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Invited review

NMDA receptors, cognition and schizophrenia – Testing the validity of the NMDA receptor hypofunction hypothesis☆

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ABSTRACT

Cognitive dysfunction is core to schizophrenia, and remains poorly treated by existing therapies. A prominent hypothesis suggests that many symptoms arise from N-methyl-D-aspartate receptor (NMDAR) hypofunction. Subsequently, there has emerged a widespread use of many preclinical and clinical NMDAR antagonist models in the search for novel treatments. Clinically, ketamine is broadly purported to induce cognitive symptoms similar to those of schizophrenia. Preclinically, acute, sub-chronic and neonatal NMDAR antagonist administration models are all utilised in this context, as well as NMDAR transgenic animals. In this review, key strengths and weaknesses of each of these approaches are described with regard to their ability to recapitulate the deficits seen in patients. Given the breadth of literature and vogue for research in this topic, instances of NMDAR antagonist effects in the desired domains can readily be found preclinically. However, it is surprisingly difficult to identify any single aspect of cognitive function that possesses complete translational integrity. That is, there does not seem to be an NMDAR antagonist regimen proven to engage NMDARs equivalently in humans and animals that reliably produces the same cognitive effects in each species. This is likely due to the diverse range of techniques and models used by preclinical researchers, a paucity of research describing pharmacokinetic–pharmacodynamic relationships of NMDAR antagonist regimens, little capability to measure target engagement, and the lack of harmonized procedures between preclinical and clinical studies. Realizing the potential of the NMDAR hypofunction hypothesis to model cognitive impairment in schizophrenia will require some of these issues to be addressed.

This article is part of a Special Issue entitled 'Schizophrenia'.

1. Cognitive dysfunction in schizophrenia

Impaired cognition is increasingly recognized as a core feature of schizophrenia and is thought to be intrinsic to its pathogenesis (Elvevag and Goldberg, 2000). Cognitive impairments often precede the first psychotic episode (Erlenmeyer-Kimling et al., 2000), are stable over time (Albus et al., 2002; Reichenberg et al., 2010) and strongly correlate with functional outcome (Green et al., 2000; Green and Nuechterlein, 2004). Existing therapies do not treat these aspects of the disease adequately, in part reflecting the generalized nature of schizophrenic deficits which span several neuropsychological domains (Heinrichs and Zakzanis, 1998). Consequently, initiatives like Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) (Green et al., 2004a,b) and its descendant Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) (Barch et al., 2009) have been established to help focus and guide research in this context. MATRICS and CNTRICS identify several broad cognitive domains as commonly altered in schizophrenic patients: attention/vigilance; speed of processing; working memory; learning and memory; executive control and social/emotional cognition (Nuechterlein et al., 2004; Barch et al., 2009).

Abbreviations: HV, human volunteer; NMDA, N-methyl-D-aspartate; NMDAR, N-methyl-D-aspartate receptor; PCP, phencyclidine.

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Resolution of the cognitive symptoms of schizophrenia into different neuropsychological domains offers advantages to the researcher. Clinically, it facilitates testing of hypotheses to determine whether specific aspects of cognition have greater impact than others on the daily activities of patients, thus highlighting their significance from a therapeutic approach. For instance, the cognitive domains of attention, working memory, and learning and memory appear to be highly correlated with everyday life dysfunction (Bryson and Bell, 2003; Green, 1996). Preclinically, MATRICS and CNTRICS domains help define the scope and breadth of assays required to equip a translational cognitive test battery in rodents that is not only essential for predicting efficacy, but also for actually determining the validity of animal assays of cognition and schizophrenia disease models themselves.

2. The NMDA receptor hypofunction hypothesis

The aetiology of schizophrenia is currently unknown. Since it is unlikely that a naturally occurring homologue of the disease occurs in non-human species, researchers wishing to identify novel treatments resort to the use of animal models, of which there are no shortage. Tens of animal models of schizophrenia exist, utilizing pharmacological, genetic, environmental and lesioning manipulations, or a combination of these approaches (Carpenter and Koenig, 2008; Marcotte et al., 2001). Such models provide a means to recapitulate aspects of schizophrenic pathology and/or the behavioural syndrome in animals, with different models being more informative of specific aspects over others (e.g. positive symptoms versus negative symptoms). The NMDA receptor hypofunction hypothesis of schizophrenia originates from the discovery that administration of NMDA receptor antagonists, such as phencyclidine (PCP) and ketamine, to schizophrenic patients exacerbated their core psychotic and cognitive symptoms (Lahti et al., 1995; Luby et al., 1959; Malhotra et al., 1997) and induced a similar psychotic state in human volunteers (HVs) (Adler et al., 1998; Hetem et al., 2000; Javitt and Zukin, 1991; Krystal et al., 1994, 2000; Malhotra et al., 1996; Newcomer et al., 1999; Parwani et al., 2005; Rowland et al., 2005). Now, several other lines of evidence suggest that NMDA receptors are involved (Javitt and Zukin, 1991; Kristiansen et al., 2007; Olney and Farber, 1995a,b). This has led to one of the most commonly used rodent and non-human primate models of schizophrenia in which it is assumed that the administration of NMDA receptor antagonists will induce homologous symptoms to those seen in HVs given the drugs, and more importantly, to the symptoms exhibited by schizophrenics themselves. A secondary intent is often to induce other neurophysiological disruptions in animals, such as EEG or BOLD signal changes, that are also measurable in HVs and patients (Boeijinga et al., 2007; Ehrlichman et al., 2009; Lahti et al., 1995; Lazarewicz et al., 2010; Littlewood et al., 2006; Northoff et al., 2005; Oranje et al., 2000; Pinault, 2008). One of the greatest attractions of the NMDAR hypofunction hypothesis and resultant NMDAR antagonist administration models lies in their translational potential, i.e. the ability to systematically test and exploit them across schizophrenic, HV and non-human studies. However, despite their extensive use, translational validity in the context of cognition and schizophrenia (i.e. the extent to which the administration of an NMDA receptor antagonist in a non-human species reproduces aspects of cognitive dysfunction as observed in HV and patient studies) is not well defined. The purpose of this review is to examine critically key publications in order to highlight some present strengths and weaknesses of the NMDAR hypofunction hypothesis and identify possible paths for future research. The relative merits of several variants of the basic NMDAR antagonist model will be discussed, including acute, subchronic, neonatal and transgenic approaches. Practical aspects of translational validity, crucial for efficient operation of drug discovery efforts, will also be a prominent discussion point.

