Published in final edited form as:
Pharmacol Ther. 2009 May ; 122(2): 150–202. doi:10.1016/j.pharmthera.2009.02.004.

Using the MATRICS to guide development of a preclinical cognitive test battery for research in schizophrenia

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Abstract

Cognitive deficits in schizophrenia are among the core symptoms of the disease, correlate with functional outcome, and are not well treated with current antipsychotic therapies. In order to bring together academic, industrial, and governmental bodies to address this great 'unmet therapeutic need', the NIMH sponsored the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative. Through careful factor analysis and consensus of expert opinion, MATRICS identified seven domains of cognition that are deficient in schizophrenia (attention/vigilance, working memory, reasoning and problem solving, processing speed, visual learning and memory, verbal learning and memory, and social cognition) and recommended a specific neuropsychological test battery to probe these domains. In order to move the field forward and outline an approach for translational research, there is a need for a "preclinical MATRICS" to develop a rodent test battery that is appropriate for drug development. In this review, we outline such an approach and review current rodent tasks that target these seven domains of cognition. The rodent tasks are discussed in terms of their validity for probing each cognitive domain as well as a brief overview of the pharmacology and manipulations relevant to schizophrenia for each task.

Keywords

Schizophrenia; cognition; MATRICS; attention; working memory

1. Introduction

Schizophrenia research has come full circle in the last decade, as the field is now reinvestigating the cognitive deficits experienced by patients of the disorder first described as *dementia praecox* (Kraepelin, 1896). The cognitive deficits characteristic of schizophrenia patients are increasingly recognized as core symptoms of this group of disorders. These deficits often precede the manifestation of psychosis (Cornblatt et al., 1998; Cornblatt et al., 1997; Erlenmeyer-Kimling, 2000), are orthogonal to positive and negative symptoms (Goldberg and Weinberger, 1995; Nieuwenstein et al., 2001), are relatively stable over time (Albus et al., 2002), continue to be present after remission of psychosis, and are relatively unaffected by antipsychotic treatment (Carter, 2005; Harvey and Keefe, 2001; Keefe et al., 2007; Mintz and Kopelowicz, 2007). This lack of effective treatment is discouraging in light of reports indicating that cognitive performance closely correlates with functional outcome experienced by patients (Green, 1996, 2006). Therefore, more research has turned towards developing drugs

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to improve cognition in schizophrenia patients and potentially improve global functions such as social interaction and employment (Floresco et al., 2005; Green, 1996, 2006). In response to the lack of effective treatments, the United States National Institute of Mental Health (NIMH) sponsored the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative (Marder et al., 2004) in order to bring together academic, industrial, and governmental bodies to address this great 'unmet therapeutic need'.

Through this collaborative effort, MATRICS developed a consensus of opinion on the core cognitive deficits suffered by schizophrenia patients. Seven cognitive domains were identified as commonly deficient in schizophrenia patients: attention/vigilance; working memory; reasoning and problem solving; processing speed; visual learning and memory; verbal learning and memory; and social cognition (Nuechterlein et al., 2004). Upon identification of these domains, a standardized test battery was developed to ensure that future cognitive testing in schizophrenia patients is consistent and comparable across studies (Marder and Fenton, 2004). Unfortunately, although the clinical program of the MATRICS has achieved a consensus of opinions on a starting point for standardized testing, there has been little development in the creation of a parallel preclinical test battery to assess novel compounds and their mechanism of action in these seven domains of interest (Floresco et al., 2005). Here we examine a number of possibilities to outline a framework that would facilitate the effective utilization of preclinical assessments in rodents to aid in the discovery and selection of candidate compounds for clinical evaluation of potential procognitive effects in schizophrenia.

1.1. Measures of cognition in animals

The subject of validating animal cognitive paradigms has become more pertinent in recent years, with a surge of publications regarding cognitive processing in rats and mice increasing by 6000% from 1980 to 2002 (Sarter, 2004). Despite this increase in research, however, little impact has been realized in the clinic, creating a 'translational bottleneck' (Hyman and Fenton, 2003). It has been suggested that the predictive validity demonstrated to date has been 'to an overwhelming degree, disappointing' (p. 645; Sarter, 2004). With respect to schizophrenia, this problem may be due in part to a lack of an effective, current treatment to use as a positive control in the validation of putative test paradigms (Floresco et al., 2005; Markou et al., 2009). Nevertheless, another explanation may reflect the tendency to use behavioral paradigms that do not properly assess the cognitive domain of interest (Sarter, 2004, 2006). Such paradigms often rely on simple assays that do not properly take into account the influences that changes in motivation, motoric capability, arousal level, sensory capability, and innate behavior can have on performance, and hence may not produce results that are reliably predictive of the complex nature of human cognition (Cahill et al., 2001; D'Hooge and De Deyn, 2001; Hagan and Jones, 2005; Sarter, 2004, 2006; Thorpe et al., 2004). More specifically, it has been suggested that preclinical assessments will be more likely to be effective in predicting the efficacy of pharmacological treatments assayed using laboratory-based endpoints in proof-of-concept tests in humans early in the clinical trial process (Jones et al., 2008; Markou et al., 2009). Thus, discussion of the cross-species translatability of cognitive paradigms between rodents and humans will be a priority in this review (D'Mello and Steckler, 1996; Geyer and Markou, 2002; Geyer and Moghaddam, 2002; Jentsch, 2003; Robbins, 1998; Sarter, 2004, 2006; Steckler and Muir, 1996). It should be noted that in this review, we generally use the term translation to refer to the comparability of measures, constructs, and effects across species, typically from rodents to humans.

The need for a preclinical test battery (Hagan and Jones, 2005; Nuechterlein et al., 2005) and the theoretical framework within which to approach the creation of such a battery has been discussed elsewhere (Floresco et al., 2005). Floresco et al. (2005) identified two approaches for developing cognitive paradigms and animal models that mimic the cognitive deficits

observed in schizophrenia: 1) manipulating specific systems that are altered in schizophrenia patients using lesions or pharmacological manipulations; and 2) developing comprehensive models of the disorder and attempting to identify cognitive deficits in the model that resemble deficits found in schizophrenia. No detailed discussion of putative animal models relevant to the specific cognitive domains identified by MATRICS, as being affected in schizophrenia, has yet taken place, though. Thus, our goal is to review the current "State of the Art" in animal cognitive paradigms and their potential for use in evaluating cognitive functioning in animal models of schizophrenia. Our focus will be placed on paradigms that specifically assess the cognitive domains disrupted in schizophrenia as described by the MATRICS program (see Table 1). In a series of meetings that followed MATRICS, under the title of Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS), more specific constructs based on cognitive neuroscience were identified as being abnormal in schizophrenia. Human tasks that assessed these constructs were evaluated in CNTRICS, but corresponding animal tests were not discussed systematically. Nevertheless, the present review has not included the constructs identified in CNTRICS, but remains focused on the seven-domain test battery developed by MATRICS. The need for compiling such a list of potential tasks was recognized by the NIMH-funded clinical TURNS (Treatment Units for Research on Neurocognition in Schizophrenia) program, which developed a preclinical subcommittee that surveyed a number of experts in the field and prepared an initial compilation of tasks that is summarized on the TURNS website (Young et al., 2006; http://www.turns.ucla.edu/preclinical-TURNS-report-2006b.pdf). Here, we have brought together and discussed a variety of cognitive tasks that probe similar cognitive domains putatively matching those assessed in the MATRICS test battery. Each task will be discussed in detail, including:

- **a.** Introduction to the human and animal tasks;
- **b.** validity of the animal task for probing the constructs probed by MATRICS tests in man;
- **c.** perturbations of task performance;
- **d.** perturbations of task performance with relevance to schizophrenia;
- **e.** effects of established antipsychotics on task performance;
- **f.** studies that have been conducted with putative novel therapeutics.

