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Animal models of cognitive dysfunction and negative symptoms of schizophrenia: focus on NMDA receptor antagonism

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Abstract

Cognitive deficits in schizophrenia remain an unmet clinical need. Improved understanding of the neuro- and psychopathology of these deficits depends on the availability of carefully validated animal models which will assist the development of novel therapies. There is much evidence that at least some of the pathology and symptomatology (particularly cognitive and negative symptoms) of schizophrenia results from a dysfunction of the glutamatergic system which may be modelled in animals through the use of NMDA receptor antagonists. The current review examines the validity of this model in rodents. We review the ability of acute and sub-chronic treatment with three non-competitive NMDA antagonists; phencyclidine (PCP), ketamine and MK801 (dizocilpine) to produce cognitive disturbances of relevance to schizophrenia in rodents and their subsequent reversal by first- and second-generation antipsychotic drugs. Effects of NMDA receptor antagonists on the performance of rodents in behavioural tests assessing the various domains of cognition and negative symptoms are examined: novel object recognition for visual memory, reversal learning and attentional set shifting for problem solving and reasoning, 5-choice serial reaction time for attention and speed of processing; in addition to effects on social behaviour and neuropathology. The evidence strongly supports the use of NMDA receptor antagonists to model cognitive deficit and negative symptoms of schizophrenia as well as certain pathological disturbances seen in the illness. This will facilitate the evaluation of much-needed novel therapies for improved therapy of cognitive deficits and negative symptoms in schizophrenia.

KEY WORDS: Schizophrenia, animal model, NMDA antagonist, cognition, memory, neuropathology, first and second generation antipsychotics

Contents

1.0 Introduction

Schizophrenia patients suffer from enduring and persistent psychotic symptoms including a chronic deficiency in their cognitive abilities (Braff et al, 1991; Steinpreis, 1996). Indeed, cognitive (and concomitant social) dysfunction is a core component of schizophrenia, present even before the onset of psychosis and has a significant bearing on patient recovery, function in society and on all aspects of everyday life (Addington et al. 2001; Green, 1996).

Given the negative impact of cognitive and social dysfunction on long-term patient function and quality of life, the lack of effective treatment is clearly a key unmet clinical need (Goldberg and Gold, 1995). The clinical literature has generally reported no consistent, substantial improvement in cognition (at best only a marginal improvement) with the current pharmacotherapies for schizophrenia (Harvey and McClure, 2006; Keefe et al. 2007). Indeed, we have conducted our own meta-analysis of the literature and found that total PANSS score improvement was not statistically greater with second-generation antipsychotics (SGAs) when compared with the first-generation antipsychotic (FGA), haloperidol (Tomes, unpublished observations), which is in agreement with findings of the recent CUtLASS study (Jones et al. 2006). Cognition was not assessed in our analysis but this provides further evidence for the urgent need for improvement in therapy.

In further recognition of the need to address cognitive dysfunction in patients with schizophrenia and to encourage the development of cognition-enhancing drugs for schizophrenia, the National Institute of Mental Health, in collaboration with the University of California at Los Angeles and the US Food and Drug Administration, initiated the MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) and TURNS (Treatment Units for Research on Neurocognition and Schizophrenia) programs (MATRICS and TURNS.ucla.edu).

One way to address the problem is the development and validation of better animal models mimicking cognitive deficits and negative symptoms of schizophrenia as suggested by the MATRICS committee. Normalisation of cognitive deficits requires the development of validated animal models which is a difficult area of study for any human disorder but most notably for schizophrenia, a complex and uniquely human psychiatric illness. Cognitive enhancement is difficult to show in 'normal' animals, as there is a small effect window, there are few validated disease models, and no current 'gold standard' medications available to use as a positive control. Therefore a reliable means of inducing cognitive impairment is necessary whether through the use of a pharmacological, genetic or neurodevelopmental approach, all of which have been attempted. There have been some excellent recent and extensive reviews in this subject area. These include - the use of the MATRICS test battery as a guide to using preclinical tests for studying novel targets for cognitive improvement in schizophrenia (Young et al. 2009); exploration of the mechanisms by which NMDA receptor antagonism provides a relevant model of schizophrenia in animals (Jentsch and Roth, 1999; Coyle, 2006; Large, 2007-focusing on novel therapies; Morris et al. 2005; Mouri et al. 2007); the use of isolation rearing as a neurodevelopmental model (Fone and Porkess, 2008); and strategies for improving pharmacotherapy of schizophrenia (Arnt et al. 2008). In addition the debate continues concerning the value (or otherwise) of current antipsychotic medication for improvement of cognitive deficit symptoms in the clinic. The current review focuses on the NMDA receptor hypofunction hypothesis of schizophrenia and the success (or otherwise) of recent studies using NMDA receptor antagonists in rodents to mimic the various domains of cognitive disturbances associated with schizophrenia and improvement by existing therapies and novel targets where appropriate.

It was initially hypothesized that a hyperdopaminergic state resulting from an excess of dopamine in the brain was the main cause for the condition of schizophrenia (Carlsson and

Lindqvist 1963; Seeman 1987). While there is much supporting evidence to validate this theory, including recent demonstration that psychotic patients release more dopamine at the synapse on stimulation with amphetamine than normal control groups suggesting increased midbrain dopamine activity (Abi-Dargham et al. 2009), a revision of this theory became necessary when it was observed that the negative and cognitive symptoms of schizophrenia could not be accounted for by an excess of dopamine in the system (Thaker & Carpenter 2001). The origin of the idea that glutamatergic neurotransmission is disrupted in schizophrenia dates back to the 1950s when it was first reported that the anaesthetic phenylcyclidine (PCP, Sernylan (R) Parke Davis) could produce psychotic effects in people (Luby et al., 1959). PCP is a non-competitive NMDA receptor antagonist, which can induce a psychotic state that has some similarities to schizophrenia. PCP or ketamine given acutely to healthy human subjects induces hyperactivity, paranoia, hallucinations, formal thought disorder and cognitive impairments (Javitt and Zukin. 1991; Krystal et al. 1994). Both PCP and ketamine exacerbate the symptoms of schizophrenia in patients (Malhotra et al. 1997). A single dose of PCP has been shown to produce hallucinations and reduce cognitive function in schizophrenia patients (Krystal et al. 1994; Steinpres 1996). While both dopamine agonists (e.g. amphetamine) and glutamate non-competitive NMDA receptor antagonists (e.g. PCP) can replicate psychosis most effectively, the latter are able to better produce the negative and cognitive deficits associated with schizophrenia. Consequently, a great deal of research emphasis is now being placed on the role of glutamate in the pathophysiology and treatment of schizophrenia.

A mechanism, which could clarify in part, the symptomatology and natural course of schizophrenia, was proposed, based on NMDA receptor hypofunction by Olney and colleagues (1999). It suggested a dysfunction of the NMDA receptor, which could be

reproduced by blocking NMDA receptors pharmacologically with PCP, ketamine or MK801. The organization and functions of the forebrain glutamatergic systems strongly implicates glutamate in the pathophysiology of schizophrenia. Additionally, several risk factors genes (eg neuregulin, dysbindin, COMT, DISC1) for schizophrenia may be linked with dysfunction of the glutamatergic system (Harrison and Owen. 2003; Harrison and Weinberger, 2005). There are several post-mortem studies and neuropathological findings, which support the hypothesis that disruption in the normal functioning of the glutamatergic system, contribute to the "symptomatic manifestations of schizophrenia" (reviewed in Kristiansen et al. 2007).

Development of a successful animal model will undoubtedly allow better understanding of the disease process and ultimately testing of novel targets for cognition in schizophrenia as outlined in TURNS. Seven domains of cognition have been identified as being typically impaired in schizophrenia patients: (1) working memory, (2) attention, (3) verbal learning and memory, (4) visual learning and memory, (5) reasoning and problem solving, (6) speed of processing and, perhaps most important of all, (7) social cognition. In our laboratory, we have attempted to validate a test for each of these domains with disruption of normal cognitive processing induced by PCP. The two domains we have not yet validated in our laboratory include working memory and verbal learning and memory, with the obvious difficulties of mimicking these deficits in animals. The latest developments in measuring performance in laboratory tests in these two cognitive domains (and indeed in each of the seven cognitive domains) have recently been reviewed by Young and colleagues (2009).

As reviewed elsewhere (Hagan and Jones, 2005; Floresco et al. 2005) animal models for cognition in schizophrenia should: (1) mimic the fundamental cognitive deficits found in schizophrenia patients (*face validity*); (2) conform to a theoretical rationale, such as the proposed pathophysiology and symptomatology in schizophrenia (*construct validity*); and (3) predict known and novel therapeutics (*predictive validity*). Our review will evaluate whether

the NMDA antagonist model is successful and can provide a reliable animal model of cognitive deficits and negative symptoms of schizophrenia.