3. Acute ketamine administration in human volunteers (HVs)

Since PCP was withdrawn from the clinical formulary because of abuse liability and neurotoxicity concerns (Olney et al., 1991, 1995a,b), ketamine has emerged as the prototypical NMDAR antagonist in HV studies. Research during the last two decades has demonstrated that a single dose of ketamine administered to HVs produces cognitive deficits resembling some aspects of schizophrenia (Adler et al., 1998; Hetem et al., 2000; Krystal et al., 1994, 2000; Malhotra et al., 1996; Newcomer et al., 1999; Parwani et al., 2005; Rowland et al., 2005). Ketamine-induced deficits have shown sensitivity to pharmacological attenuation (Anand et al., 2000; Krystal et al., 1999; Krystal et al., 2005), suggesting they might have value in the prediction of efficacy of novel therapies in patients. However, the quality and extent of cognitive disruption across studies is still unclear since the effects of acute ketamine (or PCP) in HVs has rarely been directly compared in the same study to the performance of schizophrenic patients across a broad cognitive test battery, much less the seven MATRICS domains. A PubMed search (Oct 12, 2010) with the terms “schizophrenia” and “ketamine” resulted in 303 hits. Of these, only one paper (Malhotra et al., 1997) had a design that allowed comparison of schizophrenic patients to HVs both following administration of an acute dose of ketamine. However, the goal of this paper was to investigate the interaction between disease state and sensitivity to ketamine-induced symptomatology. As such, a direct comparison between schizophrenic patients and ketamine HVs deficits was not conducted. Other work has been published investigating the resemblance between these two groups with regard to psychotic symptoms, but not cognitive symptoms (Lahti et al., 2001). A recent review has highlighted evidence for impairment in attention and working memory following acute ketamine administration, but less consistent effects for the domain of executive function (Morgan and Curran, 2006). One study of particular interest showed that ketamine impaired Wisconsin Card Sorting Test performance on first presentation of the test, suggesting that only acquisition of new rule-based information is specifically impaired and possibly not executive function in a more general sense (Krystal et al., 2000). Other reviewers have also concluded that acute ketamine disrupts acquisition, but not recall of previously learned information, and also disrupts manipulation of working memory content (Fletcher and Honey, 2006). Interestingly though, cognitive domains that are most reliably impacted by ketamine (working memory, visual/verbal learning and possibly attention) appear to be those that are more predictive of improvement in daily function in patients (Bryson and Bell, 2003; Green, 1996).

4. Repeated ketamine administration in human volunteers

Nearly all research on ketamine-induced cognitive effects in HVs has utilized acute dosing protocols. It has been suggested, however, that chronic administration of NMDA receptor antagonists may provide a more accurate model of aspects of schizophrenia in rodents, i.e. incorporating features such as enduring hypofrontality, psychosis and cognitive deficits in a drug free state (Jentsch and Roth, 1999). For obvious ethical reasons, the use of repeated dosing protocols in humans is not possible. Therefore, human evidence comes only from individuals who choose to self-administer ketamine repeatedly. Naturalistic studies are of course subject to many limitations, including poly-drug use confounds, pre-existing population differences, varying doses and purity of the

drug. In one of the few carefully controlled studies of the cognitive effects of chronic ketamine in humans (Morgan et al., 2009a,b), it was found that ketamine abusers, poly-drug control users and non-drug control subjects could not be statistically differentiated from each other, and that all performed better than first-episode schizophrenic patients in verbal learning and working memory tasks. In line with this, the first large-scale longitudinal study investigating how variations in ketamine use and abstention from prior use affect cognitive function has recently been completed (Morgan et al., 2009b, 2010). The main findings were that only frequent ketamine use (i.e. more than four times a week) was associated with impairment in episodic memory, working memory and aspects of executive function. Infrequent or recreational ketamine users (i.e. drug intake at least once a month) and ex-ketamine users (i.e. abstinent for a minimum of one month) showed increased delusional and dissociative symptoms, but did not show any cognitive impairment. Hence, when they can be detected, schizophrenia-like cognitive deficits observed in frequent ketamine users may be reversible upon cessation of ketamine use. In a subsequent study comparing the effects of an acute ketamine dose in frequent and infrequent users, ketamine caused learning and memory impairments in both groups shortly after administration. However, frequent users were still impaired three days later, suggesting frequent ketamine use might cause hypersensitivity to NMDAR blockade-induced cognitive deficits (Curran and Monaghan, 2001). Moreover, this cognitive disruption occurred long after ketamine cleared the body, indicating a temporal dissociation between cognitive disruption and exposure in frequent users. Overall, only with substantial limitations, including necessity for drug challenge and the potentially intractable heterogeneity and/or bias of populations on which these conclusions are necessarily based, do these data support that frequent ketamine use may model some of the cognitive deficits of schizophrenia.