With respect to the validation of the tasks, we focus here on face, construct, etiological, and predictive validity, as discussed in detail elsewhere (Geyer and Markou, 1995). Face validity refers to the phenomenological similarity between the behavior exhibited by the animal model and the specific symptoms of the human condition. Face validity is particularly useful heuristically in the initial phases of task design. In the present context, however, construct validity is more germane to the discussion of tasks that assess specific domains of cognition. The MATRICS neurocognition committee identified seven orthogonal domains of cognition that were deficient in schizophrenia specifically because cognition is not a unitary construct as evidenced by extensive neuropsychological studies (Nuechterlein et al., 2004). The rich literatures of psychology and neuroscience further demonstrate the phenomenological and neurobiological separations between these domains of cognition. Thus, while overall cognitive function is often described as being deficient in schizophrenia, the pharmacological tools used in psychiatric treatments influence neurobiological substrates that are specific to separate domains of cognition simply because these different domains have distinctive anatomical and neurochemical substrates (Nuechterlein et al., 2005). Hence, to identify the pro-cognitive adjunctive treatments recommended by MATRICS, it is necessary that both preclinical and clinical assessments of potential efficacy focus on validated endpoints appropriate to the specific cognitive domain of interest. Furthermore, in the series of CNTRICS meetings,

construct validity was deemed the critical and indeed the only essential aspect of task selection (Carter et al., 2008). Construct validity of a test is defined as the accuracy with which the test measures that which it is intended to measure. Hence, this critical form of validity requires careful definition of the specific cognitive construct being considered. The clarity of the definition of the construct is also an essential consideration when attempting to translate the cognitive process being probed in an animal test to the corresponding process being assessed in the clinical evaluation of patients. As emphasized by the CNTRICS program, the valid translation of tests of cognition across species will likely require the further adaptation of both animal and human tests of the key cognitive constructs that are most affected in schizophrenia (Barch et al., 2009).

The concept of etiological validity is closely related to the concept of construct validity. A model has etiological validity if the etiologies of the cognitive deficit in the animal model and the human condition are identical. Thus, assessing etiological validity involves an evaluation of the manipulation used to induce abnormal cognition in the animal model, such as a drug, lesion, or developmental insult. Insofar as the etiologies of specific cognitive deficits in schizophrenia are largely unknown, etiological validity in this context is generally limited to current hypotheses. One aspect of etiological validity that is germane to this discussion involves the anatomical substrates that have been determined to be essential to a specific cognitive construct as reflected in performance on a given task. For example, as illustrated below, the dependence of a specific learning task on an intact hippocampus may be used to evaluate the etiological validity of the task and also assess the cross-species comparability of tasks used in animals versus humans.

Predictive validity refers to the ability of a model to make correct predictions about the human phenomenon of interest. In psychiatry, the term predictive validity is often used in the narrow sense of pharmacological isomorphism, i.e. the model's ability to identify drugs having therapeutic value in humans. This form of validity is particularly problematic in the present context, however, because at present we have no established pharmacological treatments with known efficacy in the amelioration of cognitive deficits in schizophrenia (Floresco et al., 2005). Subsequent to the end of MATRICS, NIMH established a clinical trials program called TURNS, which was intended to implement the MATRICS battery using novel compounds and co-treatment experimental designs in order to identify efficacious treatments. Having one or more established treatment would provide the kind of positive control that is so essential to the assessment of pharmacological predictive validity in preclinical models (Markou et al., 2009). Although TURNS remains an ongoing effort, no appropriate treatment has been found as yet. Considered more broadly, however, predictive validity of a test can be supported by the identification of any variables that have similar influences in both the animal task and the parallel assessment made of the human construct of interest. Other forms of validity, such as discriminant and convergent validity, are not addressed here despite their relevance to this discussion.

1.2. Pharmacological manipulation models of schizophrenia

Many of the classic pharmacological procedures used to mimic aspects of schizophrenia, including behavioral disruptions produced by treatments with drugs such as amphetamine, lysergic acid diethylamide (LSD), phencyclidine (PCP), or ketamine stem from the predictive validity of these drugs to produce schizophrenia-like symptoms in humans. These manipulations generally have been developed to model the positive symptoms of schizophrenia, and are effective screening tools for typical and atypical antipsychotics, all of which that are currently approved have dopamine D_2-like receptor blocking properties (Creese, 1983; Geyer and Moghaddam, 2002; Segal et al., 1981). Because antipsychotics have largely failed in ameliorating cognitive symptoms of schizophrenia, rodent tasks of cognition that are

sensitive to existing antipsychotics will be limited by this potentially "false positive" result (Geyer, 2006; Meyer et al., 2005). Basing the manipulation on clear clinical evidence of pathology will be crucial to the refinement of these classic pharmacological manipulations to target cognitive deficits in schizophrenia specifically. For example, dopaminergic manipulations commonly produce an inverted-U shaped dose response effect on cognitive performance, with low doses of dopamine agonists improving performance while high doses are disruptive (Chudasama and Robbins, 2004; Goldman-Rakic et al., 2004). The considerable evidence for dopaminergic hypofrontality in the brains of schizophrenia patients supports the study of selective (either receptor or tissue specific) dopamine agonists and partial agonists to ameliorate cognitive symptoms in schizophrenia patients (e.g. catechol-O-methyltransferase (COMT) inhibition; Apud and Weinberger, 2007). Thus a different perspective of dopaminergic control of cortical functions is required for modeling cognitive dysfunction in schizophrenia, as opposed to classical models of psychosis.

Many of the more established cognitive tasks developed in rodents have their historical roots in models of Alzheimer's disease. Consequently, the pharmacology and neural substrates relating to the cholinergic system are the most thoroughly studied in many of these tasks. Although there have been modest effects of acetylcholinesterase inhibitors in Alzheimer's disease, the efficacy of these drugs is unclear in schizophrenia, with largely negative results in double-blind randomized placebo designs (Ferreri et al., 2006). Schizophrenia patients with poor cognition (as measured by the digit span distractibility test) showed significant improvement after withdrawal from anticholinergic medication, which supports the hypothesis that some cognitive dysfunctions in schizophrenia patients may be due to medications instead of core pathology (Mori et al., 2002). Hence, although indirect pro-cholinergic efficacy is a positive control for many of the cognitive tasks used, this efficacy could be construed as a false positive when developing these tasks to model cognitive deficits in schizophrenia. Direct agonists such as nicotine may prove to be more relevant positive controls as they do ameliorate some cognitive symptoms in schizophrenia patients (for review see Levin and Rezvani, 2006). Based on these general principles of construct and predictive validity, we will highlight pharmacological treatments and behavioral measures that we feel are best supported for modeling specific pathology and cognitive constructs relevant to schizophrenia.