2.0 Novel object recognition

Visual memory deficits may be measured by recognition tasks such as the novel object recognition (NOR) paradigm as described in TURNS [reviewed in Dere et al., (2007), Winters et al (2008), Young et al (2009)]. A recognition memory task allows the comparison between presented stimuli and previously stored information. Ennaceur and Delacour (1988) described the NOR test for rodents, which was based on the differential exploration of familiar and new objects. The NOR test is a non-rewarded, ethologically relevant paradigm based on the spontaneous exploratory behaviour of rodents that measures visual episodic memory. In most commonly used forms of the test, each session consists of two trials. In the first trial, the rats are exposed to two identical objects in an open field. During the second trial, rats are exposed to two dissimilar objects, one familiar object from the first trial and one new object. Object recognition can be measured as the difference in time spent exploring the familiar and the new object. Rats (and mice) have been shown to spend more time exploring the new object. It has been found that rats are able to discriminate between the familiar and the novel object when the inter-trial interval is between 3 minutes and 1-3 hours, but not when it is greater than 24 hours, although this effect may be sex dependent in the rat (Sutcliffe et al, 2007). The duration of each trial is also important as a preference for the novel object only lasts during the first 1 or 2 minutes, after which time preference diminishes as both objects become familiar and are explored equally.

We have recently shown that acute administration of PCP (1.5-2 mg/kg) to female hooded-Lister rats induces a selective and robust impairment in the retention trial of the NOR paradigm, using a 1 min inter-trial interval (ITI), rats were unable to discriminate between the novel and familiar object (Grayson et al., 2004). This effect was prevented by administration

of oestradiol benzoate (5-10 ug/kg) 24h prior to the acute administration of PCP (2 mg/kg) (Sutcliffe et al., 2008).

Our laboratory has shown in numerous studies that a sub-chronic PCP treatment regime, specifically, 2 mg/kg twice daily for seven days followed by a seven day washout period, induces a robust cognitive deficit in the NOR paradigm, whereby the ability of rats to discriminate between novel and familiar objects is abolished. In these studies the PCP is given prior to any habituation or testing. These deficits can be subsequently improved by the acute administration of SGAs clozapine and risperidone but not by the FGA haloperidol (Grayson et al., 2007). We have also demonstrated efficacy of sertindole (Idris et al., 2010), and several novel agents including the 5-HT$_6$ receptor antagonist, Lu AE58054 (Arnt et al. 2010); ampakines, CX546 and CX516 (Daamgard et al. 2010) and the full agonist at α7 nicotinic receptors, PNU282987 (McLean et al. 2010a). In addition, BL1020, glycine uptake inhibitors and the novel antipsychotic, asenapine also show efficacy to reverse the PCP-induced deficit in this task using a 1 min and 1 hour (for sertindole) ITI. We have recently demonstrated involvement of dopamine D$_1$ receptors (McLean et al. 2009a) while others have shown serotonin 5-HT$_{1A}$ receptor involvement (Nagai et al. 2009) in mechanisms for improvement of PCP-induced deficits in this task. This work combined with recent results from a preliminary study using female Long Evans rats suggests that the sub-chronic PCP treated rats have reduced prefrontal cortical dopamine activation in this task providing considerable support for this as a model of cognition in schizophrenia, as hypofrontality is a key feature of schizophrenia pathology (Hill et al. 2004). In our study, sub-chronic vehicle treated rats showed significantly increased prefrontal cortical dopamine levels during the retention phase of the task only, as measured by in vivo microdialysis. Rather impressively, this increase in prefrontal cortical dopamine was absent in the sub-chronic PCP treated rats,

suggesting that recruitment of dopamine in the pre-frontal cortex is necessary for memory of the familiar object and that PCP treated rats lack this ability (Snigdha et al., 2008). It remains to be determined whether the antipsychotic-induced reversal of PCP-induced NOR deficits is mediated by a restoration of prefrontal cortical dopamine.

Our findings are in agreement with Hashimoto et al., (2005) who showed an NOR deficit in mice, using a sub-chronic PCP dosing regimen of 10 mg/kg once daily for ten days, administered on days 1-5 and 8-12. This deficit was reversed by the administration of clozapine, and SSR180711 (a nicotinic α7 receptor agonist) but not haloperidol when administered once daily for 2 weeks. Using an identical sub-chronic PCP dosing regimen to Hashimoto et al (2005), 14 day treatment with the partial agonist of 5-HT$_{1A}$ receptors perospirone (3.0 and 10.0 mg/kg), or the antibiotic minocycline (at 40 mg/kg) were shown to reverse the sub-chronic PCP induced NOR deficit in mice (Hagiwara et al., 2008; Fujita et al., 2008). Nagai and colleagues employed a similar sub-chronic dosing regime in mice and administered PCP 10mg/kg once per day for fourteen days. Results from this study showed that sub-chronic PCP induced a significant reduction in novel object exploration in the retention trial which was subsequently reversed by the administration of SGA aripiprazole but not by FGA haloperidol (Nagai et al., 2009).

A small number of studies have looked at the effect of ketamine on object recognition. Pitsikas et al (2008) demonstrated that acute administration of ketamine (1-3 mg/kg) consistently impaired performance in NOR in male Wistar rats. In this study, ketamine was given both before acquisition and just after the acquisition trial followed by a 1 hour ITI, both treatments produced significant NOR deficits, indicating that ketamine can affect the acquisition and storage and/or retrieval of memory. In support of these findings, it has been shown that acute administration of ketamine (30 mg/kg, 10 times the dose used in rats above)

produces impairment in cognitive function in the NOR task in mice with a 24 h inter-trial interval, which was restored by intracerebroventricular administration of the selective mGluR5 agonist, CHPG ((RS)-2-chloro-5-hydroxyphenylglycine) and the positive allosteric modulator (of the MGluR5 receptor, DFB (3,3'-difluorobenzaldazine) (Chan et al., 2008).

Acute administration of the non competitive NMDA receptor antagonist MK801 at a dose of 0.05 mg/kg, induced an NOR deficit in a paradigm using a 2 hour ITI in male hooded- Lister rats (King et al., 2004). In support of these results, de Lima and colleagues (2005), showed that pre-training administration of MK801 (0.01-0.1 mg/kg) and a post training injection of 0.1 mg/kg produced a significant disruption in recognition memory with ITIs of 1.5 hour and 24 hour in female Wistar rats. The effect of MK801 on NOR has also been studied in mice. Following MK801 at 0.2 mg/kg, 30 min prior to the acquisition trial, with a 1.5 h ITI, mice failed to differentiate between a novel and familiar object. Surprisingly, when MK801 (0.1 and 0.2 mg/kg) was given immediately after the acquisition trial or 30 min prior to the retention trial the mice showed *increased* exploration of the novel object. These results suggest that in mice, activation of the NMDA receptors is necessary for encoding of recognition memory but not for consolidation and retrieval processes (Nilsson et al., 2007). In another study, the MK801 (0.1 mg/kg)-induced impairment in NOR following a 2h ITI in male Wistar rats was restored by acute treatment with clozapine (1.0 and 5.0 mg/kg), D-serine (800 mg/kg) and the glycine transporter inhibitor NFPS (0.3-1.0 mg/kg), while haloperidol (0.03-0.1 mg/kg) failed to restore MK801-induced deficit (Karasawa et al. 2008).

In summary the NOR task in both rats and mice is sensitive to disruption by NMDA receptor antagonists with good predictive validity, i.e. showing restoration of performance with SGAs and novel agents. The task itself is comparatively easy to run and has a good level of ethological relevance. This, combined with emerging evidence that the PCP-induced deficit is

mediated by impaired prefrontal dopaminergic neurotransmission supports its validity as a useful animal model for cognitive dysfunction of particular relevance to schizophrenia.

3.0 Reversal Learning

A reversal learning task usually comprises two distinct components, an initial phase that requires memory of a previously learned reward contingency, followed by a reversal phase, in which the reward contingency is then reversed. Animals are required to inhibit a previously rewarded strategy and acquire the new strategy. Thus, effective performance requires animals to demonstrate flexibility, attention and motivation, to suppress a previously learned response and implement a new response (Jones et al., 1991). Failure to switch, or perseveration on the previously learned response, can be readily observed in patients with schizophrenia undertaking tasks such as the Wisconsin Card Sorting test (Pantelis et al., 1999; Liddle, 2000). We suggest that this type of paradigm could provide the basis for a rodent model in which to predict the ability of novel antipsychotic drugs to ameliorate aspects of executive dysfunction associated with schizophrenia. Furthermore, the TURNS initiative has identified that reversal learning tasks, as with attentional set-shifting tasks can be used to determine the problem solving deficits described in the MATRICS cognitive battery (www.turns.ucla.edu).