5. Issues and challenges of human volunteer ketamine studies

Attempting to map ketamine-induced deficits in HVs to the generalized cognitive impairments of schizophrenia meets theoretical and practical challenges. As might be expected from a phenomenologically defined syndrome, the specific cognitive domains affected may vary considerably between schizophrenic patients despite a modicum of consistency across studies (Keefe and Fenton, 2007). As such, a particular dose of ketamine may only model impairment of a sub-population of schizophrenic patients, with little knowledge of how findings in these patients might apply to others. Conversely, while there might be some consensus regarding which cognitive domains can be impaired by ketamine, inconsistencies may arise from differences in plasma exposures between human volunteer studies, or from essentially unknown pharmacokinetic heterogeneity in ketamine abuser populations. Even when such factors are controlled, it is possible that the cognitive disruption induced by ketamine still varies between individuals, and possibly even within an individual over time. Test methodology is also a key concern: a broad yet precise cognitive battery with robust psychometric properties relating to the detection of deficits observed with ketamine and in schizophrenia is required. Whilst the Cambridge Neuropsychological Test Automated Battery (Barnett et al., 2010) and the MATRICS cognitive battery (Green and Nuechterlein, 2004; Nuechterlein et al., 2008) might serve as a basis to meet the exacting demands required, much work remains to be done to identify the most meaningful neuropsychological parameters on which to focus in order to achieve the preclinical to clinical connectivity necessary for successful drug discovery.

6. Acute administration of NMDAR antagonists in animals

A comparative analysis of the effects of acute NMDAR antagonists in animals to effects seen in man quickly becomes overwhelmed by some basic, yet frequently overlooked, factors. Firstly, two different NMDAR antagonists, PCP and MK-801, have been most frequently used in an essentially interchangeable manner in rodent behavioural studies, while ketamine has been used in non-human primates to induce a variety of cognitive disturbances (Buccafusco and Terry, 2009; Condy et al., 2005; Roberts et al., 2010a,b; Stoet and Snyder, 2006; Taffe et al., 2002a,b). In contrast, the use of ketamine in rodent studies is rare. Other available antagonists, such as APH and CPP, are even more infrequently employed in behavioural research, despite being favoured for electrophysiological, neurochemical and systems level studies (e.g. Bannerman et al., 2006). Secondly, even between these three compounds (ketamine, PCP and MK-801), different behavioural effects are often manifest (Dix et al., 2010; Gilmour et al., 2009; Smith et al., 2011). It is unlikely that studies using these different NMDA receptor antagonists can be readily assimilated into a single NMDAR hypofunction hypothesis model of schizophrenia. To add to this complexity, different doses of the same antagonist can produce disparate behavioural effects (Gilmour et al., 2009). Choice of dose is therefore critically important from the perspective of the specificity of a hypothesis for cognitive impairment versus other confounding variables. Finally, the dosing regimen itself may be a critical factor in determining the effects observed. Human studies typically employ one of several available intravenous infusion protocols of ketamine to achieve a steady state plasma exposure over a defined period (Clements and Nimmo, 1981; Domino et al., 1982; Hijazi et al., 2003). In contrast, non-human studies tend to use acute, parenteral bolus dosing of a range of NMDAR antagonists: it is not known whether lower, steady state exposures of NMDAR antagonists, equivalent to those achieved in humans, result in selective cognitive effects in animals.

7. The importance of target engagement

Comparing between NMDAR antagonists preclinically or within a single antagonist across species ideally requires a biomarker of target engagement to ensure equivalence of NMDA receptor occupancy. This approach is exemplified in psychiatric research by the relationship between occupancy of dopamine D2 receptors by therapeutic doses of atypical and typical neuroleptics, efficacy against positive symptoms of schizophrenia and the induction of extrapyramidal side effects (Farde et al., 1992; Kapur et al., 2000; Nordstrom et al., 1993; Wadenberg et al., 2001). Few attempts have been made to determine levels of occupancy by NMDAR antagonists required in the human brain to elicit psychotic or dissociative reactions (Stone et al., 2008), or cognitive disturbances (Hartvig et al., 1995), largely because of the paucity of available ligands or other methodologies for these studies (Bressan and Pilowsky, 2000; Stone, 2009). Equally, comparisons of the behavioural effects of different antagonists in animals have not yet taken differential receptor occupation over time into account. The incorporation of biomarker approaches into both clinical and preclinical studies of NMDAR antagonist effects represents a major gap that must be addressed.