1.3. Developmental manipulation models of schizophrenia

The developmental hypothesis of schizophrenia stems from observations of ventricular enlargement and decreased cortical volumes without direct evidence of neurodegeneration. Environmental factors that cause dysfunction in neural systems that normally reach maturity in late adolescence, such as a viral exposure to the developing fetus (Mednick et al., 1988; O'Callaghan et al., 1991; Takei et al., 1996) or obstetric complications (Owen et al., 1988), are also linked to schizophrenia risk. Although there are several models of pre-, peri- and post-natal insult relevant to schizophrenia (Koenig et al., 2005; Lipska and Weinberger, 2000; Powell and Geyer, 2002), two of the models most widely studied, especially within cognitive domains, have been neonatal ventral hippocampal lesions and isolation rearing. The rodent neonatal ventral hippocampal lesion (NVHL) model in rats was based on the observation of developmental abnormalities in the hippocampus of schizophrenia patients, NVHL rats exhibit numerous delayed, post-pubertal deficits with relevance to schizophrenia including dopamine agonist sensitivity (Lipska et al., 1993; Lipska and Weinberger, 1994, 2000), deficits in prepulse inhibition of startle (PPI) (Lieberman et al., 1997; Lipska et al., 1995), altered prefrontal neuronal firing (O'Donnell et al., 2002), and some evidence for cognitive disturbances (Le Pen et al., 2003). The isolation-rearing model was also developed to provide a non-lesion and non-pharmacological model to enhance our understanding of the developmentally linked emergence of neural and behavioral abnormalities in schizophrenia patients (Geyer et al., 1993). Isolation-reared rats exhibit profound abnormalities in behavior,

drug responses, and neurochemistry compared to socially reared rats (Geyer et al., 2001; Powell and Geyer, 2002; Weiss and Feldon, 2001), although the resultant phenotype is not always consistent (Cilia et al., 2005). Numerous behavioral and cognitive differences have been noted in adult rats and mice reared in social isolation, including deficits in attention, habituation, and other forms of cognition (Dalley et al., 2002; Jones et al., 1992; McLean et al., 2008).

1.4. Genetic manipulation models of schizophrenia

Genetic manipulations in mice have the potential to advance substantially our knowledge of neural systems that are relevant to symptoms of schizophrenia. The surge of interest in describing clinical "endophenotypes" that are more readily quantifiable and thus more robust measures than complex diagnoses for testing genetic associations supports both the clinical and preclinical efforts to understand genetic contributions to schizophrenia. Many of these endophenotypes, including certain domains of cognition as discussed in this review, can be modeled in animals. Caution must be exercised however, as genetic abnormalities linked to schizophrenia are often non-Mendelian, can involve mutations in non-coding regions of the genes, and may produce species-specific alterations in gene function (e.g. Disrupted in schizophrenia 1; DISC1; Clapcote et al., 2007; Low and Hardy, 2007). Nevertheless, genetic manipulations are important tools as they can specifically manipulate target systems and possible phenotypic pathology associated with genes conferring risk for schizophrenia. A recent review describes animal models for genetic disruption of select putative risk genes for schizophrenia (O'Tuathaigh et al., 2007a) including neuregulin-1 (NRG1), dysbindin (DTNBP1), regulator of G-protein signaling 4 (RGS4), COMT, proline dehydrogenase (PRODH), and DISC1. Some of these models (DISC1, Koike et al., 2006; Pletnikov et al., 2007; NRG1, O'Tuathaigh et al., 2007b) have been examined in simple cognitive tasks such as delayed matching to sample, Morris water maze, and Barnes maze and will be discussed throughout the review. Other models (e.g. null mutation of NRG1 and NMDAR1) have shown more promise in modeling "antipsychotic-sensitive" behaviors such as hyperactivity or social cognition disruptions in schizophrenia (Mohn et al., 1999; O'Tuathaigh et al., 2007b).

2. Attention/Vigilance

Knowledge regarding the cognitive domain of attention and vigilance has increased greatly over the last two decades. Consistent with revelations regarding short term memory in the 1970s and 1980s, it has become widely accepted that attention does not refer to a single cognitive process. Attention can be divided into three sub-domains of: selective, describing the process by which environmental stimuli are chosen for attention; sustained, also referred to as vigilance, where attention is focused on particular stimuli for prolonged periods; and divided attention, or attentional control, where attention is focused despite distractors, and/or on multiple tasks (Parasuraman, 1998). Schizophrenia patients exhibit impaired attentional processes (Cornblatt and Keilp, 1994), which may reflect core deficits of the disorder (Chudasama and Robbins, 2004) and provide reliable endophenotypes for genetic susceptibility (Chen and Faraone, 2000; Cornblatt and Malhotra, 2001). Attentional deficits in schizophrenia patients are most consistently measured by the continuous performance test (CPT), which more specifically assesses sustained attention (Riccio et al., 2002). Recently, the MATRICS group chose the CPT-identical pairs (IP) version as the best task to assess attention in schizophrenia patients. The CPT-IP requires the subject to monitor incoming stimuli (presented for 50 ms) and indicate (via a finger-lift from a reaction-time key) when two stimuli in a row are identical. Although administering the full task takes approximately one hour, most researchers use a limited version requiring only 4 – 14 minutes (Cornblatt and Malhotra, 2001).

Several existing animal tasks assess sustained attention in animals, including the 5-choice serial reaction (5-CSR) task (Carli et al., 1983; Robbins, 2002), the sustained attention task (SAT;

McGaughy and Sarter, 1995), and the lateralized reaction-time task (LRT; Carli et al., 1985). Several other paradigms are currently being developed to assess attention, such as the 5-arm maze (Durkin et al., 2000) and the covert attentional task, (Stewart et al, 2001), but due to limited available information on these paradigms, they will not be covered in this review.

2.1. 5-Choice Serial Reaction task

The 5-CSR task was first developed by Trevor Robbins and colleagues in the early 1980s (Carli et al., 1983) to study different aspects of attention deficit hyperactivity disorder (ADHD) and has been suggested to parallel continuous performance testing in humans (Day et al, 2008). A full description of the history, development, and original procedure of the task can be found elsewhere (Robbins, 2002). In brief, the testing chamber consists of an operant box with a curved wall at the rear, opposite the location of food delivery (magazine). Five apertures are recessed in the curved wall on the same plane (originally nine were available, and test chambers are still available with nine apertures – termed “9 hole box” and can be used under certain circumstances to alter task difficulty). The rodent is required to initiate a trial by entering (nose-poking) into the magazine, which initiates the onset of the inter-trial interval (ITI; typically 5 s), after which one of the five apertures is illuminated and the animal is required simply to nose-poke in the lit aperture. After a correct response, a food reward is delivered. Errors are punished with a time-out phase (typically 5 s). The task typically lasts for 100–120 trials or 30 min, whichever is completed sooner.

Analyzing the behavior of rodents performing the 5-CSR task produces a variety of measures, including accuracy (proportion correct responses of total correct and incorrect responses, aka % correct), omissions (proportion of omitted trials, % omissions), anticipatory responses (premature responses, responses before stimulus presentation), perseverative responses (repeated responses at the response apertures), total trials completed, as well as several response latency indices including mean correct latency (MCL; response latency), mean incorrect latency (MIL) and mean reward latency (MRL). No single measure reliably predicts attentional performance as it is the effect of treatment on all of these measures and the resultant interpretation that provides such information (Table 2). Robbins, (2002) describes the variety of possible interpretations that are available from changes in each of these measures. Suffice to say that the 5-CSR task provides information on attention (accuracy and % omissions), impulsivity (premature responses, perseveration), processing speed (accuracy and MCL), motoric effects (latency measures, % omissions, premature responses, total trials), motivation (MRL, % omissions, premature responses, total trials), and cognitive flexibility (MRL and perseveration). While earlier reviews in the literature link drug-induced effects on % omission levels to response vigor or motivation (Robbins, 2002), it has been noted that changes in omission levels can be dissociated from non-attentional effects of drugs (Mirza and Stolerman, 2000). Also, several reports suggest that % omission levels could reflect a measure of attentional function, especially sustained attention or vigilance, when concomitant changes in MCL, MRL, and total trials are not observed (Cordova et al., 2006;Fletcher et al., 2007;Inglis et al., 2001;Risbrough et al., 2002;Young et al., 2007a;Young et al., 2004). Hence, it is accepted that viewing single measures in isolation does not convey the true effect of manipulations, thus the combined effect on measures must be taken into consideration when interpreting the data. Moreover, measures observed in different versions of the task may not necessarily be interpreted similarly, for example premature responding is most akin to impulsivity measures in numerous training techniques, yet may reflect a ‘subject’s basic state of locomotor activation and motivation’ (pp. 630; Hahn and Stolerman, 2002) elsewhere. Hoyle et al. (2006) reported that while performance using one training method may result in alterations of accuracy and MCL, using another method produces effects on % omissions, in agreement with previous observations (Young et al., 2007a;Young et al., 2004).