Successful reversal learning ability relies on the intact function of the prefrontal cortex. It has been shown more specifically that lesions of the orbital prefrontal cortex (OPFC) impair reversal learning ability within the attentional set-shifting task in male Lister Hooded rats (McAlonan and Brown, 2003; Tait and Brown, 2007). These results are concurrent with those of Bohn and co-workers, showing that lesions of the OPFC impair reversal learning in an operant lever pressing-based task in male Sprague-Dawley rats (Bohn et al., 2003). These studies are also supported by recent data showing OFC lesions in male hooded-Lister rats produced a deficit in reversal learning ability (Boulougouris et al., 2007).

The reversal learning paradigm used in our laboratory was developed on the basis of our previous work using a same-day reversal learning test in the marmoset (Smith et al., 1999). We have now adapted the model for rats. The paradigm is similar to the reversal learning test of Jones and colleagues (1991), in which isolation reared rats showed impairments in acquisition of a serial reversal learning phase. In our operant reversal learning task, rats are trained in Skinner boxes to respond for food reward by pressing an active lever. On the following day, rats have 5 mins to respond on the active lever from the previous training day, they then have a 2 min time-out, before the active lever is switched to the opposite lever. Rats then have 5 mins in this reversal phase to switch their attention to the new correct lever. We have shown that in female hooded-Lister rats acute administration of the NMDA receptor antagonist PCP (1.5 mg/kg) impairs percent correct responding in the reversal phase of the task only, leaving initial phase performance intact (Abdul-Monim et al., 2003; Idris et al., 2005; 2006; 2009). We have shown that the acute PCP-induced selective deficit in reversal learning was reversed by acute treatment with clozapine as well as with phenytoin and lamotrigine but not valproate (Idris et al. 2009). However haloperidol reversed the d-amphetamine but not PCP-induced reversal learning impairment (Idris et al., 2005).

It is becoming increasingly apparent that repeated exposure to PCP can induce more robust and enduring cognitive deficits (Jentsch et al., 1997a; b). We have consistently shown that sub-chronic PCP treatment (2 mg/kg twice daily, i.p., for 7 days followed by 7 days washout period) induces a robust enduring deficit in reversal learning performance, again selective for the reversal phase leaving initial phase performance intact in female hooded-Lister rats (Abdul-Monim et al., 2006; 2007; Idris et al. 2010; McLean et al., 2009a; 2009b). Importantly rats are tested in the drug (PCP)-free state thus avoiding any confound with psychotomimetic drug-induced effects, such as motor stimulation at doses of 3 mg/kg (ip)

and above. These sub-chronic PCP-induced deficits in reversal learning were ameliorated by SGAs such as clozapine, but not by FGAs, haloperidol and chlorpromazine (Abdul-Monim et al., 2006) showing some predictive validity for the clinic. Several newer antipsychotics such as asenapine (McLean et al. 2010b) and sertindole (Idris et al., 2010) reverse the sub-chronic PCP-induced deficit in this paradigm. The dopamine D_1 receptor agonist SKF 38393 and antagonists at several 5-HT receptor subtypes including 5-HT$_6$, 5-HT$_7$, 5-HT$_{2C}$ and 5-HT$_{2A}$ (Idris et al. 2010; McLean et al., 2009a; 2009b) also show efficacy in this test making it of particular relevance for exploration of mechanisms of antipsychotics important for improvement of cognitive function. In a reversal-learning task similar to that employed in our laboratory, however, using an innovative touch screen-based system, sub-chronic PCP (5 mg/kg twice daily for 7 days, followed by a 7-day washout period) in male C57BL/6J mice did not affect reversal learning ability (Brigman et al., 2009). However, in the same strain of mice, sub-chronic PCP (1.3 mg/kg once daily for 5 days) was found to impair all stages of the attentional set-shifting task, including reversals (Laurent and Podhorna, 2004). Although it must be noted that PCP was administered 2 hours prior to testing, therefore the effects of acute PCP cannot be excluded.

PCP is not the only means of producing a pharmacological deficit in reversal learning, we have shown that acute administration of the NMDA antagonists ketamine (15 mg/kg) and MK801 (0.05 mg/kg) produce a selective deficit for the reversal phase of the task (Idris et al., 2006). Reversal learning ability can also be assessed using other tasks such as the reversal stages within the attentional set-shifting paradigm. Ketamine (30 mg/kg i.p., twice daily for 5 days followed by a 10 day washout period), did not produce a deficit in set shifting in an operant paradigm, but did produce more perseverative errors than the control group in a

reversal of the acquired set-shift in an operant procedure in male Long-Evans rats (Floresco et al., 2009).

In support of the PCP and ketamine results, as previously mentioned, whereas MK-801 (3 µg per hemisphere into the mPFC) was shown to produce selective deficits for the set 2 strategy in a maze-based set shifting task, it was found that systemic administration of MK-801 (0.1 mg/kg, i.p.) impaired set 1 and set 2 strategies in male Sprague-Dawley rats. The set 1 strategy is equivalent to reversal learning ability (Stefani and Moghaddam, 2005). MK-801 at doses of 0.06 mg/kg and 0.1 mg/kg, but not 0.03 mg/kg impaired reversal learning in a maze based reversal learning task in male and female Long-Evans rats (Chadman et al., 2006), whereby in acquisition, rats were required to go to one arm of the maze and in the reversal phase rats then had to switch contingencies and visit the opposite arm of the maze. In an operant lever pressing reversal learning task similar to that in our laboratory MK-801 (0.025 mg/kg, s.c.) produced a deficit in the reversal phase compared to the vehicle-treated group in male Wistar rats (van der Meulen et al., 2003). Following repeated reversals, rats treated with 0.025 mg/kg MK-801 showed an improvement to a similar level of responding as vehicle rats, while rats treated with MK-801 (0.05 mg/kg, s.c.) showed a partial improvement following repeated reversals, those treated with MK-801 at 0.1 mg/kg (s.c.) remained impaired (van der Meulen et al., 2003). This provides support for the work of our laboratory whereby PCP treated rats are impaired in the reversal phase of the task only.

4.0 Attentional set-shifting

One aspect of executive function is the ability to modify behaviour in response to the changing relevance of a stimulus; this is commonly assessed in patients using the Wisconsin Card Sorting Test (WCST) (Berg, 1948). In more recent years a more conclusive battery of tests known as CANTAB (Cambridge neuropsychological test battery) has been developed (Downes et al., 1989). The attentional set-shifting task represents a rat analogue of the human WCST and the CANTAB ID/ED task in which schizophrenia patients exhibit impaired set-shifting (Kolb and Wishaw, 1983; Haut et al., 1996; Pantelis et al., 1999; Tyson et al., 2004). The TURNS initiative has identified that this test can be used to determine the problem solving deficits described in the MATRICS cognitive battery (www.turns.ucla.edu).

In 2000, Birrell and Brown developed the attentional set shifting procedure for the rat. The perceptual attentional set-shifting task (Birrell and Brown, 2000) investigates the ability of a rat to learn a rule and form an attentional set within the same sorting category (intra-dimensional shift - IDS), as well as the ability to shift attentional set between different sorting categories (extra-dimensional shift - EDS). Rats must carry out a series of 7 discriminations namely, simple discrimination (SD), compound discrimination (CD), reversal 1 (R1), intra-dimensional shift (IDS), reversal 2 (R2), extra-dimensional shift (EDS) and reversal 3 (R3). Initial studies using the attentional set-shifting task showed that lesions of the medial prefrontal cortex (mPFC) produce a selective deficit in the EDS phase (Birrell and Brown, 2000), whereas lesions of the orbital prefrontal cortex in male hooded-Lister rats selectively disrupts reversal learning (McAlonan and Brown, 2003).