8. Cognitive effects of acute administration of NMDAR antagonists in rodents

Many non-cognitive effects conspire to limit the translation of NMDAR antagonist effects from animals to man. Cognitive tests in rodents typically require the animal to use co-ordinated whole

body movements (e.g. swimming or locomotion) and/or perform complex motor sequences to solve lever-based operant tasks. Yet, NMDAR antagonists have marked effects on motor activity per se that increase in severity with increasing dose (Dix et al., 2010; Gilmour et al., 2009; Smith et al., 2011). This stands in contrast to the low motor demands of human cognitive tasks: typically verbal responses or small hand movements required to control a computer. Consideration also needs be given to the potential "bottom-up" effects of NMDAR antagonists on visuo-motor processes – a factor frequently overlooked in rodent studies despite oculomotor deficits being reported in HV ketamine studies (Avila et al., 2002; Radant et al., 1998; Weiler et al., 2000) and in schizophrenics (Braus et al., 2002; Chen et al., 2006). Motivational factors that drive performance are also different between species (food reward versus instruction and voluntary compliance), and may well be differently sensitive to pharmacological manipulation. The behavioural effects of acute NMDAR antagonist treatment in rodents (mainly rats) are described below in the context of the cognitive domains proposed by the MATRICS initiative. Consideration also needs to be given to the cross-species translational validity of the animal assays used to assess cognitive function. This important area is beyond the scope of this review; but for further reading please see Young et al. (2009) and Keeler and Robbins (2011).

8.1. Attention and vigilance

PCP, MK-801 and ketamine produce marked deficits on response accuracy in the five choice serial reaction time test (5CSRT) in the rat, with higher doses also producing a concomitant increase in omissions (Smith et al., 2011). Data from mice suggest PCP can induce a deficit in accuracy with a concomitant increase in anticipatory and perseverative responding, however this effect is strain-dependent (Greco et al., 2005). A pure attentional deficit in the 5CSRT could manifest as an effect on accuracy only (Robbins, 2002), however others maintain that a failure to respond (i.e. an omission) may also reflect an attentional deficit (Amitai and Markou, 2010). Clearly, this raises difficulties with regard to the dissociation of attentional from motoric deficits with this task. Likewise, data from the 2-lever sustained attention test (McGaughy and Sarter, 1995) also requires a multivariate appraisal: a selective effect on sustained attention should manifest as a decrease in hit rate only, but this has not been observed so far for acute doses of ketamine or MK-801 (Nelson et al., 2002; Slawecki and Roth, 2005; Oliver et al., 2009).

8.2. Speed of processing

Assessment of this domain requires animals to make an overt motor response contingent upon a sensory stimulus. Drugs that produce non-specific effects on sensory or motor function can therefore confound this measure by also increasing reaction time or latencies to respond. In some tasks, however, a selective effect on speed of processing can be inferred if there is separation between effects on response latency (time taken to make response) and magazine latency (time taken to collect food reward). Literature findings here are mixed and dependent on the task and NMDAR antagonist used. For instance, acute PCP has no effect on reaction times in a lateralized reaction time task (Jentsch and Anzivino, 2004), and neither PCP nor ketamine alter either correct or magazine latencies in a 5CSRT task (Smith et al., in press). This contrasted with the effect of MK-801, where a significant increase in correct response latency but not magazine latency was observed at 0.05 mg/kg s. Interestingly, the same profile was revealed with MK-801 in a delayed matching to position (DMTP) task.

8.3. Working memory

These paradigms are often intrinsically different in rodents and humans, as is the definition of working memory itself (see e.g. Baddeley, 1986; Dudchenko, 2004; Olton et al., 1979). Here we define it as the process required to maintain information over short delays (i.e. typically seconds) or whilst needed for more complex tasks; the term is frequently used inter-changeably with short-term memory. It has been claimed that a selective working memory impairment in operant delayed choice procedures should manifest as deficits at longer delays leaving performance at short delays intact (Dunnett, 1993). Again, acute effects of NMDAR antagonists on working memory appear to be task dependent. NMDAR antagonists typically produce delay-independent deficits in DMTP tasks in rats (Han et al., 2000; Smith et al., 2011; Stephens and Cole, 1996). Critiques of rodent DMTP argue that the task reflects the ability to withhold a response and resist interference from previous trials, whereas the core working memory deficit observed in schizophrenia more likely relates to the maintenance and manipulation of information during an interval (Jentsch, 2003; Young et al., 2009). The radial arm maze is a non-operant working memory task that does require maintenance of information during the trial period, but whilst MK-801 impairs performance, PCP does not (Huang et al., 2004; Marcus et al., 2005).

8.4. Learning and memory

Schizophrenics have deficits in immediate recall, delayed recall and recognition of non-verbal stimuli (Schretlen et al., 2007), although the nature and extent of this impairment is still under debate (Butler et al., 2008; Moritz et al., 2006; Skelley et al., 2008; Tek et al., 2002). In rodents, NMDARs are considered critical for hippocampal-dependent learning and memory (Morris et al., 1986; Morris, 1989; Tonkiss and Rawlins, 1991). Beyond the hippocampus, NMDAR antagonism produces deficits in Pavlovian conditioned approach behaviour and also in the acquisition, but not expression of appetitive instrumental learning (Baldwin et al., 2000; Di Ciano et al., 2001; Kelley et al., 1997; Morris et al., 1986; Pallares et al., 1995; van der Meulen et al., 2003). A wide range of NMDAR antagonists, including MK-801, PCP and ketamine, can block the acquisition of a visuo-auditory conditional discrimination, generally in the absence of motor confounds (Dix et al., 2010). Similarly, schizophrenic patients show impairments in the acquisition of conditional discriminations (Hofer et al., 2001). The most widely used test for assessing recognition memory and arguably, mnemonic function generally in this context, is the novel object recognition test (Ennaceur and Delacour, 1988). PCP, ketamine and MK-801 have all been reported to disrupt performance (de Lima et al., 2005; Goulart et al., 2010; Snigdha et al., 2010). However, use of this task is questionable due to confounds in interpretation of the data (Sarter, 2004) and poor predictive validity (Young et al., 2009).

