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Altered excitatory-inhibitory balance in the NMDA-hypofunction model of schizophrenia

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Schizophrenia is a common psychiatric disorder of high incidence, affecting approximately 1% of the world population. The essential neurotransmitter pathology of schizophrenia remains poorly defined, despite huge advances over the past half-century in identifying neurochemical and pathological abnormalities in the disease. The dopamine/serotonin hypothesis has originally provided much of the momentum for neurochemical research in schizophrenia. In recent years, the attention has, however, shifted to the glutamate system, the major excitatory neurotransmitter in the CNS and towards a concept of functional imbalance between excitatory and inhibitory transmission at the network level in various brain regions in schizophrenia. The evidence indicating a central role for the NMDA-receptor subtype in the aetiology of schizophrenia has led to the NMDA-hypofunction model of this disease and the use of phencyclidines as a means to induce the NMDA-hypofunction state in animal models. The purpose of this review is to discuss recent findings highlighting the importance of the NMDA-hypofunction model of schizophrenia, both from a clinical perspective, as well as in opening a line of research, which enables electrophysiological studies at the cellular and network level *in vitro*. In particular, changes in excitation–inhibition (E/I) balance in the NMDA-hypofunction model of the disease and the resulting changes in network behaviours, particularly in gamma frequency oscillatory activity, will be discussed.

Keywords: network oscillations, gamma rhythm, phencyclidine, NMDA-hypofunction, interneurons

INTRODUCTION

Schizophrenia, which affects approximately 1% of the world population (Rossler et al., 2005), is characterized by episodic positive symptoms such as delusions, hallucinations, paranoia and/or psychosis and persistent and progressive negative symptoms such as flattened affect, impaired attention, social withdrawal, and cognitive impairments (Ban et al., 1984; Pearlson, 2000). It has been the dopamine hypothesis that has originally provided much of the momentum for neurochemical research in schizophrenia. It maintains that dysfunction of the dopamine neurotransmitter system underlies the behavioural abnormalities that accompany the disease. The dopamine hypothesis is based on the observation that drugs effective in treating schizophrenia share the common feature of blocking dopaminergic receptors, thereby alleviating positive and negative symptoms (Anden et al., 1970). However, altered levels of dopamine or dopamine receptors have not generally been observed upon post-mortem examination of the brains of schizophrenic patients (Knable et al., 1994) and it has since been proposed that the dopaminergic overactivity may be secondary to primary changes in other neurotransmitter systems (Coyle, 2004). Negative symptoms are less responsive to the current treatments with typical and atypical neuroleptic D_2-receptor antagonists, furthermore suggesting a non-dopaminergic mechanism underlying these components of the symptomatology (Kirkpatrick et al., 2001).

In many clinical cases, second-generation neuroleptics have been suggested to be a more effective and less side-effect-riddled treatment option, than typical antipsychotics, acting via a combination of dopaminergic and serotonergic antagonism. 5-HT-receptor antagonism seems to be essential in alleviating hallucinations and other positive schizophrenic symptoms in a more effective way (Jones et al., 1998). The dopamine/serotonin hypothesis has been examined in many post-mortem studies of schizophrenic brain tissue (Hashimoto et al., 1991; Mita et al., 1986), as well as in pharmacological studies (Krystal et al., 1993). However, the results similarly remain inconclusive. This has prompted the proposition that the neurochemical pathology is not limited to monoaminergic systems and that those changes may rather be secondary knock-on effects. In recent years, the attention has therefore shifted to the glutamate system, the major excitatory neurotransmitter in the CNS (Coyle, 2006). Since the proposition of the influential NMDA-hypofunction theory (see below) and the research which followed, increasing lines of evidence point at an abberant glutamate system in schizophrenia. Phencyclidine animal models, in which a NMDA-hypofunction state is induced, enable the testing of research hypotheses of the NMDA-hypofunction model at the molecular, cellular and network level.