We have demonstrated a selective deficit in female hooded-Lister rats in the EDS phase following administration of sub-chronic PCP (2 mg/kg twice daily, i.p., for 7 days followed by 7 days washout period). This deficit was attenuated by seven-day treatment with

clozapine and risperidone, but was unaffected by haloperidol (McLean et al., 2008). Rodefer and colleagues combined the attentional set-shifting test with a sub-chronic PCP dosing regimen in male Long-Evans rats (5 mg/kg twice daily, i.p., for 7 days followed by a 10 day drug washout period) and found a selective deficit in the EDS phase (Rodefer et al., 2005). The PDE10A inhibitor, papaverine, reversed the PCP-induced deficit in the EDS phase (Rodefer et al., 2005). In contrast, Rodefer and colleagues subsequently found that clozapine and risperidone to be ineffective in reversing the PCP-induced deficit, however sertindole and the selective $5-HT_6$ (SB-271046) and $5-HT_{2A}$ (M100907) receptor antagonists did attenuate the PCP-induced impairment (Rodefer et al., 2008), which is similar to our findings using reversal learning paradigm (Idris et al. 2010). This same dosing regime was shown again in male hooded-Lister rats to produce deficits in the EDS phase; an effect which was ameliorated by sertindole and the anti-narcoleptic drug modafinil but not by risperidone or haloperidol (Goetghebeur and Dias, 2009). Egerton and co-workers also used a sub-chronic PCP regime in male Long-Evans rats (2.6 mg/kg daily, i.p., for 5 days followed by a 3 day washout period) and found a strong tendency towards a deficit in the EDS phase of the task (Egerton et al., 2008). This group have shown more robust selective deficits using acute administration (i.p.) of 2.58 mg/kg PCP (Egerton et al., 2005) and a chronic intermittent schedule of 2.6 mg/kg of PCP once daily for 5 days followed by a single dose on days 8, 10, 12, 15, 17, 19, 22, 24 and 26 (Egerton et al., 2008). Conversely, other studies have shown that long-term intermittent administration of PCP (3 mg/kg, i.p., once per day administered Monday, Wednesday and Friday for 5 weeks, and 10 mg/kg, i.p., daily for 14 days) did not impair set-shifting ability in male Sprague-Dawley and Long-Evans rats respectively (Fletcher et al., 2005; Deschênes et al., 2006). These data would suggest that continual dosing with PCP is more effective than an intermittent regimen. An early post-natal treatment regime (10 and 20 mg/kg, s.c., on PND 7, 9 and 11) has also proved effective in

producing a selective deficit for the EDS phase of the task in male and female hooded-Lister rats (Broberg et al., 2008). A subsequent study by this group (20 mg/kg on PND 7, 9 and11) has replicated the PCP-induced deficit and this effect was attenuated by the SGA sertindole and the ampakine compound CX516 (Broberg et al., 2009).

Although most commonly used, PCP is not the only pharmacological means of producing cognitive impairments in attentional set-shifting, for example amphetamine sensitised male Sprague-Dawley rats show deficits in this task (Fletcher et al., 2005). Conversely, the NMDA receptor antagonist, ketamine (30 mg/kg i.p., twice daily for 5 days followed by a 10 day washout period), did not impair set-shifting ability in male Long-Evans rats in either a cross-maze-based task or in an operant procedure (Floresco et al., 2009). Furthermore, in both tasks ketamine unexpectedly reduced the number of perseverative errors made compared to the saline-treated group; however in a reversal of the acquired set-shift in the operant procedure, ketamine did produce more perseverative errors than the control group (Floresco et al., 2009). The authors attribute the lack of set-shifting deficit in ketamine-treated rats to a possible lack of training on the initial procedures compared to the attentional set-shifting task described by Birrell and Brown (2000), and due to the shorter duration of action of ketamine compared to PCP, i.e. ketamine-induced neuronal alterations may not have been sufficient to disrupt the mPFC dependent behaviours.

In support of the above findings with PCP, intra-cortical injections of the NMDA receptor antagonist, MK-801 into the mPFC (1 or 3 µg per hemisphere), was shown to produce selective deficits for the set 2 strategy in a maze-based set shifting task in male Sprague-Dawley rats (this is equivalent to the EDS phase in the perceptual attentional set-shifting task), whereas the AMPA receptor antagonist, LY293558 (1 µg per hemisphere), also impaired the set 1 strategy which represents acquisition of a discrimination rule (Stefani and

Moghaddam, 2003). Thus blockade of AMPA receptors may induce a more generalised cognitive deficit than that produced by NMDA receptor blockade which may be of more relevance to schizophrenia. Following this study, it was found that systemic administration of MK-801 (0.1 mg/kg, i.p.) impaired set 1 and set 2 strategies, while injections directly into the mPFC (3 µg per hemisphere) produced selective deficits in set 2 only (Stefani and Moghaddam, 2005). Therefore, the deficits observed in set 1 are not controlled by the mPFC; these studies suggest the importance of mPFC NMDA receptors in tasks of cognitive flexibility. In summary, administration of the NMDA antagonists in an attentional set-shifting task produce deficits that closely resemble the cognitive inflexibility observed in schizophrenia. Further research into this topic may provide us with the necessary understanding of the underlying neurobiological processes which contribute to attention and problem solving in schizophrenia.

5.0 Attention

Along with the myriad of other cognitive deficits associated with schizophrenia, the disorder often results in attentional dysfunction and executive impairment (Jones et al., 1994; Cornblatt & Keilp, 1994; an der Heiden & Hafner, 2000; Paine & Carlezon, 2009; MATRICS.ucla.edu). Attention is a multi-faceted system that allows an individual to detect, select and process relevant stimuli, while simultaneously filtering out irrelevant stimuli from the surrounding environment. Executive functioning, which includes abstract problem solving and behavioural inhibition, is often described as a system of higher-order cognitive processing that allows the individual to plan and execute goal-specific behaviours (Velligan & Bow-Thomas, 1999; O'Grada & Dinan, 2007). Many tasks have been developed to assess these aspects of cognitive ability in the clinic and include tests such as the Continuous Performance Task (CPT) and the Wisconsin Card Sorting Task (WCST) (Rosvold et al., 1956; Cornblatt & Keilp, 1994; Weisbrod *et al*., 2000).

5.1 5-Choice Serial Reaction Time Task

The 5-choice Serial Reaction Time Task (5-CSR) is detailed in other reviews (Robbins, 2002; Chudasama & Robbins, 2004; Young *et al*., 2009), Briefly, the 5-CSR task involves a rodent being able to detect the presentation of light stimulus in one of 5 apertures at the rear of a dark operant chamber. Following successful detection of the light stimulus, the rodent must report its detection by nose-poking the aperture in which the light was presented, within a limited time period. Following a correct response, a food pellet is delivered and the next trial is initiated when the animal retrieves the food reward, also initiating the next trial. Following an inter-trial interval (ITI), another light stimulus is presented randomly in one of the 5 available apertures. If the animal nose-pokes an aperture that the light stimulus was not presented in (incorrect response) or fails to respond within the limited time period following

the stimulus presentation (error of omission) there is a time out period where the animal doesn't receive a food reward and the house light is illuminated for a period of 5 seconds. If the animal makes a response during the ITI, before the stimulus is presented, this is deemed a premature response and results in a time out period. Also, if the animal continues to respond following a correct response, a time out period is initiated as this is indicative of perseverative behaviour, whereby the animal fails to disengage from a behaviour that previously resulted in reward.

The 5-CSR task measures elements of attention, namely sustained and divided attention, as the animal has to sustain its attention for the duration of the ITI in order to successfully detect and respond to the light stimulus, whilst dividing its attention across the 5 spatial apertures. Executive function is assessed in the form of premature or perseverative responding. Increases in premature responding indicate impairment in behavioural inhibition as the animal fails to inhibit its response until the stimulus is presented. Conversely, perseverative responding reflects the animal's inability to disengage from a response that was previously rewarded.

The 5-CSR task also measures various latencies involved in its performance such as the time taken from presentation of the stimulus to the animal making a correct response and the time taken to retrieve the food reward following a correct response. The former gives investigators insight into the animal's speed of cognitive processing (one of the 7 domains of cognition affected in schizophrenia as outlined by MATRICS; Young *et al.,* 2009) while the latter gives indications of the animal's motor function or motivation to perform the task.

Various brain regions have been implicated in successful performance of the 5-CSR task. Extensive work using excitotoxic agents to lesion specific areas of the brain has elucidated certain brain regions with direct involvement in performance of the task. The first is the

prefrontal cortex (PFC), in which specific behavioural aspects of the task can be dissociated to specific sub-regions such as the mPFC, orbitofrontal, infralimbic and prelimbic cortices. Other brain regions that have important significance in correct performance of the 5-CSR task include the anterior cingulate cortex, striatum and the thalamus (Muir *et al*., 1994; Muir *et al*., 1996; Rogers *et al*., 2001; Robbins, 2002; Chudasama *et al*., 2003)

5.2 5-CSRTT and NMDA antagonists

5.2.1 Intracerebral Injections of NMDA antagonists

Baviera *et al.,* (2008) used the competitive NMDA receptor antagonist 3-(R)-2-carboxypiperazin-4-propyl-1-phosphonic acid (CPP), which was injected directly into the mPFC of male Lister Hooded rats (50 ng/side) trained in the 5-choice task. This experiment demonstrated that selective blockade of NMDA receptors specifically located within the mPFC produced a profound impairment in the rat's ability to perform in the task. Bilateral injection of CPP (50 ng/side) in the mPFC region of the rat brain reduced choice accuracy, increased the number of omissions, increased correct latency and produced executive impairment in the form of increased perseverative and premature responding. These data clearly implicate the mPFC and a functioning NMDA glutamatergic system in successful performance of the task. These data were in agreement with results of Murphy *et al*., (2005) who also demonstrated that bilateral central infusion of CPP into the mPFC produced performance deficits in the 5-CSR task. However, Murphy *et al*., (2005) investigated the effects of CPP infusion (10 & 50 ng/side) in the prelimbic and the infralimbic cortices, which are specific sub-regions of the mPFC in male Lister Hooded rats. Their study demonstrated that blockade of NMDA receptors within different regions of the mPFC produced dissociable effects. Infusions of CPP produced a reduction in choice accuracy and an increase in omissions across both cortical regions within the mPFC; however, an increase in premature

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responding was only evident when NMDA receptors contained within the infralimbic cortex (hippocampal dominated), but not the prelimbic cortex (amygdala dominated), were blocked. Murphy *et al*., (2005) suggested that these data demonstrated a dissociable role for the prefrontal-cortical glutamatergic system in executive control dysfunction, localised to the ventromedial infralimbic region of the mPFC.