8.5. Executive control

The attentional set shifting task (Birrell and Brown, 2000) and reversal learning tasks (Abdul-Monim et al., 2003; Widholm et al., 2001) are the predominant assays used to assess this domain. For set shifting, the limited published data available suggests that the extra-dimensional (ED) shift of the IDED "digging" task is impaired following acute administration of PCP 24 h prior to test (Egerton et al., 2005). Similar effects are seen with an acute dose of ketamine some hours after dosing (Nikiforuk et al., 2010). Operant reversal studies, in contrast, appear to be more sensitive to acute administration of NMDAR antagonists (Abdul-Monim et al., 2003,

2006; van der Meulen et al., 2003). Dix et al. (2010) similarly showed significant effects of PCP and MK-801 in reversal of a visuo-auditory conditional discrimination, yet ketamine failed to produce a significant deficit in this paradigm. It is interesting to contrast these data with a recent report that when patient IQ is accounted for, set shifting performance is normal on all but reversal measures in schizophrenics (Leeson et al., 2009).

8.6. Social cognition

Deficits in social and emotional cognition are a core diagnostic feature of schizophrenia, and likely have critical involvement in determining the functional capacity of patients (Couture et al., 2006), yet translational measures in rodents have been paid little attention. In rats, acute administration of ketamine and PCP have been reported to produce deficits in social interaction (Becker and Grecksch, 2004; Sams-Dodd, 1998). Furthermore, both MK-801 and PCP can impair social recognition processes (Hlinak and Krejci, 1994). However, it may be debated whether such tasks are assessing a form of social cognition that is relevant to the human situation (Young et al., 2009).

9. Subunit selective NMDAR antagonists

Few antagonists with significant selectivity for NMDA receptor subtypes are available for study *in vivo* in animals or man. However, GluN2B preferring antagonists such as CP 101,606 and Ro 25–6981 clearly differentiate from PCP and ketamine and exhibit a potential pro-cognitive profile in otherwise normal animals in assays of sustained attention and working memory (Dix et al., 2010; Higgins et al., 2003, 2005; Smith et al., 2011). However, pro-cognitive effects are accompanied by increases in impulsive responding, and generalisation to PCP cues in drug discrimination paradigms (Chaperon et al., 2003; Nicholson et al., 2007). These latter aspects are often considered as potential indication of psychotomimetic liability. It is interesting to consider whether the "gain of function" observed in rats with GluN2B antagonists would translate in a positive or negative manner to humans – clearly another major gap in our knowledge.

10. Subchronic administration of NMDAR antagonists in animals

A key question is whether the consequences of repeated dosing with NMDAR antagonists offers a model of schizophrenia with greater validity and/or practical utility than can be achieved with acute administration, especially given the more recent work questioning its validity at the clinical level (see Section 4). In the rodent and monkey prefrontal cortex, repeated rather than acute treatment with PCP resembles the neuroanatomical and neurochemical changes observed in schizophrenics more closely (Abdul-Monim et al., 2006; Abi-Dargham and Moore, 2003; Cochran et al., 2003; Enomoto et al., 2005; Hajszan et al., 2006; Jentsch et al., 1997a,b; Lehrer et al., 2005; Murai et al., 2007; Reynolds et al., 2004; Tsukada et al., 2005), although not all work is in agreement here (Cochran et al., 2003; Van Elst et al., 2005). Acute PCP administration increases local cerebral glucose utilization use (Miyamoto et al., 2000) and enhances prefrontal dopamine and glutamate release (Adams and Moghaddam, 1998) whereas the reverse has been found following repeated dosing. A potential practical advantage of subchronic modeling is that it can enable testing in the absence of a challenge dose of NMDAR antagonist (and potentially in the absence of the consequent motor confounds), although not all studies exploit this possibility.

11. The impact of methodological differences

Moving from acute to repeated drug treatment offers a bewildering array of possible experimental designs: which drug, dose, route of administration, frequency of dosing per day, for how many days with testing when and for how long after termination of dosing? The number of possible variables makes comparison of data and evaluation of reliability and reproducibility difficult. The majority of animal studies investigating the effects of subchronic treatment with NMDAR antagonists utilize PCP as a challenge drug, although studies with ketamine or MK-801 (Ahn et al., 2009; Lannes et al., 1991; Maxwell et al., 2006; Tsukada et al., 2005; Zuo et al., 2007) have also been reported. The development of abstinence models in animals originated from early human work observing a long-lasting effect on function during abstinence from chronic ketamine use (Allen and Young, 1978; Jansen, 1990). However, recent studies suggest that this might not always be the case and those cognitive deficits can in fact be rather short lasting (Morgan et al., 2009a). To add to this complex picture, some animal studies test following repeated NMDAR antagonist administration while still exposed to drug. Other studies test animals on the day following completion of the regimen. Other studies again, probably reflecting the majority of recent publications, test animals after several (often 5–7) days following the last treatment, i.e. under abstinence conditions. This suggests that rodent abstinence models might engage fundamentally different processes from those that operate in ketamine abusers.