The purpose of this review is to summarize recent findings from work on these animal models with special emphasis on the role of altered E/I balance on aberrant network activity in NMDA-hypofunction models of schizophrenia.

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THE NMDA-HYPOFUNCTION THEORY AND GLUTAMATERGIC ANIMAL MODELS OF SCHIZOPHRENIA

There are four main lines of research which provide strong evidence in favour of pathological changes in the glutamatergic system in schizophrenia, specifically at the level of the NMDA-receptor subtype (Mouri et al., 2007). These are pharmacological studies using NMDA-receptor antagonists (Morris et al., 2005), brain imaging studies (Ohrmann et al., 2007; van Elst et al., 2005), genetic studies (Eisener et al., 2007; Harrison and Owen, 2003; Tan et al., 2007) and postmortem investigations (Akbarian et al., 1996; Dracheva et al., 2001; Guilarte et al., 2008).

The mounting evidence indicating a central role for glutamate and the NMDA-receptor subtype in the aetiology of schizophrenia has, in the mid-90s, led to proposition of the influential NMDA-hypofunction model of schizophrenia (Olney and Farber, 1995). It suggests that schizophrenia is associated with a loss of NMDA receptors, particularly on interneurons. The theory pertains, that this loss of inhibition leads to a secondary overstimulation in the glutamatergic and monoaminergic neurotransmitter systems. Taken together, the dopamine/serotonin hypothesis and glutamate hypothesis are in the process of being empirically unified and recent developments point towards a complex interaction of the dopaminergic and glutamatergic systems in schizophrenia (Carlsson et al., 1999; Flores and Coyle, 2003; Javitt and Zukin, 1991). Whereas numerous lines of research have aimed at identifying mechanisms by which the glutamate system influences dopaminergic neurotransmission, causing the dopamine-associated symptoms treatable with classical and non-classical antipsychotics, Olney et al. (1999) suggest that the dopaminergic system can exert a major functional influence over the NMDA system, thereby explaining the efficacy of dopaminergic antagonists by an indirect action on the glutamate system (Olney et al., 1999). The mechanism they propose is that D_2-receptors may regulate glutamatergic transmission, thereby reinstalling the normal levels of glutamate activation (Sesack et al., 2003).

One further consequence of NMDA-hypofunction is an excessive release of glutamate (Adams and Moghaddam, 1998; Moghaddam et al., 1997), as well as acetylcholine (Kim et al., 1999) in cortical regions. One assumption of the NMDA-hypofunction theory is that this increased release of excitatory neurotransmitter leads to an overstimulation of downstream excitatory neurons, as well as to a further disinhibition through a lack of NMDA receptor excitation on interneurons and a consequent loss in overall network inhibition (Homayoun and Moghaddam, 2007). According to this model, this complex disinhibitory syndrome leads to a hyperstimulation in primary corticolimbic networks and to the development of positive and negative psychotic symptoms. The fact that loss of NMDA receptors is presumed to affect primarily cortical interneurons suggests that functional changes in network behaviour should result, representing a substrate underlying aspects of the schizophrenic symptomatology at the electrophysiological level. Since interneurons are involved in the generation, maintenance and timing of oscillatory patterns (for review see Bartos et al., 2007), which are thought to establish the temporal framework of cognitive processing, a loss of inhibition is likely to functionally compromise these complex population activities and thereby cause a range of cognitive symptoms.