5.2.2 Systemic Administration of an NMDA receptor antagonist

Amitai *et al*., (2007) investigated effects of systemic exposure of PCP on the performance of rats in the 5-CSR task and showed that acute administration of PCP (1.5 – 3mg/kg s.c. in male Wistar rats) produced a wide range of impairments in the task. Amitai *et al*., (2007) described these impairments as a nonspecific response-suppressive effect and suggested they were the result of a global inability of the rat to perform in the task. The effects included a reduction in choice accuracy and percent correct responding and an increase in the correct latency. As accuracy can be interpreted as a measure of attentional processing, Amitai *et al*., (2007) suggested that a single injection of PCP may have induced an attentional-specific impairment in task performance. These findings are in agreement with previous studies which demonstrated that antagonism of the NMDA receptor by either MK-801 or PCP resulted in a reduction in choice accuracy in the 5-choice task in rats and mice. (Grottick & Higgins, 2000; Higgins *et al*., 2003; Greco *et al*., 2005).

A single dose of PCP resulted in a reduction in the number of premature responses, which may be attributed to the response-suppressive nature of an acute exposure to the drug rather than an effect on response inhibition. In addition, acute exposure to PCP resulted in an increase in response latency, which was not accompanied by an increase in magazine latency (Amitai et al. 2007). The group suggested that the increase in the time taken to respond is due to PCP interfering with the animal's ability to processes cognitive information, consistent

with previous studies (Grottick & Higgins, 2000). Alternatively, a transient cognitive impairment rather than motor or motivational impairment as locomotor or motivation impairment would also produce an increase in the time taken for the animals to retrieve the food reward. Moreveor, acute administration of PCP produced no significant effects on perseverative responding in the 5-CSR task. These data strongly suggest that when PCP is administered systemically, it has the ability to disrupt the ability to perform in the 5-choice task (Amitai et al 2007).

Amitai *et al*., (2007) also investigated the effects of a repeated PCP dosing regime (two initial doses of PCP (2mg/kg s.c.), followed by 5 consecutive doses of PCP) and its ability to induce impairment in the performance in the 5-CSR task. What the group concluded was that the repeated administration of PCP resulted in cognitive impairment, leading to significant reductions in accuracy, correct responses, increased premature responding and a significant increase in correct latency, without an effect on total trials completed or latency to collect the food reward. What this result indicates is that repeated PCP administration produces significant impairment in cognitive elements associated with successful performance with the task, without the motor or motivational disruption that is associated with acute PCP dosing. This method, therefore possibly represents a more reliable way to induce cognitive impairments that are associated with schizophrenia in the 5-CSR task, compared to acute PCP administration (Amitai *et al*., 2007)

Preliminary studies in our laboratory showed that our sub-chronic PCP treatment regime produced no overt impairment in 5-choice performance, despite resulting in deficits in other behavioural tasks. However, when the criteria of the 5-CSR task were subtly manipulated, impairments in performance became evident. More specifically, when the ITI was reduced, subtle impairments in attentional functioning became apparent, resulting in slight yet

significant reductions in accuracy and percent correct responding, coupled with an increase in percent omissions, compared to control animals. These data are preliminary but support the idea that sub-chronic PCP may produce attentional impairments of relevance to schizophrenia.

MK-801 also produced impaired performance of the 5-CSR task. Acute administration of MK-801 (0.008 – 0.25mg/kg i.p.) in male Sprague-Dawley rats produced a profile similar to the behavioural impairment that results from acute PCP exposure, namely a reduction in response accuracy coupled with an increase in the number of omissions and premature responding (Paine *et al*., 2007; Paine & Carlezon, 2009).

5.3 5-CSR and Antipsychotics

Amitai *et al*., (2007) reviewed the effects of several FGAs and SGAs, including haloperidol, clozapine, olanzapine, risperidone, and quetiapine, on the performance in the 5-CSR task, without previously impairing performance via pharmacological means or manipulating test parameters, in male Wistar rats. What this group concluded was that a selection of antipsychotic drugs produced no significant effect on the performance in the 5-CSR task, except at the higher doses used, which generally resulted in a reduction in correct responding coupled with a reduction in total trials completed. This indicates that higher doses of antipsychotics resulted in motor or motivational impairments consequently resulting in impaired performance of the task. The exception to this is that risperidone produced a significant reduction in premature responding at a dose (0.2mg/kg i.p.) that did not significantly affect correct responding, possibly indicating enhancement of behavioural inhibition manifesting itself as a reduction in impulsive behaviour.

Amitai *et al*., (2007) also demonstrated that chronic clozapine (4mg/kg/day) exposure via osmotic minipumps for 14 consecutive days was effective in partially attenuating some of the

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cognitive impairments induced by the repeated PCP dosing regime. They demonstrated that chronic clozapine attenuated the reduction in accuracy and reduced the increase in premature responding which resulted from the repeated exposure to PCP. In contrast, in a similar study, Amitai & Markou (2009) demonstrated that the attentional impairment and behavioural disinhibition induced by repeated exposure to PCP, was not attenuated by chronic exposure to quetiapine (10mg/kg/day via osmotic minipump). However, this study did demonstrate that attentional and executive impairments are reliably produced in rats following repeated treatment with PCP.

In summary, the 5-CSR task is sensitive to the disruptive effects of NMDA antagonism and may be a valid behavioural paradigm that models aspects of cognitive dysfunction seen clinically in schizophrenia, namely attentional impairment and behavioural disinhibition. However, the 5-CSR task can detect the efficacy of some SGAs but not all, and is insensitive to any beneficial effects of such compounds, unless the rodent's task performance is previously impaired by pharmacological means.

6.0 Social behaviour deficits: A model of negative symptoms of schizophrenia

There are a number of social behavior(s) which are relevant to schizophrenia and many of these are utilized to establish preclinical behavioural tests of negative symptoms in a variety of species ranging from rodents to non-human primates. The one model which is most widely used in this respect is social interaction. Some less well studied models include social communication (measuring vocalisation) and social motivation (e.g. working for access to a conspecific, ie an animal of the same species, in our case a female rat from the same batch, but from a different cage).

The social interaction task measures a range of behaviours displayed by a subject (typically rats, mice or monkeys) when exposed to an unfamiliar conspecific. It involves the evaluation of social or asocial responses of the subject to the conspecific and is quantified differently by different research groups. However, there is a reason for the extensive use of this task to mimic negative symptoms of schizophrenia in animals. Firstly, measurements of social interactions in animals are relatively straightforward in comparison with other negative symptoms, such as flattened affect or apathy. These symptoms are difficult to imitate and even identify in animals since lack of response to emotion evoking stimuli in animals may be completely independent of lack of emotion. Some attempts, however, have been made to model anhedonia by measuring reward seeking behaviours in the past. In contrast to many unsuccessful attempts to model the above mentioned aspects of negative symptoms, several groups have been able to successfully show inhibition of social interaction, induced by NMDA-receptor antagonists in animals (Becker and Grecksch, 2004; Bruins-Slot et al. 2005; Ellenbroek and Cools 2000; Sams-Dodd et al., 1999; Snigdha and Neill 2008a; b).

As is the case with most preclinical tests, a major factor for determining the usability and reliability for the social interaction test is that of cross-species translatability, face, construct and predictive validity. The concept of translatability is closely associated with face validity or resemblance between behaviours observed by the subject in an animal model and those of the human condition. Face validity in the context of the social interaction test with NMDA antagonist is deemed fairly accurate with most manipulations successfully interfering with normal social interaction in animals using either PCP (Sams- Dodd et al., 2005, Snigdha et al., 2008a, b) ketamine (Becker and Grecksch, 2004) or MK01 (Rung et al., 2005) and resulting in deficits similar to that seen in patients with schizophrenia (Andreason et al., 1990). An extensive literature search reveals that of all the NMDA antagonists that are used to induce social interaction deficits, phencyclidine (PCP) is the most commonly used, followed by MK-801 and ketamine. Different groups have used different methodologies to study the behavioural changes induced by NMDA antagonists in the social interaction test. In Table 1 we attempt to summarize some of the differences in the methods employed by groups that use adult rats for testing.