12. Cognitive effects of repeated administration of NMDAR antagonists in rodents

Repeated treatment with PCP and testing in abstinence can lead to impaired performance across a variety of preclinical tests relevant to cognitive domains impaired in schizophrenia. At the level of attentional processing, deficits in accuracy in the absence of increased latency to obtain reward have been observed in 5CSRT performance (Amitai et al., 2007; Amitai and Markou, 2009). The monkey oculomotor delayed response task (Tsukada et al., 2005) and rat T-maze delayed alternation (Jentsch et al., 1997b; Seillier and Giuffrida, 2009) suggest deficits in working memory. On the other hand, rat T-maze delayed alternation performance is unchanged (Stefani and Moghaddam, 2002), and preserved function has been seen in a radial arm maze reference memory task (Li et al., 1997), while novel object recognition (Damgaard et al., 2010; Grayson et al., 2007; Harte et al., 2007; Hashimoto et al., 2005; Idris et al., 2010; McLean et al., 2009a,b; Nagai et al., 2009; Pichat et al., 2007), and water maze acquisition is impaired (Didriksen et al., 2007; Mandillo et al., 2003; Podhorna and Didriksen, 2005). Finally, for the domain of executive function, impaired reversal learning (Abdul-Monim et al., 2006; Idris et al., 2010; McLean et al., 2009a,b), and deficits in ED shifting (Broberg et al., 2009; Goetghebeur and Dias, 2009; McLean et al., 2008; Rodefer et al., 2005) have been found. Note, however, that not all studies find effects on executive function (Fletcher et al., 2005). Also, another study has failed to see set shifting impairment after 33 days of PCP treatment (Deschenes et al., 2006). Overall, subchronic regimens can lead to impaired performance across a variety of preclinical tests relevant to cognitive domains impaired in schizophrenia, although reproducibility of effects is not guaranteed.

13. Neonatal administration of NMDAR antagonists in animals

Neonatal administration of (usually) PCP or MK-801 is an evolution of the standard NMDA hypofunction hypothesis,

incorporating a neurodevelopmental element (Deutsch et al., 1998; Fatemi and Folsom, 2009; Lewis and Levitt, 2002). It may also be referred to as the perinatal or postnatal model in the literature. The model applied to rats and mice aims for increased construct validity by triggering drug-induced changes during early development that subsequently cause molecular, anatomical and behavioural abnormalities during adolescence and adulthood. In general, the treatment period focuses on the first two weeks of postnatal life of the rat, which correspond to the second late trimester in human pregnancy in neurodevelopmental terms (Clancy et al., 2001). NMDARs are hypersensitive during this period (Ikonomidou et al., 1989). Given their role as primary mediators of glutamatergic fast excitatory neurotransmission in the brain, NMDAR activation during this period is critical for processes such as neuronal survival, differentiation, network formation and cell migration. Indeed, neonatal manipulation with PCP or MK-801 in rodents results in increased neurodegeneration (Ikonomidou et al., 1999; Harris et al., 2003; Wang et al., 2003; Wang and Johnson, 2005), disturbed cortical lamination (Reiprich et al., 2005) and a decrease in parvalbumin-positive cells and spine density (Nakatani-Pawlak et al., 2009; Wang and Johnson, 2005). Experimental protocols for rats usually schedule daily dosing at postnatal days (PND) 7, 9, 11 with 10 mg/kg PCP or at PND 7–10 with 0.5 mg/kg MK-801. Animals are subsequently assessed for phenotypic abnormalities within a large time window, spanning from around PND 35 up to PND 100 and beyond. Alterations to these protocols have been described where doses administered can be up to 2-fold greater than those mentioned above, and the number of treatment days can be as many as fourteen. Note that these are high, potentially neurotoxic doses compared to acute administration protocols.

14. Cognitive effects in neonatal NMDAR models

Despite differences in dosing protocols, neonatal NMDAR antagonist treatment has been shown to cause deficits in preattentive processing, working memory, executive function and social cognition. To the knowledge of the authors, little data is available with respect to attentional readouts, although one study shows slower acquisition of the 5CSRT (Le Pen et al., 2003). Neonatal PCP treated rats show deficits in working memory and reversal learning tasks in the Morris water maze, but only modest or no disruption during acquisition (Andersen and Pouzet, 2004; Nakatani-Pawlak et al., 2009; Secher et al., 2009). Working memory may also disrupted in a delayed-non-match-to-position task by neonatal PCP administration (Kawabe and Miyamoto, 2008), although these results suggest that the impairment is delay-independent. In contrast to the water maze data described above, neonatal MK-801 treatment impairs acquisition of a spatial memory task (Gorter and de Bruin, 1992; McLamb et al., 1990). A deficit in executive function, as assessed by the attentional set shifting assay, is inherent to both neonatal PCP and MK-801 treatment (Broberg et al., 2008, 2009; Stefani and Moghaddam, 2005). Finally, impairments in novelty discrimination were observed in a social recognition task following neonatal PCP treatment (Boulay et al., 2008; Harich et al., 2007; Pichat et al., 2007; Terranova et al., 2005).