The NMDA-hypofunction theory can also account for the developmental vulnerability associated with schizophrenia, as well as for its typical age of onset in early adulthood (Thompson et al., 2004). Thus it has been shown, that during the early developmental stage of synaptogenesis, neurons carrying NMDA receptors are extremely sensitive towards the level of glutamatergic activation they receive, reacting with excitotoxic neurodegeneration towards excessive levels (Ikonomidou et al., 1989) and with apoptosis towards deficient glutamate stimulation (Ikonomidou et al., 1999). Therefore an imbalance in glutamate concentrations during this stage, which could be triggered by a simple mechanism such as *in utero* compression of the umbilical cord, will lead to a selective loss of NMDA-bearing neurons, resulting in a structurally implemented NMDA-hypofunction state (Olney et al., 1999). This vulnerability is assumed to come into play only in early adulthood, when further developmental processes, such as synaptic pruning, render the brain susceptible to these disease factors (Granger, 1997). It has been shown that the systemic application of phencyclidines during development can lead to neurodegenerative patterns in corticolimbic regions (Corso et al., 1997; Ellison, 1994; Ellison and Switzer, 1993; Wozniak et al., 1998), which resemble the structural changes associated with schizophrenia (Heckers et al., 2002; Konradi and Heckers, 2001).

PHENCYCLIDINE MODELS OF SCHIZOPHRENIA

Already in the 1950s it had been recognized that the anaesthetic compound phencyclidine could induce positive and negative symptoms which closely resemble those observed in schizophrenic patients (Javitt and Zukin, 1991; Luby et al., 1959). Later it was conclusively shown that the mechanism behind these effects was the blockade of the glutamatergic NMDA receptor (Lodge and Anis, 1982).

Early studies suggested aberrations in glutamate levels in schizophrenic patients (Kim et al., 1980), the ability of phencyclidine to mimic psychosis in healthy subjects and to induce an aggravation of the symptoms in schizophrenic patients (Lahti et al., 1995). These studies prompted the use of NMDA-antagonists, such as ketamine or MK-801, as model systems for schizophrenia and the proposition of a glutamatergic/NMDA-related disease mechanism in schizophrenia. Phencyclidines are non-competitive antagonists of the N-methyl-D-aspartate subtype of glutamate receptor and protect cortical neurons against ischemia. Paradoxically, phencyclidines produce neurotoxic effects in corticolimbic regions, including neurons of the entorhinal cortex (EC) (Olney et al., 1989). The mechanisms underlying these paradoxical effects and their potential relationship to psychotic symptoms are still unknown.

The use of phencyclidine models has also furthered our understanding of the pharmacological and functional points of convergence between the implicated monoaminergic neurotransmitter systems. Pharmacological studies have revealed that MK-801 increases dopaminergic and serotonergic neuronal activities in several brain regions (Hiramatsu et al., 1989; Loscher et al., 1991). Antipsychotic dopamine receptor antagonists are also effective in preventing phencyclidine-induced abnormal behaviour such as hyperlocomotion and stereotyped behaviours in animals (Kitaichi et al., 1994; Noda et al., 1995).

A number of phencyclidine compounds, such as dizocilpine, phencyclidine and ketamine have been used to model schizophrenia in rodents, either by acute or chronic systemic exposure or by focussing on the period of withdrawal after repeated application (Jentsch and Roth, 1999; Mouri et al., 2007). Acute and repeated exposure to phencyclidine induces positive symptoms such as increased locomotor activity (Nabeshima et al., 1983; Nagai et al., 2003) and supersensitivity in hyperlocomotion (Jentsch et al., 1998; Kitaichi et al., 1995), effects which can be reversed by typical and atypical neuroleptic medication (Kitaichi et al., 1994). Correlates of human negative symptomatology induced by NMDA-receptor antagonists include impairment in social interaction (Qiao et al., 2001; Sams-Dodd, 1995, 1996) and decreased motivation (Murai et al., 2007; Noda et al., 1995, 1997). Furthermore cognitive deficits can be observed in these animals, such as impairments in memory and learning (Abdul-Monim et al., 2003; Idris et al., 2005). Further evidence for the validity of the phencyclidine models of schizophrenia and the associated NMDA-hypofunctional state comes from recent studies, which show that the repeated exposure to ketamine can produce changes in the expression of hippocampal proteins, such as parvalbumin and nitric oxide synthase, similar to the changes seen in human schizophrenia (Keilhoff et al., 2004) and also mimic the changes of cortical gene expression seen in schizophrenics (Kaiser et al., 2004). Taken together this evidence indicates that acute and chronic phencyclidine animal models of schizophrenia induce

effects which are comparable to the human symptomatology and may be valuable in exploring the pathophysiology of schizophrenia (Braun et al., 2007; Enomoto et al., 2007; Rujescu et al., 2006; Wang et al., 2007).