2.1.1. Validity of the 5-CSR task for assessing attention/vigilance—Robbins (2002) and Chudasama and Robbins (2004) both provide thorough reviews on the 5-CSR task in relation to the neuroanatomy of the task. Neuroanatomical discussion here will be limited to that which relates to attention in humans (Table 3). Performance of the 5-CSR task has been subject to numerous lesion (Carli et al., 1983; Christakou et al., 2001; Chudasama et al., 2003; Granon et al., 1998; Kirkby and Higgins, 1998; Muir et al., 1996a; Muir et al., 1996b; Passetti et al., 2002), microdialysis (Passetti et al., 2000; Passetti et al., 2003), as well as 2DG analyses (Barbelivien et al., 2001), and genetic manipulation studies (Hoyle et al., 2006; van Gaalen et al., 2003; Young et al., 2007a; Young et al., 2004). Specifically, the medial prefrontal cortex (mPFC) appears to be important for attentional processes, particularly the dorsal mPFC (Barbelivien et al., 2001; Muir et al., 1996b; Passetti et al., 2002), while the lateral mPFC appears to mediate perseverative behaviors (Passetti et al., 2002). The frontal cortex is important for human attentional performance as well (Ogg et al., 2008; Rueckert and Grafman, 1996; Salgado-Pineda et al., 2003); and imaging studies indicate enhanced activation of the frontal lobes during CPT performance in normal subjects (Salgado-Pineda et al., 2003). Further similarities between brain regions that subserve human and rodent sustained attention are found where lesions of the hippocampus do not impair rat performance of the 5-CSR task (Kirkby and Higgins, 1998), but see discussion below regarding ventral hippocampal lesions (Le Pen et al., 2003), and the hippocampus is not active during normal human performance of the CPT (Cohen et al., 1998). Moreover, the thalamic regions of both rats (Baunez and Robbins, 1999) and humans (Salgado-Pineda et al., 2003) have been implicated in sustained attention performance. Surprisingly, however, parietal cortex lesions do not impair rat performance of the 5-CSR task (Muir et al., 1996a), despite this area being the presumed locus of the posterior attentional system in primates where damage has been linked to attentional disturbances (Posner and Petersen, 1990). The parietal cortex is important for a subject's ability to disengage from an attentional focus in order to attend to a target elsewhere (Parasuraman, 1998; Petersen et al., 1988; Posner et al., 1984; Robinson et al., 1995; Sarter et al., 2001). Thus, the parietal cortex appears to execute a 'matching function', where two stimuli can appear and differing responses are required dependent upon the stimulus (Broussard et al., 2006; Bunge et al., 2002; Robinson et al., 1995). Thus it is perhaps not surprising that damage to this region does not impair sustained attention performance in the 5-CSR task where the same response is required for a unitary stimulus. Such an assumption is supported by parietal cortical firing in rats performing the SAT where two differing responses are required (see below; Broussard et al., 2006). Additional similarities between human CPT and rat 5-CSR task performance arise, however, when testing normal subjects. As with humans in the CPT (Mani et al., 2005), reduced attentional performance is observed with increased age in rats (Grottick and Higgins, 2002; Jones et al., 1995; Muir et al., 1999). Sleep deprivation, known to cause attentional impairments in humans (Caldwell et al., 2000; Jewett et al., 1999), can also impair 5-CSR task performance in rats (Cordova et al., 2006; Godoi et al., 2005). With respect to drug treatments, predictive validity has also been demonstrated using the 5-CSR task (Grottick and Higgins, 2002). The effects of psychostimulants and cognitive disrupters have been assessed in the 5-CSR task under various procedures. These effects will be discussed below in greater detail with relevance to schizophrenia relevant disruption and putative cognition enhancers. Overall, the 5-CSR task has demonstrated validity on a number of parameters related to human CPT, with construct and etiological validity regarding neuroanatomical specificity, and predictive validity in that similar manipulations impair (age and sleep deprivation) and improve performance (psychostimulants) in attention across rodents and humans.

2.1.2. Perturbation of 5-CSR task performance—Numerous perturbation studies have been performed in the 5-CSR task, ranging from systemic to intra-cerebral administrations in normal or poor-performing animals, lesions of many types and locations, and the use of numerous task challenges. The lesion studies and their effects on performance have been

described above, with frontal lesions providing relevance to the hypofrontality hypothesis of schizophrenia. Challenges to standard task performance have also been utilized widely (Grottick et al., 2003; Grottick and Higgins, 2002; Mirza and Stolerman, 2000). For example, reducing the stimulus duration (SD) or stimulus brightness, introducing an increased ITI, varying the ITI, extending the session duration, interpolation of distractors, or combinations of these manipulations (Robbins, 2002) have all been used to alter task performance. It must be noted, however, that any change to the protocol of the task, e.g. introducing a longer ITI when training was on a shorter ITI, may introduce a learning confound in the task whereby performance could be improved by faster learning (adaptation) to the novel protocol (Hahn et al., 2003). Although reduced and increased event rate (increasing and reducing the ITI respectively) represent viable challenges of attention in humans (Parasuraman, 1998), humans are not trained repetitively over several months utilizing one ITI (Riccio et al., 2002). Pharmacological disruptions of task performance have also been conducted. Considering the size of this literature, however, and the two reviews already available for the 5-CSR task (Chudasama and Robbins, 2004; Robbins, 2002), our focus will be placed on perturbation studies relevant to schizophrenia.

2.1.3. Perturbation of 5-CSR task performance with relevance to schizophrenia

—Although numerous lesion studies have been conducted in rats performing the 5-CSR task, there have been limited publications specifically addressing perturbations relevant to schizophrenia, with most appearing within the past five years. Neurodevelopmental models have thus far yielded mixed results. The NVHL model of schizophrenia, developed by Lipska and Weinberger (1995), induces some attentional deficits in the 5-CSR task (Le Pen et al., 2003). Rats with adult lesions to their ventral hippocampus (Le Pen et al., 2003) also exhibited deficits, however, indicating non-specificity of this effect to neurodevelopmental origins. This non-specificity is in contrast to the study by Kirkby and Higgins, (1998), where hippocampal lesions did not impair rat performance of the 5-CSR task, although the reasons for the differing effects were not determined. NVHL rats did exhibit hypersensitivity to the disrupting effects of the psychotomimetic PCP when compared to both sham-lesioned and adult ventral hippocampal-lesioned rats (Le Pen et al., 2003), providing some neurodevelopmental and environmental support for this model. The NVHL model has been argued in the past to model the delayed, post-pubertal emergence of schizophrenia symptomatology (Lipska and Weinberger, 1995). Thus, the question of validity for any developmental model of schizophrenia in 5-CSR task performance, however, can be addressed only by assessing animals pre- and post-puberty, a study that is unlikely to occur in the 5-CSR task due to the extended training period required. The isolation-rearing model has also been explored in the 5-CSR task, although the results on attentional measures were disappointing. Performance was not impaired during baseline performance of the task, and thus the rats were subjected to reduced stimulus durations, high or low event rates, vITI and white noise distracter challenges, but no attentional deficits were observed (Dalley et al., 2002). The isolation-reared rats did exhibit increased perseveration and MRL, however, which was interpreted as demonstrating cognitive inflexibility (Dalley et al., 2002), a cognitive deficit observed in schizophrenia patients. Sustained attention, as assessed by the extended duration version of this task (Grottick and Higgins, 2002), has not yet been used in either developmental model. Recently, amphetamine was reported to reverse attentional deficits in dorsal lateral prefrontal cortex lesioned rats (Chudasama et al., 2005), but this model is novel and based only on the fronto-striatal pathology observed in schizophrenia patients as acknowledged by Chudasama et al (Chudasama et al., 2005). While acute amphetamine may improve 5-CSR task performance, a chronic sensitizing regimen of amphetamine has been used to model the dopaminergic dysregulation apparent in schizophrenia patients (Fletcher et al., 2005; Martinez et al., 2005). This model produces long-lasting impairment in 5-CSR task performance in rats, observed primarily as increased omission errors (Fletcher et al., 2007). Although this deficit was reversed

by intra-mPFC administration of a D1 agonist (Fletcher et al., 2007), the effects of systemic compounds have yet to be investigated.