15. NMDAR transgenic approaches

Mutant mice represent alternative tools with which to explore the role of NMDARs in the pathophysiology of schizophrenia. Numerous NMDAR mutant and transgenic lines are available, and given the lack of subtype selectivity of PCP, MK-801 and ketamine, researchers have to decide which NMDAR subunit to manipulate in either a constitutive or conditional manner. Constitutive knockout mice continually and ubiquitously express their mutation from conception and likely provide most information about the involvement of the gene/protein under question during developmental processes. The downside is that these mice cannot avoid confounding compensatory processes (Nakajima and Tang, 2005). Alternatively, in conditional transgenic animals mutations can be spatially restricted to selected brain regions or cell types and/or temporally restricted to specific developmental stages. Furthermore, inducible knockouts allow control of the temporal expression of mutations, which can be switched on and off by the experimenter (Beglopoulos and Shen, 2004; Bockamp et al., 2002). More subtle transgenic manipulations like this permit more selective testing of hypotheses about gene/protein function, and arguably may be more relevant from the perspective of modeling cognitive impairments in schizophrenia. So far, nearly all NMDAR mutants (whether constitutive or conditional) have been generated for use in studies of learning and memory processes, rather than the role of NMDARs in schizophrenia. Thus, systematic pharmacological, neurophysiological and MATRICS-like cognitive characterization is more often than not missing for any particular mutant. All of the usual caveats relating to the use of transgenic animals apply here, and careful consideration of many ancillary features of the work is required before truly meaningful comparisons between studies and models can be accomplished (Bailey et al., 2006; Linder, 2006).

16. Constitutive, conditional and inducible NMDAR phenotypes

Constitutive GluN1-knockdown mice exhibit an approximate 90% decrease in global brain expression of the GluN1 subunit (Mohn et al., 1999), and show a schizophrenia-like reduction in brain metabolism in prefrontal cortex and in hippocampus (Duncan et al., 2002). Although cognitive characterization of these mice remains incomplete, several impairments have been described. Notably, working memory deficits are detected during radial-maze performance (Dzirasa et al., 2009). Neurophysiological approaches applied to these mice also suggest potential deficits in selective attention processes (Bickel et al., 2007). GluN1-knockdown mice exhibit tendencies towards social withdrawal as demonstrated by general behavioural assessment, resident-intruder and social preference models (Duncan et al., 2004; Halene et al., 2009; Mohn et al., 1999). Overall, it would be worthy for constitutive GluN1-knockdown mice to receive a broader characterization as required to determine their true value in modelling cognitive disruption in schizophrenia.

Considering the role that cortico-limbic abnormalities might play in schizophrenia (Tamminga and Holcomb, 2005), selective transgenic manipulation of NMDARs in these brain regions may prove informative. Recently, a mouse line has been generated with selective postnatal ablation of GluN1 subunits in approximately 50% of hippocampal and cortical interneurons (Belforte et al., 2010). Some schizophrenia-like cognitive disruptions are present, including mnemonic deficits in Y-maze and social recognition tasks. In addition, a social withdrawal phenotype is accelerated by social isolation in these animals, highlighting a genotype-$\times$ environment interaction possibly akin to those proposed in some human studies (Van Os et al., 2008). Other conditional mutants exist lacking only hippocampal GluN1 or GluN2B subunits. Hippocampal-forebrain GluN2B or hippocampal CA1-GluN1 deficient mice show deficits in a diverse range of spatial and non-spatial memory tasks such as the Morris water maze and novel object recognition (Rampon et al., 2000; Tsien et al., 1996; von Engelhardt et al., 2008). Deletion of the GluN1 subunit in the dentate gyrus, or the GluN2B subunit in both CA1 and dentate gyrus induces working memory and reversal learning deficits without

affecting reference memory (Niewoehner et al., 2007; von Engelhardt et al., 2008). Several other studies suggest that lack of hippocampal NMDARs impair the rapid processing and flexible use of contextual information (Huerta et al., 2000; McHugh et al., 2007; McHugh and Tonegawa, 2009; Nakazawa et al., 2002, 2003; Rajji et al., 2006; Rondi-Reig et al., 2006), a profile with resemblance to that observed in patients. To the knowledge of the authors, only one animal with selective knockdown of prefrontal GluN2B subunits has been generated (Zhao et al., 2005). These animals display impairments in contextual fear memory processing, but otherwise remain poorly characterized.

Genetic modification of NMDA receptors thus offers a potentially valuable approach to modeling schizophrenic symptoms in mice. However, it is too early to know which gene(s) to focus on or whether a constitutive or conditional approach is the best one to take.

17. Conclusions

The authors of this review have been brought together under the auspices of the European Union's Innovative Medicines Initiative (IMI) funding the project entitled "Novel Methods Leading to New Medications in Depression and Schizophrenia" or "NEWMEDS". A key aim of NEWMEDS is the identification of statistically and biologically validated animal assays and models of schizophrenia. As part of this process, the article has sought to understand whether NMDAR hypofunction models might be informative with regard to cognitive impairments associated with schizophrenia. The conclusion at present is mixed: while each model generates potentially relevant findings, claims of translational validity are still uncertain, both from the context of the induction of similar changes in animals and man, as well as the similarity of those changes to schizophrenic symptoms. It is notable that all NMDAR hypofunction models manage to recapitulate some aspects of the cognitive dysfunction of schizophrenia, but the effects of acute administration of ketamine in HV studies have never been compared to schizophrenics in the same study using the same cognitive test battery. In addition, there is less evidence than one might have suspected from a clinical perspective to support the preclinical use of repeated dosing and/or abstinence models of NMDAR antagonist administration. The driving force behind such work is two-fold: as a means of avoiding motor confounds (through the development of motoric tolerance) and the ability of such treatment to model the underlying pathology itself.