(Insert Table 1 here)

Examination of social behaviours following acute exposure to PCP (2.5 mg/kg, and 4 mg/kg s.c) showed a reduction in social interaction in adult male rats (Bruins- Slot et al., 2005; Sams-Dodd, 1998). Both these studies used a 3 day pre-treatment time with PCP (prior to acute exposure) to allow for tolerance to the initial response to the drug to develop. Our group has shown that a treatment regime of sub-chronic PCP (2 mg/kg twice daily for seven days followed by a 1 to 6 week washout period) reliably impairs social interaction in adult female rats (Snigdha and Neill. 2008a; b). More recently, Audet et al. (2009) have shown compromised social interaction behaviours using another sub-chronic PCP treatment regime

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in male rats (10 mg/kg, once a day for 15 days) when tested 20 h after the 1st, the 8th and the 15th injection. Social behaviour deficits have been reported in mice during withdrawal (for up to 28 days) from chronic PCP treatment (10 mg/kg/day for 14 days; Quia et al., 2001). Impairments in social interaction have also been reported in rats treated with PCP (10 mg/kg, s.c.) on postnatal days 7, 9, and 11 (Harich et al., 2007) and in adolescent rats (PD 50–51) injected with PCP (9 mg/kg), twice per day at a 12-h interval for two consecutive days. Drug effects were tested during the acute drug state (PD 50–51) and post-drug phase (PD 54–80) and in adulthood (after PD 80) and PCP was shown to decrease social interaction during the first 8 min of the test (White et al., 2009).

MK-801 has been shown in some but not all studies to produce similar deficits in social behaviours in adult male rats following both acute treatment (0.2 mg/kg, ip; Rung et al., 2005) and a sub-chronic dosing regime (0.13 mg/kg/day ip for 14 days; Matsuoka et al., 2005). Sams-Dodd in 2004 used different dosing regimes of MK-801 (group 1: 0.063 or 0.5 mg/kg for 7 days, s.c with mini osmotic pumps) where the rats were tested in the social interaction test 21 days post drug administration and (group 2: 5mg/kg of MK-801, on alternate days for 4 days) with the rats were being tested following a 7 day washout period. The same study also reported the effect of PCP (5.0; 10.0; 20.0 and 30.0 mg/kg/day for 6 days, s.c with mini osmotic pumps) with testing in social interaction conducted 7 days later. These doses are known to produce mild to extensive non specific regional neurotoxicity (including the retrosplenial cortex- in contrast to the specific GABA interneuron deficits in PFC and hippocampus induced by lower doses) but failed to provide additional support for the face validity of this model in that rats tested 7 to 21 days after the last drug administration did not show impaired social behaviour. To the best of our knowledge, no studies have reported the effect of MK-801 treatment in the social interaction test in female rats.

Even fewer studies have reported the effects of ketamine on social behaviours in animals. An acute low dose of ketamine (7 mg/kg) has been reported to reduce social interaction in adult male rats (Silvestre et al., 1997). Another study by Becker et al., (2003) has reported that two weeks after the final ketamine injection dose (30 mg/kg ip ketamine daily for five consecutive days), the percentage of nonaggressive behaviour (sniffing, following and grooming the partner, social play) was decreased in ketamine-treated rats. These studies suggest that treatment with both acute and sub-chronic doses of ketamine may induce social interaction deficits relevant to negative symptoms of schizophrenia. However it must be noted that the construct validity of these models is harder to achieve and/or to assess for a condition such as schizophrenia not only because the etiology of the condition still remains to be ascertained but also because very few studies in the literature report any findings about the electrophysiological or neurobiological effects of manipulations used to study social interaction deficits. In this respect, Katayma et al., (2009) have recently reported that systemic administration of PCP (10mg/kg) induces long-lasting activation in only half of the neurons that exhibited an increase in firing rate during normal social interaction in the basolateral amygdala. Interestingly, monkeys with amygdala lesions show several social deficits and are expelled from the social group. Another study by Matsuoka et al. (2008) demonstrated a down-regulation in 23 genes and up-regulation in 16 genes, with the gene encoding arginine-vasopressin being most down-regulated, and that for transthyretin (Ttr) most up-regulated in the amygdala following MK-801 (0.13 mg/kg for 14 days) treatment in adult male rats. Indeed it has been suggested that there is a close relationship between dysfunction of the amygdala and social behaviour deficits seen in patients with schizophrenia. However, no studies to date have reported a direct correlation between social interaction behaviours (post sub-chronic NMDA antagonism) and any neurobiological substrates. Future studies are required to further investigate the association between possible

neural mechanisms involved in the origin and development of social interaction deficits in animal models. At present, most studies in the literature relate to the predictive validity of the social interaction task. This refers to the ability of a task to accurately estimate and predict the therapeutic value of drugs for the human condition. The effect of different drugs on social interaction deficits observed following NMDA receptor antagonism is discussed beneath.

Effects of antipsychotic drugs on the social interaction test

Sams-Dodd (1997) identified that SGAs such as remoxipride, risperidone, sertindole, olanzapine and quetiapine all improved PCP- induced social interaction deficits in male Wistar rats. Thereafter in 2005, a study by Bruins-Slot and colleagues showed that antipsychotic drugs with 5-hydroxytryptamine$_{1A}$ (5-HT$_{1A}$) receptor partial agonist properties attenuate PCP-induced disruptions in social interaction in male Sprague–Dawley rats. This was followed by studies which confirmed that compounds having combined 5-HT$_{1A}$ receptor agonist/D$_2$ receptor antagonistic properties, but not selective D$_2$ antagonism reversed PCP-induced social interaction deficits in both male (Boulay et al., 2004; Depoortere et al., 2007) and female rats (Snigdha and Neill 2008b).

The effects of ketamine induced disruptions (30 mg/kg ip ketamine daily for five consecutive days in Sprague–Dawley rats) also have been shown to be reversed by both clozapine and risperidone but not haloperidol (Becker and Grecksch 2004) and those of MK-801 (0.2 mg/kg given acutely 30 minute prior to testing) in male Sprague–Dawley rats have reportedly been reversed by dopamine stabilizers but not by clozapine or haloperidol (Rung et al., 2005). The dopamine stabilizer, OSU6162 has also demonstrated some improvements in reducing both positive and negative symptoms in schizophrenia patients (Gefvert et al., 2000). On the contrary, FGAs have poor efficacy on negative symptoms (Möller, 2003) and the ability of clozapine to alleviate negative symptoms has been a subject of much debate. Taken together

these findings suggest that the social interaction model may have some predictive validity for identification of the anxiolytic or pro social effects of novel antipsychotic compounds.

With the use of NMDA receptor antagonists in the social interaction task, behavioural impairments are observed in both the drug-free state after repeated NMDA antagonist administration followed by a lengthy washout (Audet et al., 2009; Snigdha and Neill., 2008a, b) and following repeated NMDA antagonist pretreatment to allow for tolerance to preliminary nonspecific behavioral disruption, but examination of behaviour during acute exposure to the drug (Sams-Dodd 1999; Bruins-Slot et al., 2005). Both social behaviour deficits observed during acute exposure of the animal to NMDA antagonists, and behavioural deficits observed after drug washout following repeated treatment with NMDA antagonists, are potentially relevant to schizophrenia pathology and allow for an interesting means to explore the mechanisms involved in impaired social functioning in schizophrenia patients.

7.0 **Neuropathology**

There is substantial evidence for neuronal abnormalities in schizophrenia. Results from both neuroimaging and neurochemical studies have identified a number of macroscopic findings indicative of neuronal dysfunction in a number of important brain regions implicated in the disorder, namely cortical and medial temporal lobe structures. These include increases in ventricular size, volume decreases and reduced energy metabolism (Lawrie and Abukmeil, 1998; Wright et al, 2000). At a more microscopic level, there have similarly been reports of changes in a variety of neurotransmitter systems. As it is beyond the scope of this manuscript to review all of the systems in detail we will focus on changes relating to the major inhibitory neurotransmitter of the human brain, namely γ–aminobutyric acid (GABA). We shall also investigate the correlates with animal models based on the administration of NMDA receptor antagonists.