Systemic injections of MK-801 or ketamine in mice and rats were therefore used as a model of the acute psychotic state, inducing the characteristic hyperlocomotion and stereotyped behaviours (Dugladze et al., 2004; Gloveli et al., 1997; Kehrer et al., 2007; Vaisanen et al., 1999). Systemic administration of MK-801 selectively alters the field potentials evoked in layer III of the medial EC (Gloveli et al., 1997). Moreover, phencyclidine may have an influence on signal transfer from the EC to the hippocampus (Dugladze et al., 2004). It was shown, that MK-801 causes disinhibition of layer III projection cells and may therefore cause strong, pathological activation of the direct layer III-CA1 pathway (Dugladze et al., 2004), a fact which indicates that changes at the network level may be a likely result. In a more recent study, the kainate-induced gamma frequency oscillations in the area CA1 were shown to be significantly increased in MK-801 pretreated animals, a finding in line with *in vivo* observations that systemically injected MK-801 leads to increased spontaneous gamma activity in freely behaving rats (Ma and Leung, 2000). Interestingly in this study the authors could block the behavioural effects of MK-801 and reverse the increases in CA1 gamma activity by applying muscimol, a GABA-A receptor agonist onto the medial septum. Since the DG and CA2/3 receive projections from the medial septum, whilst the septal input connectivity to CA1 stems mainly from horizontal and ventral diagonal band areas (Yoshida and Oka, 1995) this result demonstrates an indirect effect of the muscimol-induced changes on the electrical activity in CA1, mediated by other hippocampal subfields. This suggests that DG and CA3 network activity can have limiting effects on CA1 gamma activity, which is supported by *in vitro* findings showing that control slices with cut Schaffer collateral connections exhibited significantly more increased kainate-induced gamma band activity than slices which had been spared and in which the CA1 was not isolated from the CA3 synaptic input (Kehrer et al., 2007). A number of studies have shown that the CA1 region of schizophrenics is the least affected hippocampal subfield. This holds true for markers of glutamatergic activity (Gao et al., 2000; Harrison et al., 2003; Heckers et al., 2002) as well as GABAergic activity (Kalkman and Loetscher, 2003; Lewis et al., 2005). Therefore the hippocampus in schizophrenics is functionally compromised at the level of CA1 inputs, whilst sparing the CA1 circuit to a greater extend.

Similar to clinical observations, in the NMDA-hypofunction models of schizophrenia both increased (Kehrer et al., 2007; Pinault, 2008) and decreased gamma activities (Cunningham et al., 2006) have been demonstrated. Therefore, further investigation needs to be undertaken to address possible model- and region-specific alterations in the gamma network oscillatory activity in animal models of the NMDA-hypofunction state. Establishing the contingencies of increased versus decreased gamma band activity is of high importance since aberrant network oscillatory activity may underlie the cognitive decline observed in schizophrenic patients and may furthermore offer vital clues as to the relationship between positive and negative symptoms in schizophrenia at a network level (Bucci et al., 2007; Cho et al., 2006; Ford et al., 2007).