In the move from clinical to preclinical work, translational validity continues to be challenged by lack of justification of choice of NMDAR antagonist model. All human work is based on ketamine administration, yet preclinical work uses a variety of compounds including ketamine, PCP and MK-801. These antagonists are studied in an interchangeable manner preclinically at doses and regimens that have not yet been shown to bear relationship to any human ketamine administration model. Ideally, each model should therefore be grounded in a demonstrably similar pathological mechanism before it can be considered valid. Arguably, subchronic and neonatal NMDAR administration models aim to recapitulate more of these aspects of schizophrenic neuropathology, although further work is needed to confirm the similarities and difference to the disease state.

There are instances where acute, subchronic and neonatal administration of NMDAR antagonists to non-humans results in selective cognitive deficits that might be relevant to schizophrenia. However, the experience of the authors would suggest that while it is possible to observe selective cognitive impairments by specific antagonists in specific assays, these effects tend to occur within narrow and labile dose ranges, and often do not have sufficiently high test–retest reliability within or between labs to be useful within a drug discovery program. It is important also to note that appropriate assay selection with due consideration to the translational validity of the task is critical. The increased use of transgenic mouse models also necessitates that equivalent and appropriate tasks are developed in the mouse. It is fair to say that many potentially informative mouse mutants have simply not received an appropriately thorough assessment to reach conclusions about their respective value.

For drug discovery, the single most important attribute of any NMDAR hypofunction model is predictive validity. A model can be deemed valid if it can predict which therapies will exhibit efficacy in patient populations. Indeed, many therapies have already been tested for their efficacy in normalizing the cognitive effects of an acute dose of an NMDAR antagonist in animals (Boulay et al., 2004; Pichat et al., 2007; Schlumberger et al., 2009). Several novel pharmacological interventions have been reported to attenuate the cognitive deficits induced by subchronic NMDAR blockade, including D1 agonism, AMPA positive allosteric modulators, nicotinic alpha7 agonism, 5-HT2A antagonism, 5-HT2C antagonism, 5-HT6 antagonism and PDE10 inhibition (Damgaard et al., 2010; Idris et al., 2010; McLean et al., 2008, 2009a,b; Pichat et al., 2007; Rodefer et al., 2005, 2008; Thomsen et al., 2009). In terms of approved antipsychotics, studies have reported efficacy of atypical agents such as clozapine (Amitai et al., 2007; Didriksen et al., 2007; Grayson et al., 2007; Hashimoto et al., 2005; Jentsch et al., 1997a; McLean et al., 2008), risperidone (Didriksen et al., 2007; Grayson et al., 2007; McLean et al., 2008; but see Goetghebeur and Dias, 2009 for contrary results), sertindole (Broberg et al., 2009; Didriksen et al., 2007) and aripiprazole (Nagai et al., 2009). Other studies do not report effects of the typical antipsychotic haloperidol in subchronic regimens (Didriksen et al., 2007; Goetghebeur and Dias, 2009; Grayson et al., 2007; Hashimoto et al., 2005; McLean et al., 2008; Nagai et al., 2009). Some neonatal PCP deficits have been reported to be reversed with clozapine (Harich et al., 2007; Nakatani-Pawlak et al., 2009). Finally, some of the cognitive deficits reported in GluN1-knockdown mice improve following acute injection of clozapine (Mohn et al., 1999). For the targets that are not currently approved for treatment of cognitive dysfunction in schizophrenia, predictive validity of this work described above is essentially unknown. Would not the preclinical models be more clinically valid if atypical neuroleptics were inactive? Indeed, no currently marketed antipsychotic has been approved for the treatment of cognitive symptoms of schizophrenia. While there are studies showing that pro-cognitive effects can be observed in humans (Woodward et al., 2005), it remains debatable whether the effects are merely statistically significant or actually clinically relevant. Clearly, this answer to this debate will help determine the utility of any NMDAR hypofunction model to predict therapeutic effects.

In the end, expecting one dose of one NMDAR antagonist, or one particular NMDAR hypofunction model to provide all of the information required to model cognitive symptoms of schizophrenia in animals is unrealistic, despite claims to the contrary made in the introductions of many papers. When robust ketamine-induced neuropsychological deficits are carefully delineated in HVs, their relationship to functional outcome in schizophrenics must be established in order to determine their relevance and utility. At this point, the relevance of the neuropsychological and/or neurophysiological equivalents of the HV ketamine findings in animal models can be determined.

Given that acute administration of an NMDAR antagonist currently represents the only feasible means to approach this topic in HVs, this work should be imperative. However, other preclinical NMDAR hypofunction models should not be ignored, as each may

offer distinct advantages over the others and all may provide a significant body of evidence stronger than any single model in isolation. It would be a important step forward to truly rationalize the way in which different NMDAR antagonist tools and NMDAR hypofunction models are used to build up a more complete and accurate picture of cognitive endophenotypes in schizophrenia, hopefully resulting in production of novel treatments for this most debilitating aspect of the disease.

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