7.1 Human post-mortem studies

A defect in neurotransmission involving GABA in schizophrenia was first proposed in the early 1970s (Roberts et al., 1970). Since then an accumulation of evidence for abnormalities of the GABA system in schizophrenia has emerged with numerous post-mortem studies consistently reporting deficits relating to interneurons that contain GABA as their neurotransmitter (Blumm and Mann, 2002).

Benes et al. (1998) reported a reduced density of GABA interneurons in the CA2/3 region of the hippocampus. These deficits were unrelated to antipsychotic treatment, suggesting a role of the disease process. In support of these findings others have reported both an increase in $GABA_A$ receptors in the hippocampus probably a consequence of a compensatory up-regulation of the post synaptic receptors (Benes et al., 1996), along with a decrease in GABA

uptake sites (Reynolds et al., 1990). Taken together these studies provide initial evidence for abnormalities of GABA transmission in the brain in schizophrenia.

More recently researchers have taken advantages of the availability of antibodies against a number of calcium binding proteins (CBP). These CBPs, namely parvalbumin (PV), calbindin (CB) and calretinin (CR) have been used as markers of specific subpopulations of non-overlapping GABAergic interneurons in the brain. Deficits in PV-immunoreactive cells have been reported in both the frontal cortex (Beasley and Reynolds, 1997; Beasley et al., 2002; Refs) and hippocampus (Zhang and Reynolds, 2002) in postmortem brain tissue from patients diagnosed with schizophrenia. Whether these studies reflect deficits in the density of PV interneurons or that the interneurons are present but PV is not detectable was not answered. In a more recent study, Hashimoto et al., (2003) reported that at the cellular level a decrease in signal intensity for PV mRNA was attributable principally to a reduction in PV mRNA expression per neuron rather than by a decreased density of PV mRNA-positive neurons.

One of the most consistent findings in post-mortem studies is that of reductions in mRNA and protein for GAD_{67}, a synthesizing enzyme for GABA, in the prefrontal cortex (PFC) of schizophrenia patients (Akbarian et al., 1995; Guidotti et al., 2000; Volk et al., 2000). Furthermore, Hashimoto et al., (2003) demonstrated that mRNA expression deficits for both GAD_{67} and the GABA transporter (GAT1) in schizophrenia brain tissue, are selective for the PV-containing subclass of PFC GABA neurons. Taken together, these results suggest that both GABA synthesis and reuptake appear to be altered at the level of gene expression only in the PV subset of GABA neurons, and the resulting changes in GABA neurotransmission may contribute to PFC dysfunction and as such cognitive deficits in schizophrenia (Lewis et al., 2005).

7.2 Animal post-mortem studies

Some neuropathological features of schizophrenia, in particular alterations of local GABAergic interneurons, have been investigated in animal models of psychosis, based on prolonged exposure to NMDA receptor antagonists. Employing this model, numerous studies have reported deficits in PV-immunoreactive neurons with, when investigated, no change in the CR subset. These findings, which are summarised below, are consistently reported for the prefrontal cortex and hippocampus in the rat.

7.2.1 Phencyclidine

Acute administration of phencyclidine (PCP) has been found to produce deficits in PV mRNA in the reticular thalamus with no change in the prefrontal cortex. These pathological deficits are accompanied by deficits in a perceptual set shifting task, comparable to an aspect of executive dysfunction in schizophrenia (Egerton et al., 2005). However using a regime of chronic intermittent exposure to PCP, Cochran et al., (2003) reported decreases in PV mRNA expression in both the rat prefrontal cortex and reticular nucleus of the thalamus. Moreover, chronic PCP treatment given according to this regime also elicits a metabolic hypofunction, as demonstrated by reductions in the rates of glucose utilization, within these two regions, key structures displaying similar changes in schizophrenia.

Using a sub-chronic PCP treatment regime we and others have reported deficits in PV-immunoreactive neurons in the hippocampus of adult rats. Similar to the studies mentioned above, these deficits occurred alongside cognitive and behavioural alterations (Abdul-Monim et al., 2006; Jenkins et al., 2008). Post-natal administration of PCP (on post-natal day 7) to rats has also been shown to selectively reduce cortical PV neurons, with no change in the hippocampus. This treatment regime does not affect the CR subset (Wang et al., 2008).

Through the use of cellular markers of apoptosis and neurogenesis the authors determined that the loss of PV-containing neurons was not due to an effect of PCP on proliferating neurons, but rather an effect on post-mitotic neurons.

7.2.2 MK-801

Studies using the NMDA receptor antagonist MK-801 have also reported deficits in PV interneurons in the hippocampus (Braun et al., 2007; Rujesca et al., 2006). As a functional consequence, local inhibition of pyramidal cells which is largely mediated by recurrent axon collaterals, originating from GABAergic interneurons, was altered. Following this treatment regime, these animals also showed cognitive deficits resembling findings in schizophrenia patients.

Prenatal exposure (E15-E18) to MK-801 has also been shown to reduce the density of PV-immunoreactive neurons in rat medial prefrontal cortex. This GABAergic neurodevelopmental disruption of GABAergic interneurons was present both pre- (day 35) and post-adolescence (day 63) (Abekawa et al., 2007).

7.2.3 Ketamine

Studies in rats repeatedly treated with ketamine found a decrease in the density of PV expressing cells in the hippocampus (Keilhoff et al., 2001). Repeated exposure of mice to ketamine induces the dysfunction of a subset of cortical fast-spiking inhibitory interneurons, with loss of expression of PV and GAD_{67} (Behrens et al., 2007). Ketamine also activates the innate immune enzyme NADPH-oxidase in the brain, and that the superoxide produced is responsible for the dysfunction of cortical PV neurons (Behrens et al., 2007).

Neuronal production of interleukin-6 (IL-6) is necessary and sufficient for the ketamine-mediated activation of NADPH-oxidase in brain. In vivo studies utilizing IL-6-deficient

mice, prevented the increase in superoxide by ketamine and rescued the interneurons (Behrens et al., 2008). Interestingly the effects of activation of the IL-6/ NADPH-oxidase pathway on the PV system are reversible in the adult brain, but irreversible in the developing cortex (Behren and Sejnowski, 2009). These studies provide an insight into the mechanism behind NMDA receptor antagonist induced reduction in PV neurons. Whether similar mechanisms hold true for PCP and MK-801 remains to be examined.

The PV deficit appears consistently in the literature. Studies employed to date have reported these deficits in experiments utilizing different types of NMDA receptor antagonists, in different species and sexes, following a number of different treatment regimes and at a number of different testing points (Table 2 below provides a summary of these different studies).

 Insert Table 2 here.

As can be seen from the Table 2, the pathological deficits in these studies are often reported in association with other behavioural and neurochemical changes relevant to those reported for the human studies. Findings of both behavioural and pathological deficits in the NMDA receptor antagonist model similar to those found in schizophrenia, serve to further increase the face-and-construct validity of the NMDA receptor antagonist models. In particular deficits in prefrontal cortical pathology may be of particular importance with respect to the cognitive deficits found in these animals (Lewis et al., 2005).

8.0 Discussion and Conclusions

8.1 General issues

There are a number of important issues that arise from inspection of the work reviewed above. First the evidence seems almost overwhelming in favour of the use of NMDA antagonists to mimic cognitive (and some aspects of negative) symptoms in rodents along with associated neuropathological changes. The second issue is the inconsistencies between different studies in doses, dosing schedule used, strains of rats and variabilities in the test procedures, which are inescapable features of preclinical studies. A third issue is the use of female subjects in our studies and males in almost all other studies. It is important to acknowledge the clear sex differences in brain, behaviour and pharmacokinetics in rodents and humans, which affect outcome and ideally both male and female subjects should be used (see Cahill 2006 for review).

8.2 Limitations of the NMDA antagonist model

The NMDA antagonist model does not incorporate neurodevelopmental or genetic approaches, which are key to the etiology of schizophrenia in humans. This represents a limitation of the NMDA antagonist model in adult animals and must be duly acknowledged. One way to address this is the emerging use of neonatal NMDA antagonist treatment, most notably PCP on post-natal days 7, 9 and 11 (as recently demonstrated by Broberg et al. 2008; 2009). We had attempted to combine a pharmacological approach with a neurodevelopmental one and treated isolation reared rats with PCP in our laboratory but we were not successful in producing greater or more robust cognitive deficits than those produced by our sub-chronic PCP regime alone (unpublished studies). The validity of using a pharmacological method to induce schizophrenia symptoms in animals should be questioned since not many cases of

schizophrenia are solely caused by using such drugs, even if they induce similar symptomatology in the short term as described in the Introduction.