SCHIZOPHRENIA AND NETWORK OSCILLATORY ACTIVITY

Inhibition-based population activities

Oscillatory population activity can be observed in a number of different brain regions, occurring at different, characteristic frequencies associated with specific tasks (Buzsáki and Draguhn, 2004). Gamma and theta rhythms can coexist or occur separately in the hippocampal formation, in which they form major components of the recordable, rhythmic activity (Bragin et al., 1995; Csicsvari et al., 2003). In the hippocampus of rodents, theta rhythms (4–12 Hz) can be detected during exploration and walking (Vanderwolf, 1969; for review see Buzsáki, 2002), whilst gamma band activity (30–80 Hz) emerges during immobility, periods of rest and sleep. Network oscillations are thought to be important in sensory processing (Averbeck and Lee, 2004; Laurent and Davidowitz, 1994), motor programming (Murthy and Fetz, 1996) associative learning (Buzsáki, 2002) and attention (Jensen et al., 2007). Furthermore it has been proposed to be the key mechanism enabling perceptual binding (Roelfsema, 1998; Singer, 2001). It has been hypothesized that rhythmic population activity is the temporal framework in which patterns of neurons that fire concomitantly are grouped together, thereby enabling information to be presented via combinations of neuronal output patterns (Singer and Gray, 1995).

Inhibition based gamma oscillations in cortical and hippocampal slice preparations can be elicited in a number of ways, amongst them puff and bath application of kainate or carbachol, metabotropic glutamate receptor activation or high frequency tetanic stimulation protocols (Dugladze et al., 2007; Fisahn et al., 1998; Gloveli et al., 2005a; Mann et al., 2005; Whittington et al., 1995; for review see Bartos et al., 2007). Recent observations suggest that certain types of GABAergic interneuron have different and most likely unique roles in the generation and maintenance of oscillatory activity. It has been shown *in vitro*, that hippocampal oscillations also depend upon the specific orientation of the cross section, in such a way that longitudinal slices of hippocampus will show predominantly theta-frequent population activity, whilst the transverse slice preparation mainly exhibits gamma oscillations upon kainate receptor activation (Gloveli et al., 2005b). The reason for this is an orthogonal arrangement of interneuron microcircuits alongside the longitudinal and transverse axis, and the firing properties of certain classes of interneurons during theta and gamma frequency oscillations (Gloveli et al., 2005a; Kopell et al., 2007; Tort et al., 2007). Specifically the parvalbumin-containing, soma-inhibiting interneurons and the neuropeptide somatostatin-containing, distal dendrite-inhibiting interneurons fire at gamma and theta frequencies respectively in the active network, due to their intrinsic and synaptic properties, and are thought to play key roles in the generation of gamma and theta activity (Gloveli et al., 2005a; Mann et al., 2005; Somogyi and Klausberger, 2005).

Altered gamma oscillatory activity in schizophrenia

Since there is ample evidence for the importance of oscillatory population activity in perceptual processing, it has been proposed that some or all of the positive and cognitive symptoms may result from pathological changes in rhythmic network activity (Lee et al., 2003a). It is the finely-tuned and balanced interplay between excitation and inhibition which is thought to be crucial to the functioning of population activity, such as theta and gamma band activity (Bartos et al., 2007). Due to the extensive evidence indicating changes in the major neurotransmitter systems and subclasses of interneurons, it is reasonable to assume that the functional network behaviours which they support may be altered within the schizophrenic brain (Ford et al., 2007). The investigation of this assumption is somewhat hindered by the low resolution of the EEG at the level of subcortical structures. Phencyclidine animal models and *in vitro* electrophysiology may therefore offer a second route to investigating changes in population activity following the NMDA-hypofunction state.

It has been proposed that the cognitive impairments associated with schizophrenia may be related to a failure in integrating sensory inputs at the level of local and distributed neuronal circuits, firing in precisely timed rhythms (Lee et al., 2003b). The synchronous firing of large populations of neurons in cortical regions in the gamma frequency range has been proposed as a candidate mechanism for the integration of complex sensory percept and is also thought to be involved in higher-order memory functions. The cognitive symptoms observed in schizophrenia point at a failure in integrative processing, suggesting that mechanisms of gamma activity may be compromised in these patients (Herrmann and Demiralp, 2005).