PCP administration is another putative animal model of schizophrenia. Unfortunately, however, there have been very limited studies assessing the effects of this model in the 5-CSR task. As already discussed, Le Pen et al., (2003) administered PCP to rats performing the task and observed hypersensitivity of NVHL rats to PCP. In normal animals, PCP treatment produces attentional deficits as measured by reduced correct trials, increased MCL, premature and perseverative responding, and reduced total trials, similar to effects reported by Jin et al., (1997) in rats performing a 3-choice version of the task. Similar effects have been described with MK-801 treatment (Terry et al., 2002). Although Carli et al, (2006) demonstrated that competitive NMDA receptor antagonism induced impairment in sustained attention following 3-(R)-2-carboxypiperazin-4-propyl-1-phosphonic acid (CPP) administration, PCP remains the more widely used NMDA antagonist model for schizophrenia.

Recent studies have compared the effects of acute versus chronic PCP on rat performance (Amitai et al., 2007). Administered acutely between 1.5–3.0 mg/kg, PCP effectively lowered the level of responding in rats, observed as reduced total trials, fewer premature responses, slower MCL and reduced % correct response (which in this case included omissions and change was likely to be driven by increased omissions as accuracy was unchanged; Amitai et al., 2007). In the chronic PCP regimen, however, the effect of decreased trial number was no longer significantly different from baseline by day 2, although a deficit in accuracy and % correct responses was still apparent as was increased mean correct latency (Amitai et al., 2007). This pattern of deficient attentional performance was apparent with further injections of PCP nine days later, although at this stage premature responding also increased (Amitai et al., 2007). The effects of acute PCP administration have also been assessed in two strains of mice, C57BL/6 and DBA/2 (Greco et al., 2005), which have been demonstrated to differ in standard performance of the 5-CSR task (Greco et al., 2005; Patel et al., 2006; Young et al, *unpublished observations*). Interestingly, PCP had more pronounced deleterious effects on DBA/2N performance as compared to C57BL/6N performance (Greco et al., 2005), demonstrated as reduced accuracy and increased premature and perseverative responses in DBA/2J vs. increased premature responses in C57BL/6J mice. Despite increased error rate and thus time outs, the animals administered the highest dose of PCP (3 mg/kg) also exhibited a trend toward increased total trials, suggesting perhaps the deficit was a result of hyper-responsiveness (Greco et al., 2005) as PCP induces hyperactivity in motor activity paradigms at this dose (Chartoff et al., 2005).

To date, the only genetically modified mice assessed in the 5-CSR task with relevance to schizophrenia has been α7 nicotinic acetylcholine receptor (nAChR) knockout mice (KO; Young et al., 2007a; Young et al., 2004), as schizophrenia patients exhibit reduced α7 nAChR expression (Ripoll et al., 2004). α7 nAChR KO mice exhibit impaired attentional performance in the 5-CSR task, with evidence of gene dosage effects (Hoyle et al, 2006; Young et al., 2007a; Young et al., 2004). Further work is required however in assessing genetic mouse models as well as the cognitive consequences of combined genetic/neurodevelopmental models.

2.1.4. Effects of Established Antipsychotics on 5-CSR task Performance—Few studies have investigated the effects of acute or chronic dosing of antipsychotic drugs on normal performance of the 5-CSR task with even fewer investigating their effects on models of disruption of performance. In a recent study, Amitai et al, (2007) described the acute dose-response effects of risperidone, olanzapine, clozapine, quetiapine, and haloperidol on normal-performing rats. Risperidone and olanzapine impaired performance in the task predominantly observed as a reduction in responding (Amitai et al., 2007). The other atypical antipsychotics,

clozapine and quetiapine, also impaired performance, observed as a reduction in % correct of total trials (including omission levels), with no effect on accuracy calculated as correct versus incorrect responding was observed (Amitai et al., 2007) – effects on omission levels alone were not reported. Clozapine also slowed MCL at the highest dose (Amitai et al., 2007). The effects of risperidone, olanzapine and the putative antipsychotic asenapine were also assessed in normal rats in the 5CSR-task elsewhere (Marston et al, manuscript submitted). Each of these antipsychotics impaired performance by increasing % omissions, while olanzapine and high doses of asenapine lowered % correct. The putative remediating effects of acute clozapine and risperidone on PCP-induced deficits have also been investigated (Amitai et al, 2007). PCP-induced deficit in 5-CSR task performance was potentiated by clozapine and risperidone to the extent that significant reductions in total trials were observed only with the administration of PCP and an atypical antipsychotic (Amitai et al., 2007). Importantly, the authors investigated the effects of chronic clozapine treatment on rats also subjected to repeated acute injections of PCP. With chronic dosing, significant attenuation of PCP-induced deficits as measured by % correct trials and premature responses were observed (Amitai et al., 2007). This result supports the use of both repeated PCP dosing model of schizophrenia as well as investigating the effects of chronic antipsychotic treatment as clozapine can also attenuate, but not reverse, cognitive deficits in schizophrenia when using low doses (Harvey et al., 2005).

2.1.5. Putative Targets for Cognitive Enhancement Evaluated in the 5-CSR task

—Several drugs are known to enhance sustained attention/vigilance in normal humans, and generally fall into the classification of psychostimulants (see Koelega, 1993) such as caffeine and amphetamine. Grottick and Higgins (2002) demonstrated that by extending the session duration and reducing the stimulus duration – increasing the attentional load - during 5-CSR task test periods, both amphetamine and caffeine improve attention as measured by an increase in accuracy, reduction in % omissions, and faster MCL. As the task was not altered during drug challenge, these effects could not be accounted for by learning confounds, where similar to human CPT testing, performance did not improve within a session, providing pharmacological predictive for the 5-CSR task. Also, consistent with reports in humans, both amphetamine and caffeine increased perseverative and premature responding (increased motoric function and impulsivity). Such studies provide the task with a degree of predictive validity and demonstrate that improvements in performance can be observed. They also highlight the importance of test procedure for drug sensitivity, as Grottick et al., (2003) observed the greatest amphetamine effects between trials 100–250, while the test procedure of Muir et al., (1995) went to only 100 trials and only observed enhanced MCL with amphetamine administration. Moreover, in the procedure utilized by Bizarro and Stolerman (2003), amphetamine increased % omissions and reduced premature responding. One study found less consistent results of amphetamine and caffeine, with improvements in only some measures of accuracy while response speed was reduced (Bizarro et al., 2004). These studies were however likely to have been confounded by learning experience as the challenge used altered the protocol the rats were trained on thereby requiring them to adapt to the new protocol. Evidence of this learning period is observed as performance of the rats improves over time (Hahn et al., 2003). Improved performance over time is in contrast to the vigilance decrement observed in human CPT testing, where poorer performance is observed over time (discussed above),

