have shown that Wistar rats showed reductions in PPI during adulthood when they were injected with MK-801 in their postnatal days (Uehara *et al.*, 2009, 2010; Lim *et al.*, 2012a, 2012b). These studies suggest that early exposure to NMDAR antagonists has a long-term effect on PPI, particularly in the postpubertal phase.

Metabotropic glutamate receptor 5 modulates *N*-methyl-D-aspartate receptor-mediated prepulse inhibition deficits

The mGluR5 is comprised of a large extracellular *N*-terminal domain containing the glutamate-binding site and seven-helical transmembrane segments (7TM) (Romano *et al.*, 1996), which can connect to most glutamate agonists, such as positive allosteric modulators (PAMs) and negative allosteric modulators (NAMs) (Hovelsø *et al.*, 2012). As mGluR5 associates with NMDARs by physical binding and scaffold proteins, and activation of mGluR5 enhances NMDAR function (Vinson and Conn, 2012), it is reasonable to postulate that mGluR5 modulates NMDAR-mediated PPI. This view is supported by evidence that mGluR5 agonists and PAMs normalize the NMDAR antagonist-induced impairments of PPI, whereas mGluR5 antagonists and NAMs aggravate these PPI deficits.

It has been found that enhancements in mGluR5 function might induce antipsychotic effects. Administration of the mGluR5 agonist/PAM 2-chloro-5-hydroxyphenylglycine (CHPG) could reverse the PCP-induced (Kinney *et al.*, 2003) or ketamine-induced (Chan *et al.*, 2008) PPI impairments. However, pretreatment with another selective mGluR5 PAMs alone, 3-cyano-*N*-1,3-cyano-*N*-(1,3-diphenyl-1*H*-pyrazol-5-yl)-benzamide (CDPPB), did not alter PPI (Chen *et al.*, 2011). In contrast, pharmacological disruptions of PPI could be exacerbated by mGluR5 antagonists. Administration of 2-methyl-6-(phenylethynyl)-pyridine (MPEP), an mGluR5 selective antagonist, potentiated PCP-induced PPI deficits in rats. However, MPEP had no effect on PPI when injected alone (Campbell *et al.*, 2004). This evidence for mGluR5 agonists/PAMs and antagonists/NAMs suggests that mGluR5 modulates NMDAR-mediated PPI, but cannot influence PPI by itself.

To understand the detailed interactions between mGluR5 and NMDARs, different mGluR5 agonists and PAMs have been compared among different NMDAR antagonist-induced PPI impairments. Chen *et al.* (2011) investigated how three mGluR5 agonists, namely, CHPG, 3,3′-difluorobenzaldazine (DFB), and CDPPB, interacted with three NMDAR antagonists, namely, ketamine, D-2-amino-5-phosphonovaleric acid (D-APV), and ifenprodil. It was found that CHPG, DFB, and CDPPB reversed the suppressive effects of ketamine on NMDAR-mediated field potentials. However, unlike CHPG and CDPPB, DFB did not prevent the D-APV-induced blockage of NMDARs (Chen *et al.*, 2011). Similarly, another study has shown that CHPG and DFB had distinct efficacies in attenuating ketamine-induced PPI deficits (Chan *et al.*, 2008). These two studies indicate that the potency of DFB is much lower than that of CHPG. It is possible that the two agents affect different subsets of mGluR5s in the neural circuits involved in PPI (Chan *et al.*, 2008).

Conversely, different NMDAR antagonists have various effects on the potency of mGluR5 agonists and PAMs. An interesting finding is that CHPG reversed the suppression by ketamine of D-APV-induced field potentials, but did not reverse the effect of ifenprodil. As ifenprodil

specifically antagonizes NMDAR subunit NR2B, this result might indicate that NR2B does not participate in mGluR5 regulation of NMDA-mediated PPI impairments (Chan *et al.*, 2008). Another study found that a PKC inhibitor blocked the potentiation by DFB, CHPG, and CDPPB of NMDA-induced field potentials, and a PKC activator enhanced this potentiation (Chen *et al.*, 2011). This indicates that at a cellular level, regulation of mGluR5 on both the activation and the suppression of NMDARs might rely on PKC pathways.