Since interneurons are central to the genesis and maintenance of complex network behaviours, the proposed disinhibition caused by the NMDA-hypofunction state suggests the possibility of consecutive changes at the network level. Llinas and colleagues compared the EEG gamma

activity of patients with different neurological and psychiatric diseases with those of controls and found positive symptoms across conditions to be associated with increased amplitudes of gamma frequency activity (Llinás et al., 1999). A number of other pathologies were similarly found to be accompanied by unidirectional or bidirectional changes in gamma activity. Increased gamma activity has been noted in unmedicated children suffering from attention-deficit hyperactivity disorder (Yordanova et al., 2001) and in epilepsy patients (for review see Herrmann and Demiralp, 2005), whilst decreases in gamma activity were observed in Alzheimer's disease in regards to overall activity (Loring and Largen, 1985, for review see Herrmann and Demiralp, 2005) and in response to visual and auditory stimulation (Politoff et al., 1995, 1996). During mental tasks on the other hand, Alzheimer disease patients showed increased gamma activity (Loring and Largen, 1985) pointing at the complexity and regional specificity of changes in gamma frequent EEG rhythms in neurological disease.

A number of studies have shown changes in EEG activity in the gamma band in schizophrenic patients. Reduced gamma activity was found in stimulus-dependent responses in the auditory and visual cortex of schizophrenics (Clementz et al., 2003; Kwon et al., 1999; Lee et al., 2001; Spencer et al., 2008). Similarly changes in neuronal synchrony during high frequency activity have also been found in schizophrenics (Spencer et al., 2004). Although most studies have found reductions in gamma band activity in schizophrenics (Slewa-Younan et al., 2001), there appears to be a symptom specific pattern in the alterations in gamma activity indicating that increases in amplitude and power are associated with positive symptoms, particularly hallucinations and reality distortions, whereas negative symptoms, such as psychomotoric deficits are linked to decreased gamma activity (Baldeweg et al., 1998; Bucci et al., 2007). To determine the mechanisms of these changes at a molecular level, research now turns to phencyclidine animal models of schizophrenia.

GABAergic interneurons in schizophrenia

The major inhibitory neurotransmitter, GABA, was first implicated in the pathophysiology of schizophrenia by E. Roberts in 1972 (Roberts, 1972). Since his proposal, a role for GABA in the pathophysiology of schizophrenia continues to be formulated in the context of complex interactions between GABA and other neurotransmitter systems (Lewis and Moghaddam, 2006). An abnormality in GABAergic regulation of dopamine cell bursting has been postulated to underlie some of the symptoms of schizophrenia (Grace, 1991; Moore et al., 1999). Others have noted the direct modulation of the dopaminergic system by GABAergic neurons, a potential mechanism whereby an abnormality in the GABAergic system could be involved in the dopaminergic dysfunction in schizophrenia (Carlsson, 1988). In the original model, Olney and Farber (1995) proposed that the NMDA hypofunction state may either be caused by intrinsically hypofunctioning NMDA receptors or through the excitotoxic loss of NMDA receptor-bearing GABAergic neurons. Loss of GABAergic interneurons in the hippocampal formation, possibly secondary to excitotoxic injury (Benes, 1999) or to loss of glutamatergic neurons has also been hypothesized (Deakin and Simpson, 1997). A dysfunction of the 5-HT2A receptors on GABAergic interneurons in the frontal cortex has been proposed as a further putative site of pathophysiology in schizophrenia (Dean, 2001).

GABAergic interneurons can be broadly classified into several classes on the basis of different criteria, such as action potential firing properties, somato-dendritic architecture and axonal ramification pattern, neurochemical content, voltage and ligand-gated conductances as well as plastic changes in excitatory synaptic transmission (for reviews see Freund and Buzsaki, 1996; McBain and Fisahn, 2001). Functionally, at least three main GABAergic cell types coexist in hippocampal networks: perisomatic inhibitory neurons controlling the firing of principal cells, dendritic inhibitory interneurons regulating dendritic electrogenesis, synaptic input and Ca^{2+} signalling (Miles et al., 1996), and GABAergic cells specifically innervating other inhibitory interneurons (Miles et al., 1996; Somogyi and Klausberger, 2005).