As has been discussed previously, because there are no established cognitive enhancers commercially available for the treatment of schizophrenia, none have been tested in rodents performing the 5-CSR task. Nevertheless, treatments for the cognitive deficits in Alzheimer's disease do exist, most of which are acetylcholinesterase inhibitors (AChEIs) such as tacrine, donepezil, physostigmine, and galantamine, (see Johannsen, 2004). Some studies suggest that such treatments may also prove beneficial in treating cognitive deficits in schizophrenia, including attention (Buchanan et al., 2007; Chouinard et al., 2007a; Chouinard et al., 2007b; Sharma et al., 2006), although negative findings have been observed in double-blind studies

(Chouinard et al., 2007a; Chouinard et al., 2007b; Kohler et al., 2007; Stip et al., 2007). In the 5-CSR task, AChEIs produce no improvement in normal-performing animals, but tacrine, donepezil, and physostigmine all reversed scopolamine-induced deficits in performance, predominantly by normalizing % omissions levels (Kirkby et al., 1996; Lindner et al., 2006). Despite the possible receptor tautological explanation of the observation, further support for AChEI improving attention comes from the donepezil-induced reversal of performance deficits caused by AMPA-induced lesions of the nucleus basalis (Balducci et al., 2003). Donepezil treatment specifically reversed the reduced accuracy, increased % omissions, and increased MCL lesion-effect without altering the lesion-induced increase in premature and perseverative responses (Balducci et al., 2003). These data suggest donezipil may improve attention in these animals, but not improve inhibitory control.

One drug that acts on the cholinergic system and has proven efficacious in improving attention in schizophrenia patients is nicotine (Barr et al., 2007; Newhouse et al., 2004; Sacco et al., 2005). Numerous studies have now confirmed the performance-improving effects of nicotine in the 5-CSR task in both rats (Grottick et al., 2003; Grottick et al., 2001; Hahn and Stolerman, 2002; Mirza and Stolerman, 1998; Muir et al., 1995) and mice (Young et al., 2004;van Gaalen et al, 2008). Improved performance with nicotine administration has been observed using several techniques, in the classic procedure in rats with basal forebrain lesions (Muir et al., 1995), in intact poor performers (Grottick and Higgins, 2000), altering the task during testing (Day et al., 2007; Hahn et al., 2002b; Mirza and Stolerman, 1998), as well as normal-performing animals (Young et al., 2004). Nicotine has also been shown to improve attentional performance in healthy human subjects (Levin et al., 1998). In an attempt to circumvent the undesirable effects of nicotine, groups have also developed subtype-selective nAChR ligands. SIB 1765F, a selective α4β2 nAChR agonist mimicked the effects of nicotine in poor performers and during selected task challenges, increasing accuracy, reducing % omissions and MCL, and increasing premature responses (latter only: (Grottick et al., 2003; Grottick and Higgins, 2000). Under task challenges, similar positive attentional effects were observed following treatment with epibatidine (Hahn et al., 2003), a potent α4β2 nAChR agonist that also exhibits affinity to α7 nAChRs (Briggs et al., 1995), though not all effects matched those of nicotine. The selective α4β2 nAChR agonist ABT-418 (Papke et al., 1997), however, did not improve attentional performance under conditions where improvements were observed with nicotine, with no discernible reasons for this apparent discrepancy (Hahn et al., 2003). The β4 preferring agonist SIB-1553 had no effect in normal animals but did reverse dizocilpine-induced deficits in accuracy, suggesting that nicotine's effects may also be mediated by nAChRs other than α4β2, or α7 nAChRs (Terry et al., 2002). Administration of the α7 nAChR agonist AR-R17779 had no effects on any measure of performance (Grottick et al., 2003; Grottick and Higgins, 2000; Hahn et al., 2003). Recent reports however question the brain permeability of AR-R17779 (Cilia et al., 2005). Since α7 nAChR KO mice exhibit impaired attentional performance in the task (Young et al., 2007a; Young et al., 2004), further investigation of α7 nAChR agonists is required. Another method that has been used to assess nicotine-induced improvement involves altering the paradigm during testing (increasing the inter-trial interval from a normal 5 s to 30 s), thus requiring the rat to learn to respond to the novel paradigm within a test session (Hahn et al, 2003). Introducing this change in protocol means however that nicotine-induced improvement in learning cannot be discounted. In fact during testing, studies have repeatedly demonstrated improved % correct performance within a session in control rats (Hahn et al., 2003), contrasting with the reduction in performance over time observed in human studies (Parasuraman, 1998). This within-session learning suggests that learning is an important factor in the performance of these rats, thus, the improved performance of nicotine-treated rats could simply reflect a shift to the left of the learning curve in these animals (Levin et al, 2006). Interestingly, such a within session learning phenomena has also been observed in rats performing the SAT during a low event rate challenge (McGaughy and Sarter, 1995). While these findings provide cross-task validity, they also highlight the learning

component of this challenge. While initial studies utilized poor performers to observe nicotine-induced improvements (Grottick and Higgins, 2000), subsequent studies observed nicotine effects when the stimulus duration was reduced or in aged animals (Grottick et al., 2003; Grottick and Higgins, 2002; Jones et al., 1995; Muir et al., 1999). As this task did not alter the protocol, the authors were able to observe a vigilance decrement as well as a subsequent improvement that was not confounded by possible learning effects. Another method to assess putative therapeutics in normal rats has been to identify poor performers, then attempt to improve performance. Granon et al, (2000) utilized this technique and demonstrated that a D1 agonist, SKF 38393, infused intra-mPFC improved % correct in poor performers, while the D1 antagonist SCH 23390 impaired performance in good performers. SKF 38393 infused intra-mPFC also improved performance of rats that had been impaired by amphetamine sensitization administration (Fletcher et al, 2007). Thus D1 agonists remain a target as therapeutic compounds for the treatment of poorly performing neuropsychiatric patients. These D1 agonist effects in poor performers were not observed with systemic administration however, thus caution must be used when interpreting these data.

The increased interest in research on putative cognitive enhancers has led to a surge in publications of 5-CSR task studies. Navarra et al., (2007) observed limited increases in % correct responding in normal rats treated with methylphenidate and atomoxetine in the 5-CSR task challenged with a longer and variable ITI (4–10 s) compared to the ITI on which they had been trained (5 s). This challenge has been utilized successfully in the past by numerous groups to identify the serotonergic system as mediating 'impulsive-like' behavior of rats (see Robbins, 2002). While these data are promising, the challenge used raises concerns that the effect may be as a result of reduced impulsive responding or in fact within session learning (discussed above for Hahn et al, 2003). In the study by Navarra et al., (2007), they observed a 10-fold increase in premature responses at the 10 s ITI and a 4-fold increase at the 7 s ITI due to the challenge. Such a deviation from normal responding highlights the rat's use of a temporal strategy when performing the 5-CSR task, whereby change in the temporal protocol leads to highly aberrant responding. Atomoxetine also reduced premature responding as well increasing % correct in the challenge (Navarra et al, 2007). Thus the added complication of introducing a learning effect in the challenge (as discussed above) leads to difficulties in interpreting results as attentional and not impulsive or learning in nature as the improvements observed under atomoxetine administration (Navarra et al., 2007) could have been mediated by faster learning of the new protocol (Hahn et al, 2003, Levin et al, 2006; Young et al, unpublished observations). Support for such a learning effect comes from the mechanism of action of atomoxetine, as it acts as a norepinephrine reuptake inhibitor (Gehlert et al., 1995) and increases extracellular levels of norepinephrine. While norepinephrine levels do not change during performance of the task under baseline conditions (Dalley et al., 2004; Dalley et al., 2002), they increase when task contingencies are altered and the rat needs to learn or adapt to the new protocol (Dalley et al., 2004). Moreover, reducing levels of norepinephrine in rats does not impair baseline responding but leads to an inability of the rat to adapt to novel conditions (Carli et al., 1983; Cole and Robbins, 1987). Therefore, the improved performance of the rats under the novel condition (Navarra et al., 2007) could simply reflect enhanced adaptation to the new condition due to increased norepinephrine levels. Furthermore, independent interpretation of the results would have been easier had the authors also presented data on % omissions or mean reward latencies. These findings were interesting however and merit further investigation for the use of atomoxetine in schizophrenia research. Atomoxetine did increase accuracy in rats trained on the LRT (see below), although increased % omissions and mean correct latency were also observed (Jentsch et al, 2008), suggesting that the rats may be using a different response strategy, again indicative of learning (e.g. speed/accuracy trade-off). Atomoxetine also improved attentional set-shifting, a problem solving paradigm with a heavy learning component, in rats with mPFC lesions (Newman et al, 2008), further supporting that atomoxetine may act via improved learning. Plausibly, the effects of atomoxetine could also