To develop new drugs for treating patients with schizophrenia, recent studies have focused on the binding sites of mGluR5 agonists and PAMs. Most mGluR5 modulators, such as DFB and CDPPB, act mainly on MPEP sites,

(Bullock *et al.*, 2009). The hypofunction of NMDARs in isolation-reared rats results in PPI deficits. For example, rats reared in isolation showed deficits in PPI, associated with increased NR2A mRNA expression in the medial PFC (Turnock-Jones *et al.*, 2009). PCP treatment of mice on postnatal days caused an upregulation of NR2B and these mice also showed deficits in PPI (Anastasio and Johnson, 2008). The glutamate system is also dysfunctional in isolation-reared rats (Bristow *et al.*, 1995; Stefani and Moghaddam, 2010; Hickey *et al.*, 2012), which is confirmed by the fact that mGluR5 PAMs could reverse deficits in PPI observed in isolation-reared rats (Stefani and Moghaddam, 2010). Furthermore, relative to rats reared in an enriched environment and a normal environment, the capacity of mGluRs, which could affect extracellular glutamate levels in the PFC, was significantly blunted in isolated/impoverished-reared animals (Melendez *et al.*, 2004).

In sum, social isolation influences the development of the brain, causing dysfunctions at the behavioral, cellular, and molecular levels. The aberrant neuroanatomical and neurotransmitter changes within the brain contribute toward the behavioral impairments in isolation-reared rats, especially deficits in PPI. Thus, the isolation-rearing animal model is a viable approach to both the etiology of schizophrenia and the development of novel treatments.

Adolescent brain development

Adolescence is a critical phase for brain development, characterized by neuronal maturation and rearrangement processes, such as myelination, synaptic pruning, and dendritic (Giedd et al., 2008). The endocannabinoid system plays an important role in fundamental brain developmental processes such as neuronal cell proliferation, migration, and differentiation (Harkany *et al.*, 2008). As the most popular illusion-inducing drug used, cannabis consumption during adolescence could render an individual more susceptible to developing psychoses, such as schizophrenia (Malone *et al.*, 2010). Mice administered cannabinoids during adolescence (postnatal day 30–35) showed both deficits in PPI and

considered to model symptoms of schizophrenia (Becker *et al.*, 2005).

Both NMDARs and mGluR5 have been implicated in the vitamin-D deficiency model of schizophrenia. It has been shown that the mGluR5 agonist CHPG completely normalized the hole-board habituation in deficient animals (Becker and Grecksch, 2006), whereas administration of the NMDAR antagonist MK-801 to vitamin-D deficient rats caused increased locomotion in the hole-board task and enhanced auditory response, but no alteration in PPI (Kesby *et al.*, 2006), which suggests that vitamin-D depletion did not impair sensorimotor gating.

Summary

In sum, compared with drug-induced PPI deficits, developmental manipulations of PPI are less robust as many unknown and ungoverned factors influence the results. For social isolation rearing, the duration should be sufficiently long (e.g. 6–8 weeks) that rat pups show cognitive and motor impairments. Bakshi and Geyer (1999) found that deficits reach significance around the time of puberty (Bakshi and Geyer, 1999). In addition to a long rearing time, other manipulations to increase stress levels should also be considered. During isolation, hearing the calls of an owl or a cat (the rat's natural enemies), water and/or food deprivation during isolation, or watching a fearful video showing peers being eaten by cats, induces stressful states in rats, which cause the appearance of schizophrenia-like symptoms (Selten *et al.*, 2017). Future isolation manipulations should involve these stressful factors, rather than isolated-housing only. For models of adolescent damage and maternal separation, the length of the critical window to be manipulated, which influences the extent of PPI, should be investigated. The potential malnutrition should also be controlled. Indeed, studies indicate that maternal deprivation without malnutrition had no effect on PPI (Finamore and Port, 2000) and that prenatal protein deprivation on its own disrupted PPI (Palmer *et al.*, 1997). The prenatal vitamin-D deficient model is newly implicated in schizophrenia, and the mechanism is still under investigation. Thus, the neurodevelopment model of PPI should be further improved in future studies, which should be combined with drug and genetic manipulations to fully explore the etiology and treatment of schizophrenia.

Genetic models of prepulse inhibition deficits

Molecular genetic techniques in mutant mouse models have been used widely. There are four types of such models: mice with deletion of specific genes, deletion of whole chromosomal regions, insertion of new genes, and spontaneously mutated genes (Geyer *et al.*, 2002). Here, we focus on PPI deficits shown by mutant mice carrying deleted single genes that regulate NMDARs, mGluR5, and their connecting proteins. The findings from PPI studies clearly show that mutant mouse models are a powerful tool to investigate the interactions between mGluR5 and NMDARs that contribute toward some symptoms of schizophrenia.