Previously it has been reported that phencyclidines induce paradoxical neurotoxic changes in specific layers of the cingulate and retrosplenial cortices (Olney et al., 1989). It was speculated that specific NMDA-receptor-subtypes on GABAergic interneurons could be responsible for loss or impairment of inhibition in the cingulate cortex and other subcortical regions of patients with schizophrenia (Olney and Farber, 1995). In line with this, interneurons in the entorhinal cortex receive strong NMDA receptor-mediated input (Jones and Buhl, 1993) whereas some other interneurons (e.g. some hippocampal GABAergic cells) may have low synaptic NMDA receptor content (Nyíri et al., 2003) or not have NMDA receptors at all (McBain and Dingledine, 1993). These differences may contribute to regional vulnerabilities in phencyclidine-induced neurotoxicity, as well as to subtle changes in network behaviours produced by selective alterations in subpopulations of interneurons. The chandelier or axo-axonic subclass of GABAergic interneurons containing the calcium binding protein parvalbumin have attracted the most scrutiny in studies of schizophrenia (Behrens et al., 2007; Howard et al., 2005; Sakai et al., 2008; Wang et al., 2007). This cell type provides inhibitory synapses at the axon initial segments of principal cells very close to the site of action potential generation, and thus is positioned to powerfully regulate the output of pyramidal cells (Howard et al., 2005). Recent results furthermore indicate that chandelier cells may also act as uniquely powerful excitatory neurons in the neocortex, instead of solely inhibiting the axon initial segments of pyramidal cells (Szabadics et al., 2006). Therefore, the functional consequences of their alterations in schizophrenia remain unclear.

Determining the causes and consequences of altered GABAergic transmission in the cortical and hippocampal networks of schizophrenics requires knowledge of which subpopulations of GABAergic neurons are affected. Interneuron alterations in schizophrenia, especially parvalbumin and somatostatin containing interneurons are likely to have significant effects on the network oscillatory activity and therefore on cognitive processes depending on the integration of neuronal signals in the brain (Gonzalez-Burgos et al., 2007; Morris et al., 2008). However, extensive functional studies of specific interneuron populations at the cellular and systems level in different brain regions were hampered by the difficulty of identifying these neurons during experiments. Using enhanced green fluorescence protein expressing mice under the control of different (e.g. parvalbumin or somatostatin) gene promoters has significantly facilitated the identification of these types of cells in the acute slice preparation (Meyer et al., 2002; Oliva et al., 2000). In addition, given the relative ease with which oscillatory activity can be induced in slice preparations, it follows that these network activities and the participating interneurons can be investigated *in vitro* in NMDA-hypofunction models (see e.g. Behrens et al., 2007; Braun et al., 2007; Cunningham et al., 2006), thereby increasing our understanding of complex electrophysiological behaviours in the NMDA-hypofunction model of schizophrenia.

CONCLUSIONS AND PERSPECTIVES

The potential of phencyclidines in mimicking schizophrenia has led to their use in the development of animal models, enabling researchers to investigate the predictions of the NMDA-hypofunction theory *in vivo* and *in vitro*. It has thus become possible, with the use of these models, to investigate the electrophysiological changes observed in schizophrenia, thereby increasing our knowledge of the electrophysiological implications of NMDA-hypofunction at the cellular and network level. In order to assess the functional mechanisms underlying changes in population activity in schizophrenic patients at the cellular and network level *in vivo* and *in vitro* investigation of these properties in phencyclidine animal models of schizophrenia constitute a novel and powerful approach, which can advance our knowledge of the interface between cognitive processing and cortical cellular and network activity.

CONFLICT OF INTEREST STATEMENT

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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