be mediated by reducing impulsivity (Robinson et al., 2007). When interpreting effects of manipulations on 5-CSR task performance, care must be taken when attributing effects to modulation of attention only, and as much data as possible should be provided to assist in data interpretation.

2.1.6. Rat and Mouse Testing in the 5-CSR task—As discussed throughout this section, both rats and mice can be trained to perform the 5-CSR task. While training the two species - and indeed strains within the species - does not differ, major differences in their performances during training and at baseline have been observed. For example, rats commit more premature responses and fewer omissions compared to mice, while mice are more accurate in the task. These differences suggest that rats tend to be more responsive in the task than mice, perhaps using a strategy of responding more than simply responding to light. This hypothesis was confirmed using a modified 5-CSR task with a constant ITI, whereby withholding from response earns a reward in a no stimulus light condition, while a response was punished with a time-out phase. When challenged with such a paradigm, rats were found to respond 90% of the time in comparison with mice who will respond only 10% of the time (Spratt et al., 2000). Thus rats respond despite the lack of light-stimulus onset. It appears that when a rat does not detect the location of the target hole, they respond randomly given the 1 in 5 chance of gaining a reward and a 4 in 5 chance of an error thus lowering their response accuracy. Mice however, appear to respond only when the cue light is detected, prompting them to exhibit significantly higher omission levels compared to rats. These innate differences suggest that care must be taken when compariing results in specific measures across species. Furthermore, while rats will continue to respond even after 250 solid food pellets (Grottick and Higgins, 2003), mice become satiated faster on solid food rewards. Hence, most experimenters use liquid reinforcement in mice and solid in rats, though liquid reinforcmenet can also be used in rats. Finally, there is evidence that mice are less robust than rats when assaying pro-cognitive effects in cross-over designs (Grottick and Higgins, 2001; Hahn et al, 2001), compared to between subject sub-chronic administration (Young et al, 2004; Pattij et al, 2007, compared to Hoyle et al, 2006). Cross-over design studies may be less sensitive in mice than in rats for investigating pro-cognitive compounds compared to between subject designs. Finally, it should be noted that the neuroanatomy discussed in this section derives from rat studies – more work is required to confirm these findings in mice.

2.1.7 Conclusion and Future Studies for the 5-CSR task—Despite the complexity and length of training, the 5-CSR task is one of the most widely used tests of sustained attention in rodents today. Studies have already demonstrated its validity as a test of sustained attention, and with confirmation of pro-cognitive effects observed in this task as in the CPT, its predictive validity has also received support. The numerous measures used in the task provide valuable insight as to a drug's effects, because non-attentional mechanisms affecting performance can be identified. The 5-CSR task will no doubt be utilized heavily in future preclinical studies investigating cognitive enhancement for schizophrenia. As has been discussed above however, care must be taken when selecting the procedure used for training as well as testing. Moreover, to further increase the validity of the task as an analogue of the CPT, introducing a procedure whereby the rodent also has to ignore irrelevant stimuli, similar to the CPT, may prove beneficial. The inability to measure false alarm responding distinguishes the 5-CSR task from human CPT tasks and is not accounted for when comparisons have been made between the two tasks (Day et al, 2008). Measuring false alarm responding would allow a greater demonstration of stimulus control and also increase the difficulty of the task. The 5-choice CPT (5C-CPT) provides a paradigm in which rodents must attend to relevant and irrelevant stimuli, and thus provides measures of hit rate, false alarm rate, correct rejections, and misses consistent with human CPTs (Young et al., 2009). This recently developed variant of the task provides increased potential for cross-species translatability from 5C-CPT to human CPT,

whereby the sensitivity index d' can be calculated. Regardless of further development however, the 5-CSR task will remain a well characterized and widely used tool in the search for pro-cognitive compounds for the treatment of schizophrenia.

2.2 Sustained Attention Task

Following Sarter and Bushnell's (Sarter and Bushnell, 1995) discussion on the merits of assessing sustained attention and ensuring validity, Bushnell et al, (1994) - with subsequent developmental work provided by McGaughy and Sarter (1995) - developed the sustained attention task (SAT). This task is also operant based, but in contrast to the 5-CSR task, the SAT requires lever presses as opposed to nose pokes. In its current form, the rats are required to detect a light signal, which can vary in intensity and hence saliency. This 'signal' occurs just prior to the two levers being presented. Once the levers are presented, the rat is required to press one lever if it detected the signal and the opposite lever if it did not detect the signal (a correct rejection). Thus, measures of correct hits (the animal correctly pressed the signal lever when the signal was presented; number correct hits/number of signal trials) and false alarms (the animal incorrectly pressed the signal lever when actually no signal had been presented; number of false alarms/number of blank trials) are generated.

2.2.1. Task validity of SAT for assessing attention/vigilance—This task is sensitive to a vigilance decrement engendered either by reductions in signal intensity, addition of distractors (flashing house-light), or increases in event rate (reduced ITI). The latter is in line with human vigilance tasks (Baddeley and Coquhoun, 1969; Parasuraman, 1998), providing construct, theoretical, and cross-species translational validation of the task as a test of sustained attention (although it has been suggested that this vigilance decrement may be lost with extensive training, Turchi et al, 1995).

Further predictive validation of this test comes from the finding that aged rats exhibit significantly poorer performance than do young rats (McGaughy and Sarter, 1995; Burk et al, 2002), similar to that observed in humans in the CPT (Mani et al 2005). This paradigm demonstrates compatibility with the 5-CSR task insofar as increased acetylcholine levels have been reported in rats performing the task (Himmelheber et al, 2000a), although the specific role of acetylcholine in task performance is unclear (Himmelheber et al 2001; Kozak et al, 2006). Unlike the 5-CSR task, very little work has been done as yet to identify possible strain differences in the SAT, which could provide another point of comparison of the two tasks. Two rat strains have been used to identify drug-induced effects, Long Evans (Turchi et al., 1995) and BNNia/F344 (McGaughy et al., 1999), with the latter exhibiting a lower baseline performance and putatively allowing drug-induced improvement to be observed. Presumably due to the challenges in training mice to lever press (Caine et al., 1999), we have found only one publication in mice in this task (Martin et al., 2006). Thus, unlike the 5-CSR task (Greco et al., 2005; Humby et al., 1999; Young et al., 2007a; Young et al., 2004), this task may not be suitable to examine the effects of genetic modification in mice on sustained attention using current techniques (although theoretically it could be converted to a nose poke response task).