N-methyl-D-aspartate receptor mutants

Hypofunction of NMDARs has been implicated in the pathophysiology of schizophrenia. The NMDARs contains at least one NR1 subunit, together with different combinations of NR2 and NR3. The NR2 subunit comprises four components, namely, NR2A-D, and the NR3 subunit contains the NR3A and NR3B components. Within the channel of the NMDARs, there is one binding site, which is the target of the NMDAR antagonist (e.g. ketamine, MK-801), and a second site on the NR1 subunit for glycine/D-serine, which must be combined with glutamate to open this channel (Berger *et al.*, 1998). These two binding sites interact closely with mGluR5, acting as potential drug targets in the treatment of schizophrenia.

Many genetic studies have focused on structural abnormalities of the NR1 subunit. NR1 hypomorphic mice with reduced NR1 expression showed deficits in PPI (Duncan *et al.*, 2004), which could be ameliorated by both typical and atypical antipsychotic drugs (Duncan *et al.*, 2006). Moreover, the NR1-deficient mice, generated from heterozygous breeder pairs, showed higher startle response amplitudes, and were more sensitive to the disruptive effects of amphetamine on PPI (Moy *et al.*, 2006). Deletion of the NR1 gene in the nucleus accumbens (NAcc) restricted apomorphine-induced suppression of the auditory startle response (Glass *et al.*, 2013). These two studies may show that NR1 participates in the regulation of behavioral responses to acoustic stimuli startle, which could be mediated by apomorphine. The functions of NMDARs go through a series of chemical modifications, such as phosphorylation. The aberrant phosphorylated modification of the NR1 subunit led to hypofunction of NMDARs (Ali and Salter 2001). Neonatal ventral hippocampus-lesioned rats, in which NR1 phosphorylation was significantly decreased in the medial PFC and hippocampus, showed impairments in PPI, which could be improved by acute risperidone treatment (Yabuki *et al.*, 2013). In addition, phosphorylation of the NR1 subunit at serine 897 (S897) was markedly reduced in patients with schizophrenia (Emamian *et al.*, 2004). Mice in which the NR1 S897 was replaced with alanine showed impairment in NMDAR synaptic incorporation and NMDAR-mediated synaptic transmission, and also showed deficits in PPI (Li *et al.*, 2009). Moreover, mice underexpressing the NR1 subunit ($NR1^{neo/neo}$) showed enhanced startle amplitude and deficits in PPI, both of which could be restored by selective kainate antagonists (Duncan *et al.*, 2010, 2012). These studies indicate that abnormal chemical modifications of NR1 are implicated in deficits in PPI,

suggesting that this could be a target site for the treatment of schizophrenia.

Hypoexpression of NR2 subunits is also implicated in the hypofunction of NMDARs. For example, patients with schizophrenia have an abnormal NR2 structure, which contains limited fast-firing interneurons, which are critical for gamma oscillations (Lewis *et al.*, 2005). NMDAR blockade of the NR2A subunit, rather than the NR2B subunit, resulted in a marked increase in aberrant gamma activity, paralleled by deficits in PPI (Kocsis, 2012). Selective genetic knockout of NR2A or pharmacological inhibition of NR2B did not disrupt PPI, but combining the two manipulations produced robust PPI deficits (Spooren *et al.*, 2004). Taken together, these results indicate that various NR2 subunits regulate PPI in different ways.

The NR3A subunit also participates in reglating PPI. For example, NR3A KO mice showed enhanced NMDAR-induced dysfunctions (Tong *et al.*, 2008). Deletion of the NR3A subunit results in sex-specific and age-specific increases in PPI. For example, male NR3A KO mice showed an increase in PPI at postnatal 3 and 4 weeks, whereas PPI was not altered at any other ages. However, female NR3A KO mice did not show any increase in PPI at any point during development (Brody *et al.*, 2005).