8.3 Validity of the NMDA antagonist model

This brings us onto the next key issue, which is the predictive validity of the NMDA antagonist model. Many of the studies show positive effects of SGAs and lack of effect of the FGAs and cite this as a good example of predictive validity of the model which could be argued to not accurately represent the clinical situation, given the lack of efficacy of SGAs for improving cognitive deficits. However it is important to remember that we are using animals to mimic aspects of a complex human disease where patients have genetic and neurodevelopmental predispositions for the disorder, may have co-morbid drug abuse, and are commonly prescribed different pharmacological medications. In marked contrast, our animals have no genetic predisposition (unless transgenic mice are used) and no previous drug exposure. Instead they are genetically identical (if using an inbred strain) and live in optimal conditions (lighting, noise level, humidity etc) for that species with minimum stress. This makes it even harder to fully mimic a human disorder (particularly a psychiatric disorder) and this caveat is important to recognise.

8.4 Sub-chronic versus acute NMDA antagonist dosing schedules

A further important issue is the use of acute vs. chronic dosing schedules of NMDA antagonists. In our view, the use of a chronic (or sub-chronic) dosing schedule is of considerably more value in attempting to replicate the symptomatology and neuropathology of a chronic illness than acute drug induced effects, although this does not preclude the use of acute studies where appropriate. In the sub-chronic studies, , animals receive a fixed dosing regime of the NMDA antagonist at adulthood (in our laboratory this is 7 days treatment with 2 mg/kg of PCP given twice daily at approx 9 am and 4 pm followed by at least a 7 day drug-

free period before animals are tested). This dosing regime leads to robust and enduring cognitive, social behaviour and neuropathological deficits of relevance to schizophrenia as outlined above. Clearly this is of more value in providing a valid animal model than an acute pharmacological challenge, which mainly produces transient neurochemical alterations, but may have some value for a fast screening paradigm, often leading to proper dose selection of the appropriate antipsychotic drug for consequent chronic studies. The lasting deficits induced by this regime also allow us to retest our animals after acute effects of antipsychotics have worn off, thus making some attempt to adhere to the principles of the 3Rs (ie replacement, reduction and refinement). Other advantages of such a paradigm include testing the animals in a drug-free state, therefore eliminating any confounding acute NMDA antagonist effects. Importantly, as evidenced in the neuropathology section, chronic treatment with NMDA antagonists induces lasting neurobiological changes of relevance to schizophrenia whereas acute treatment does not. The possibility of inhibiting or preventing such pathological changes with novel targets and therapies is a particularly exciting area of research and could lead to real advances in therapy for patients.

8.5 Acute versus sub-chronic antipsychotic dosing schedules

Another limitation stems from the efficacy of single doses of antipsychotic drugs in our animal models, whereas repeated treatment is often required in the clinic. The majority of studies showing a reversal of cognitive deficits in the animal models for some of the paradigms discussed above, involve acute administration of a drug (e.g. antipsychotic, specific receptor agonist/antagonist, novel cognitive enhancer etc.) immediately prior to testing. The resultant pharmacological effect of these drugs appears sufficient to reverse the deficit. Whether the reversal represents a complete loss of the deficit is unlikely, more a short term reversal due to a pharmacological effect of the particular treatment. For example, we

have previously shown that acute administration of clozapine reverses the deficit in NOR in the sub-chronic PCP animal model (Grayson et al. 2007). However if these animals are tested again in the NOR paradigm, the deficit reappears. More studies utilising long term treatment regimes with testing post-dosing could provide a better insight into effects of drugs that are more likely to result in molecular/pathological changes and that could abolish cognitive dysfunction in the long-term and provide a real benefit for patients. We attempted this with a 28 day dosing schedule with asenapine in reversal learning where the improvement was still present the following day in the absence of asenapine treatment on day 17 (McLean et al. 2010b)

8.6 Summary

In summary, in spite of the limitations outlined above, the use of NMDA antagonists to mimic cognitive and social behaviour deficits provides a relatively valid animal model for schizophrenia. Sufficient studies were conducted to show that acute and sub-chronic dosing regimes produce deficit symptoms of relevance to schizophrenia. More work is clearly needed to refine the model. However, we recommend the use of PCP in a sub-chronic dosing regimen combined with the use of several different tests to assess the various domains of cognition affected in schizophrenia as outlined by MATRICS in addition to social behaviour and neuropathological studies.

9.0 References

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TABLE 1

Drug	Dose	Time of testing	Sex/Strain	Duration of test	Pairing of animals	Reference
PCP	Subchronic 2.5 mg/kg for 3 days	Tested 45 minutes later	Male Wistar	10 minutes	saline/saline, drug/drug	Sams-Dodd, 1995
PCP	Subchronic 2.5 mg/kg for 3 days	Tested 45 minute later	Male Sprague-Dawley	10 minutes	saline/saline, drug/drug	Bruins Slot et al., 2005
PCP	Subchronic 3mg/kg for 14 days	Tested 24 hours later	Male Sprague-Dawley	10 minutes	saline/saline, drug/drug	Lee et al., 2005
PCP	Subchronic 10 mg/kg, for 15 days	Tested 20 hours later (on days 1, 8 and 15)	Male Long-Evans	10 minutes	saline/saline, saline/drug	Audet et al., 2009
PCP	Subchronic 2mg/kg, bi-daily for 7days	Tested 1-6 weeks later	Female hooded-Listers	10 minutes	saline/saline, saline/drug	Snigdha and Neill 2008a,b
Ketamine	Acute 7mg/kg	Tested 30 minutes later	Male Wistar	10 minutes	saline/saline, drug/drug	Silvestre et al., 1997
Ketamine	Subchronic 30mg/kg for 5 days	Tested 10 days later	Male Sprague-Dawley	7 minutes	saline/saline, saline/drug	Becker et al, 2003
MK801	Acute 0.2mg/kg	Tested 30 minutes later	Male Sprague - Dawley	30 minutes	saline/saline, drug/drug	Rung et al., 2005
MK801	Sub-Chronic 0.13 mg/kg/day for 14 days	Tested 45 minutes later	Male Wistar	10 minutes	saline/saline, drug/drug	Matsuoka et al., 2005

Table 1: A comparative table showing some of the differences in sex, strain, dosing regime and method of testing used by different groups (using adult rats) in the social interaction test.

Drug/Dose	Time of testing	Sex/Strain	Parvalbimun	Brain Region	Behavioural Deficits	References
Phencyclidine						
Acute (2.58 mg/kg)	24hrs	Male hooded Long -Evans	Deficit in mRNA	Reticular Thalamic Nucleus	Deficit in Attentional Set-Shifting	Egerton et al (2005)
Chronic Intermittent Exposure (2.58 mg/kg)	72hrs	Male hooded Long –Evans	Deficit in mRNA	Reticular Thalamic Nucleus, Prefrontal Cortex	Metabolic Hypofunction in Prefrontal Cortex	Cochran et al (2003)
Subchronic (2 mg/kg bi-daily for 7 days)	6 weeks	Female Lister Hooded	Deficit in PV IR neurons	Hippocampus	Deficits in Reversal Learning	Abdul-Monim et al (2007)
Subchronic (2 mg/kg bi-daily for 7 days)	6 weeks	Male Lister Hooded	Deficit in PV IR neurons	Hippocampus	Disturbances in Social Interaction	Jenkins et al (2008)
Subchronic (2 mg/kg bi-daily for 7 days)	6 weeks	Male Lister Hooded	Deficit in PV IR neurons	Prefrontal Cortex	Deficits in Novel Object Recognition	Jenkins et al (2010)
Neonatal (10 mg/kg on PND 7)	PND56	Male Sprague Dawley	Deficit in PV IR neurons	Cortical deficits	No change in calretinin immunoreactive neurons	Wang et al (2008)
MK-801						
Chronic (0.02 mg/kg for 21 days)	24hrs	Male Long-Evans	Deficit in PV IR neurons	Hippocampus	No change in calretinin IR neurons	Braun et al (2007)
Chronic (0.02 mg/kg for 14 days)	24hrs	Male Long-Evans	Deficit in relative number of PV IR neurons	Hippocampus	Cognitive deficits (Hole Board)	Rujesca et al (2006)
Prenatal exposure (0.2 mg/kg on E15-E18)	PND 35 & 63	Male & Female Sprague Dawley	Deficit in PV IR neurons	Prefrontal Cortex	Enhances PCP induced hyperlocomotion	Abekawa et al (2007)
Ketamine						
Subchronic (30mk/kg for 5 days)	2 weeks	Male Sprague Dawley	Deficit in PV IR neurons	Hippocampus		Keilhoff et al (2004)

Table 2: Summary of studies evaluating the effect of NMDA receptor antagonists on parvalbumin expression in the rat brain. The table highlights some of the differences in dosing regimens, time of testing following last treatment, sex, strain, and regions tested by a number of research laboratories. It also highlights any behavioural changes reported in the same studies. PND = post natal day; PV = parvalbumin; IR = Immunoreactive