Metabotropic glutamate receptor 5 mutants

In patients with schizophrenia, there is dysregulation of mGluR5 in the PFC (Ohnuma *et al.*, 1998) accompanied by reduced levels of mGluR5 message and deficits in mGluR5 signaling (Grottick *et al.*, 2005). This evidence stimulated investigation of mGluR5 mutants in animal models. An essential role of mGluR5 in PPI has been well studied using mGluR5 KO mice, from two different strains, 129SvPasIco and C57BL/6, which showed deficits in PPI (Brody *et al.*, 2004a). Moreover, these impairments were independent of breeding strategy or postnatal mothering behavior in the postnatal environment (Brody and Geyer, 2004b). Although the NMDAR antagonist MK-801 disrupted PPI at both low and high dosages in rodents (Zhao *et al.*, 2013), Lipina *et al.* (2006) found that PPI deficits in mice carrying a null mutation of the mGluR5 gene could not be further disrupted by MK-801 at low dosages, but could be further disrupted at the highest dosage. As stated earlier, administration of mGluR5 agonists alone did not alter PPI (Kinney *et al.*, 2003; Campbell *et al.*, 2004; Chen *et al.*, 2011), but could potentiate PCP-induced deficits in PPI in rats (Kinney *et al.*, 2003). Thus, the resistance to NMDAR antagonists at low concentrations in mGluR5 mutants may result from a complex interaction between NMDAR hypofunction together with a missing mGluR5 complex (Lipina *et al.*, 2006). Taken together with the studies on mGluR5/NMDAR-related drugs, it seems that the effects of NMDAR modulation on mGluR5 depend not only on the activities of both types of receptor but also on their signaling/molecular pathways, which may make the results of drug studies and genetic studies divergent.

The mGluR5 KO mice may serve as an animal model for screening novel antipsychotic drugs. *N*-acetylcysteine, which indirectly activates cystine-glutamate antiporters to increase extra-synaptic glutamate levels, could ameliorate PPI deficits in mGluR5 KO mice. This recovery was not blocked by the mGluR5 antagonist, LY341495 (Chen *et al.*, 2010), which indicates that *N*-acetylcysteine could be a novel candidate drug for the treatment of schizophrenia.

Homer mutants

Homer proteins act as scaffolding proteins that link surface mGluR5 proteins to their postsynaptic densities, implicated in glutamate intracellular signaling pathways (Sala *et al.*, 2005). Moreover, the Homer protein can regulate cell surface expression and clustering of mGluR5. The Homer family consists of the Homer1, Homer2, and Homer3 genes. Spellmann *et al.* (2011) found an association between Homer1 polymorphisms and psychopathology in patients with schizophrenia. This suggests that aberrant expression of Homer proteins may affect mGluR5 and induce schizophrenia-like symptoms.

Homer1a mRNA expression was increased temporally within the PFC and the primary auditory cortex after 2 and 24 h treatments with PCP (Cochran *et al.*, 2002), and administration of ketamine resulted in a significant change in Homer1a in the ventral striatum (Iasevoli *et al.*, 2007). Damage to multimerization of Homer proteins correlated with reduced glutamatergic postsynaptic currents (Hayashi *et al.*, 2009). These pharmacological studies indicate that Homer protein is involved in mGluR5 and NMDARs signaling pathways (Cochran *et al.*, 2002), and lead to genetic studies of Homer genes. The Homer1 gene may regulate extracellular levels of glutamate within limbo–cortical–striatal structures, which were impaired in patients with schizophrenia (Ary *et al.*, 2007). In animal models, Homer2 null mutant mice showed reduced intracellular calcium amounts coupled to mGluR5 (Shin *et al.*, 2003), and a decreased level of glutamate in the NAcc and an increased level in the PFC, with parallel impairments in PPI (Szumlinski *et al.*, 2005). Because of the three distinct isoforms of Homer protein, Homer1a and Homer1c are differentially involved in the regulation of glutamate within the PFC. Restoration of Homer1c expression within the PFC could reverse PPI deficits in Homer1 KO mice, whereas infusion of Homer1a could not ameliorate PPI deficits (Lominac *et al.*

surface of mGluR1and mGluR5 *in vivo*, the distribution of which in the brain resembles that of mGluR5 (Wang *et al.*, 2009). Norbin is a cytosolic protein localized in the somatodendritic region of neurons in both the central and the peripheral nervous system (Shinozaki *et al.*, 1999). The two dimers of Norbin bind to different membrane receptors, including mGluR5 and NMDARs (Wang *et al.*, 2010), but whether Norbin mediates the cross-talk between the two receptors is still unknown.

Norbin influences the expression of mGluR5 on the cell surface, and neuronal mGluR5 levels increase with the co-presence of Norbin (Wang *et al.*, 2009). More importantly, Norbin KO mice, with deletion of the gene for Norbin protein in the postnatal forebrain, also showed a reduced level of mGluR5 on their cell surface and showed deficits in PPI (Wang *et al.*, 2009), which indicates that Norbin participates in the regulation of sensorimotor gating. Thus, Norbin appears to be an important endogenous modulator of mGluR5 and may provide a novel target for the treatment of schizophrenia.

Neuregulin mutants

Neuregulins is a family of four structurall[redacted]teins (NRG 1–4), which bind to the ErbB family of receptor tyrosine kinases (Chang *et al.*, 1997). It has been found that neuregulin modulates the activity of the NMDAR through its receptor, ErbB4, on synaptic spines (Bennett *et al.*, 2012) and in the hippocampus (Yamazaki and Sumikawa, 2017). Moreover, recent studies have confirmed that there is cross-talk between NRG1–ErbB4 signaling pathways and NMDARs through the scaffolding protein postsynaptic density protein 95, which may be implicated in the behavioral abnormalities of schizophrenia (Li *et al.*, 2013). Taken together with the neurobiological evidence, the neuregulin-mutant mouse model has been developed to mimic the cognitive and behavioral deficits of schizophrenia. For example, neuregulin-1 mutant mice (Schneider *et al.*, 2017) and neuregulin-2 knockout mice (Yan *et al.*, 2017) showed deficits in PPI. In addition, a combination of NRG1 deletion and maternal immune activation also causes deficient PPI and other cognitive deficits relevant to schizophrenia, which illustrates interactions between the gene and environment for interpreting the etiology of schizophrenia (O'Leary *et al.*, 2014).

Disrupted-in-schizophrenia-1 mutants

Genetic studies have confirmed that disrupted-in-schizophrenia-1 (DISC1) is a risk factor for schizophrenia (Brandon and Sawa, 2011). Knocking down DISC1 increased expression of the NR2A NMDAR subunit in the PFC; the resulting NMDAR hyperfunction could be blocked by PKA inhibitors (Wei *et al.*, 2014). This finding indicates the role of DISC1 in NMDAR activity and its signaling pathways (Forrest *et al.*, 2013; Wei *et al.*, 2014). Moreover, recent studies have shown that deletion of DISC1 altered homeostatic activity of multiple receptors, including mGluR5 in the NAcc (Kim *et al.*, 2015). As DISC1 is considered to be the candidate gene for inducing symptoms of schizophrenia, the DISC1 mutant model has been developed to mimic cognitive impairments of schizophrenia. Specifically, the $129DISC1^{Del}$ mutant mice showed a shorter full length of DISC1 expressed in the hippocampus paralleled by deficits in PPI (Gómez-Sintes *et al.*, 2014). Moreover, deficient PPI in DISC1 knockout mice could be reversed by P21-activated kinase inhibitors (Hayashi-Takagi *et al.*, 2014), indicating the efficacy of the DISC1 mutant model for screening some antipsychotic drugs.

Summary

In general, exploring the relationships between the specific genes and PPI performance is a reliable means of investigating the pathophysiology of schizophrenia. The abnormal expression-6860a1614TD0T(r)316x14.7(f(i)13.M(s)15.DA(s)25(

r(r)14.e1(6)74.3(n)25.(1)03.1(e)7.26(w)12.h(p)11.7(i)13.1(a)15.1(,)0313.7(i)1

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years, more studies have used attentional modulation of PPI in animal models to mimic the attentional deficits found in patients with schizophrenia.

Emotional attentional modulation of prepulse inhibition

Emotional modulation of prepulse stimuli elicits larger PPI than emotionally neutral prepulse stimuli in healthy humans (Bradley *et al.*, 2006). The prepulse stimuli, which were paired with unpleasant shock delivery, could significantly heighten PPI relative to stimuli presented with random shock delivery or without shock (Cornwell *et al.*, 2008). Recent rodent studies have shown that PPI could be enhanced in socially reared rats by auditory fear conditioning by precisely pairing the prepulse stimulus with foot-shock (Huang *et al.*, 2007; Du *et al.*, 2009; Wu *et al.*, 2016). This indicates that fear conditioning of prepulse stimuli, which have ecological value, could drive patients' attention and build up deep processing of the prepulse and enhance PPI.

Long-term potentiation (LTP) and long-term depression (LTD) reflect synaptic plasticity, which have been suggested to be the physical substrates for changes underlying fear conditioning. Recent studies have found that mGluR5 mediates the expression of LTD and LTP through synaptic transmissions within the brain. For example, mice with genetic deletion of mGluR5 showed deficits in LTP in the hippocampus (Jia *et al.*, 1998). The selective mGluR5 PAMs induced a robust form of LTD at the Schaffer collateral-CA1 synapse in the hippocampus (Palmer *et al.*, 1997) and enhanced both electrical stimulation and pharmacological manipulation-induced LTD (Ayala *et al.*, 2009), which suggests that potentiation of mGluR5, mediated by glutamatergic afferents, enhances both LTP and LTD. Recent studies have found that Norbin protein, which connects to the mGluR5, participates in the mediation of LTP and LTD. Shinozaki *et al.* (1997) initially described the expression of this Norbin protein in rat hippocampal tissues relevant to LTP-like enhancement. Recent study has shown that deletion of Norbin reduced the mGluR5-related synaptic changes, measured as LTD or LTP, in the hippocampus (Wang *et al.*, 2009). This suggests that Norbin protein may influence mGluR5-induced synaptic plasticity.

Fear conditioning is based on the role of NMDARs in the lateral nucleus of amygdala (LA). To be specific, during the formation of fear conditioning, the presentation of the conditioned stimulus results in the release of glutamate, which binds to glutamate receptors, including NMDARs and mGluRs on LA cells, and the unconditioned stimulus then depolarizes these cells while glutamate is bound to NMDARs (Rodrigues *et al.*, 2004). It was reported recently that neonatal MK-801 exposure did not abolish the PPI enhancement induced by fear conditioning, but these rats cannot differentiate the fear-conditioned prepulse from a neutral prepulse (Wu *et al.*, 2016), which indicates that NMDARs specifically affect the attentional modulation of PPI.

The mGluR5 also plays a role in synaptic plasticity through its close mutual associations with NMDARs during the formation of fear conditioning (Fendt and Schmid, 2002; Rodrigues *et al.*, 2002). The LA is critical for fear conditioning (Kyung Lee *et al.*, 2002; Rodrigues *et al.*, 2002): for example, damage to the LA prevented fear conditioning (Nader *et al.*, 2001). It has been shown that LTP occurs at LA synapses during fear conditioning (Huang and Kandel, 1998), and induces an associative LTP-like change in the responses of LA neurons (Rogan *et al.*, 1997). Many studies have confirmed that mGluR5 is involved in the formation of fear conditioning in the LA (Fendt and Schmid, 2002; Rodrigues *et al.*, 2002). Du *et al.* (2009) found that blocking mGluR5 in LA elimi-

the lead sound and listeners perceive a single fused image. This phenomenon is called the 'precedence effect' (Litovsky *et al.*, 1999; Li and Yue, 2002). As a sound source is more correlated with its time-delayed reflections and less correlated/uncorrelated with other sources, this perceptual integration associated with the precedence effect facilitates the perception of spatial segregation of signals from other sound sources.

In healthy humans, this perceived spatial segregation of target and masker facilitates the listener's selective spatial attention to target signals and improves speech intelligibility (Freyman *et al.*, 1999; Wu *et al.*, 2005). However, patients with schizophrenia were more vulnerable to masking noise than healthy individuals in the noisy environment (Wu *et al.*, 2012, 2013), and had more difficulty in differentiating the target sound among many distracters (Luck *et al.*, 2012).

In socially reared rats, perceived spatial segregation of unconditioned prepulse and background noise could not alter PPI, but perceived spatial segregation of a salient prepulse (e.g. when the prepulse was paired with footshock) and noise masker markedly enhanced PPI (Du *et al.*, 2009). However, isolation-reared rats did not show enhancement of PPI induced by perceived spatial separation between the prepulse and the noise masker even when the prepulse became ecologically significant (Du *et al.*, 2009; Wu *et al.*, 2016). Melendez *et al.* (2004) found that decreased activity of mGluR5 in the PFC could explain PPI deficits in isolation-reared rats because of the impairments in inhibitory control (Melendez *et al.*, 2004). The posterior parietal cortex is also crucial in spatial attention, and blocking mGluR5 in the posterior parietal cortex eliminated the perceptual spatial separation-induced PPI enhancement (Du *et al.*, 2011), which indicates that mGluR5 plays a role in the perceived-spatial-separation attentional modulation of PPI. Moreover, the location specificity in the perceived-spatial-separation-induced PPI enhancement could be eliminated by extinction learning, the effects of which could be abolished by the mGluR5 antagonist, MPEP (Lei *et al.*, 2014).

Patients with schizophrenia show spatial attentional deficits (Park *et al.*, 2002; Dalmaso *et al.*, 2013). A recent study found that in the paradigm established in laboratory rats (Li *et al.*, 2009), individuals with schizophrenia show deficits in the perceived-spatial-separation-induced modulation of PPI (Yang *et al.*, 2017), similar to the findings that the perceived spatial separation failed to modulate PPI in isolation-reared rats (Du *et al.*, 2009, 2010; Wu *et al.*, 2016). In addition, the extent of perceived-spatial-separation-modulated PPI is associated with their positive and negative symptoms in patients with schizophrenia (Yang *et al.*, 2017). Thus, the perceived-spatial-separation attentional modulation of PPI provides a new procedure to assess spatial attention and its relevant neural/chemical mechanisms in animal models of schizophrenia.

Summary

This review has focused on disturbances in glutamatergic and NMDA functions in three types of animal models using the PPI paradigm. The pharmacological model of PPI shows that NMDAR antagonists induce schizophrenic symptoms in healthy patients, and these can be alleviated by the administration of mGluR5 agonists and PAMs. The neurodevelopment model of PPI suggests that the developmental factors associated with abnormal expression of mGluR5 have a huge influence on the evolution of schizophrenia. The genetic model of PPI emphasizes the genes regulating NMDARs, mGluR5, and their scaffolding proteins, supporting the interaction between two receptors in schizophrenic symptoms. In the future, the above animal models could be combined to investigate the behavioral phenotypes of schizophrenia. For example, Lim *et al.* (2012b) combined two manipulations to produce a 'two-hit' model (neonatal MK-801 treatment and isolation rearing), and found that this model showed a more robust behavioral phenotype of aspects of schizophrenia compared with individual manipulations alone, including baseline PPI deficits.

PPI is widely considered as a promising behavioral paradigm for assessing sensorimotor gating in animal models and in patients with schizophrenia. There are several reasons to select PPI as a potential measurement. First, the cross-species comparability means that the results from animals and humans can be compared. Second, as reviewed, the manipulation of prepulse can elicit fast and stable changes in motor responses PPI is quite sensitive in response to parametric manipulations, which enables investigators to explore cognitive performance. However, PPI has some potential weaknesses. For example, alterations in PPI may result from other factors not related to schizophrenia. For example, poor PPI in humans can result from hearing deficits. Some strains of mice have shown hearing loss with age so that they cannot detect the prepulse (Geyer *et al.*, 2002). PPI, with its high test–retest reliability, has been used to verify both typical and atypical antipsychotics in individuals with schizophrenia. Classical antipsychotics can improve but not normalize PPI deficits, and atypical antipsychotics, such as clozapine and risperidone, improve PPI more effectively (Oranje *et al.*, 2002). It should be noted that previous studies of reversal of PPI by antipsychotics used small sample sizes and between-subjects designs, leading to some uncontrollable factors that confounded the interpretation of the results (Leumann *et al.*, 2002).

Thus, we propose that the attentional modulation of the PPI paradigm is a new tool to investigate the four cognitive layers in animal models of schizophrenia. To be specific, this new paradigm can assess baseline startle amplitude,

baseline PPI, fear-conditioning-induced PPI enhancement (emotional attention), and perceived-spatial-separation-induced PPI enhancement (spatial attention). We anticipate that our new PPI paradigm will be essential not only for assessing the cognitive deficits (particularly attentional deficits) shown in animal models but also for probing potential antipsychotic treatments for schizophrenia. Recent studies have found that the attentional modulation of PPI involves the capacity of NMDARs and mGluR5 (Zou *et al.*, 2007; Du *et al.*, 2010, 2011; Lei *et al.*, 2014; Wu *et al.*, 2016). Further investigations will be required to determine the full potential of these two receptors in the realm of treating the cognitive deficits and negative symptoms that occur in schizophrenia.

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Conflicts of interest

There are no conflicts of interest.

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