Lesion studies indicate the SAT performance is subserved by the basal forebrain (McGaughy et al., 1999; McGaughy et al., 1996; McGaughy and Sarter, 1998), consistent with the 5-CSR task (Muir et al., 1996b; Risbrough et al., 2002). Moreover, the pattern of deficits exhibited by rats with mPFC lesions in this task mimic deficits in executive function (Miner et al., 1997), again exhibiting similarities with the 5-CSR task (Granon et al., 2000). No effects of 6-hydroxy-dopamine (6-OHDA) lesions of the dorsal noradrenergic bundle (DNAB) on performance were observed in comparison to sham-lesioned animals, despite the use of distractors (McGaughy et al., 1997), although a high event-rate challenge was not used (McGaughy and Sarter, 1995). This finding contrasts with impaired performance of rats in the 5-CSR task following

lesion to the DNAB during distractors in a different modality and a variable ITI challenge (Carli et al., 1983; Cole and Robbins, 1992), which may emphasize the need for the DNAB in response to temporal challenges or changes in protocol, as opposed to control of attention.

2.2.2. Perturbations of SAT performance—Numerous studies have been published on rats performing the SAT. In normal animals, most pharmacological manipulations appear to exert disruptive effects on SAT performance. The SAT is sensitive to glutamatergic manipulations, with NMDA receptor agonists or antagonists impairing performance by increasing false alarm rates or lowering hit rates respectively (Nelson et al., 2002; Turchi and Sarter, 2001). Similarly, administration of either GABA-A receptor agonists (chlordiazepoxide) or inverse agonists (beta-CMM) into the basal forebrain impaired performance in the task (Holley et al., 1995). Some separation of effects on specific measures is noted, in that chlordiazepoxide reduced the number of correct hits made while beta-CMM increased the number of false alarms (Holley et al., 1995). The impairments observed with chlordiazepoxide also manifest after systemic administrations in young, old, and aged rats (McGaughy and Sarter, 1995; Turchi et al., 1996). Both non-selective nAChR antagonism and α4β2 nAChR agonism impaired performance, though the latter only in the final block, and the former throughout the task. Taken together, these results lead to the conclusion that normal animals are operating at near peak performance in this task, since perturbations of cholinergic systems in either direction leads to a performance decrement. Indeed, a subsequent study demonstrated that ABT-418 induced improvement in the high event-rate task in sham-operated animals (McGaughy et al., 1999), likely due to the fact that this study used a strain that has relatively poor performance ~70% hit; (McGaughy et al., 1999) vs those used in the previous study (~90% hit; Turchi et al., 1995). Thus, consistent with other cognitive tasks, SAT may be best utilized for modeling specific disruptions relevant to schizophrenia, such as neurodevelopmental, genetic, or pharmacological, which can then be reversed by test compounds.

2.2.3. Perturbations of SAT performance with relevance to schizophrenia—Few studies have been performed in the SAT in animals with perturbations relevant to schizophrenia. When administered acutely, dizocilpine significantly impaired rat performance of the task (Rezvani and Levin, 2003). Amphetamine administration also impairs performance in the task by increasing false alarm rates despite allowing for improvements and avoiding ceiling effects by using BNNia/F334 rats (Deller and Sarter, 1998; McGaughy and Sarter, 1995). This finding contrasts with amphetamine-induced improvement observed in human tests of sustained attention (see Koelega, 1993) and rats performing the 5-CSR task (Grottick et al., 2003). Similar to the 5-CSR task, however, chronic dosing of amphetamine leads to a hypersensitivity to subthreshold doses of amphetamine, impairing sustained attention (Martinez et al., 2005). This disruption may be linked to abnormal cholinergic regulation (Kozak et al., 2007; Martinez et al., 2005) and could be reversed by chronic low doses of antipsychotic treatment (Martinez and Sarter, 2008), consistent with modest attentional improvements observed in schizophrenia patients with low (50% D2 receptor occupancy) doses of antipsychotics (Green et al., 2002; Keefe et al., 2006; Rollnik et al., 2002). The cross-species translation of effects observed in these rats to observations in schizophrenia patients remains impressive in this study. Further work is required however, to identify the effects of clinically relevant doses of antipsychotic treatment as a high level of D_2 receptor occupancy (70%) is required for antipsychotic efficacy (Farde et al., 1992; Nordstrom et al., 1993). Thus most investigators anticipate that pro-cognitive treatments for schizophrenia will be developed as adjuncts to antipsychotic treatment, as noted in the MATRICS consensus meetings.

2.2.4 Effects of Established Antipsychotics on SAT performance—Rezvani and Levin, (2004) and Rezvani et al, (2006) have identified that clozapine, risperidone, and

haloperidol treatment impair rat performance on this task, each of which can be attenuated with chronic nicotine treatment. Not surprisingly, nAChR antagonist treatment results in impairments (Rezvani et al., 2002). However, to date, no nAChR subunit selective compounds have been examined against antipsychotic-induced deficits. Moreover, these antipsychotics were administered acutely and to normal-performing animals. It would be interesting to examine their effects under chronic treatment, perhaps in conjunction with nicotine. Chronic dosing of clozapine and haloperidol was recently investigated in amphetamine-sensitized rats, where chronic low doses of antipsychotics reversed low dose amphetamine-induced deficits in performance (Martinez and Sarter, 2008). While this effect is promising, possible receptor tautological effects or complications with dosing required for antipsychotic efficacy (where higher doses are required to treat the positive symptoms of schizophrenia) have not been addressed.

2.2.5. Putative Targets for Cognitive Enhancement in the SAT—Initial studies suggest that unlike normal humans (Levin et al., 1998) and mice performing the 5-CSR task (Young et al., 2004), nicotine does not improve normal rat performance of the SAT (Bushnell et al., 1997; Rezvani et al., 2002; Rezvani et al., 2005, 2006; Rezvani and Levin, 2003, 2003b; Turchi et al., 1995). Neither methylphenidate nor AChEIs improved performance in normal or basal forebrain lesioned rats (McGaughy et al., 1999; McGaughy et al., 1996; McGaughy and Sarter, 1998). Alterations to the task (e.g., using light as a signal; Bushnell et al., 1997), however, do unmask a positive effect of nicotine treatment on some attentional measures both in normal and dizocilpine- or alcohol-treated rats (Rezvani et al., 2002; Rezvani et al., 2005, 2006; Rezvani and Levin, 2003, 2003b), suggesting that reversal of deficits is the more sensitive measure of cognitive enhancement in this task. In contrast, consistent improvements in both correct hits and correct rejections were observed following chronic nicotine administration which disappeared during withdrawal (Rezvani et al., 2005), suggesting that compensatory mechanisms (e.g. receptor desensitization/sensitization) may be required.

2.2.6. Rat versus Mouse Testing in the SAT—The literature provides numerous examples of rat performance of the SAT, in several different laboratories. Multiple strains (e.g. Long Evans and BNNia/F344 rats) have been tested in the SAT and it appears that specialized training per strain is not required, with differing baseline performance apparent (McGaughy et al., 1999; Turchi et al., 1995). Training mice to perform the SAT appears more challenging however, possibly as a result of poorer lever pressing behavior in mice compared to holepoking (Caine et al., 1999). Thus while numerous publications on holepoking in mice in the 5-CSR task exist (Greco et al., 2005; Humby et al., 1999; Young et al., 2007a; Young et al., 2004), we found only one SAT mouse publication (Martin et al., 2006). Moreover, the performance of mice in this study was not validated in terms of sustained attention (Martin et al, 2006 compared to McGaughy and Sarter, 1995). Thus, unlike the 5-CSR task, the SAT may not be amenable to examining the effects of genetic modification in mice on sustained attention.

2.2.7. Conclusions and Future Studies for the SAT—Although it has been suggested that this task lacks construct validity as a test of attention (Bushnell, 1998; Echevarria et al., 2005), this view has been challenged (Sarter and McGaughy, 1998) and certainly the available evidence supports its use as a rodent test of attention (Burk, 2004; McGaughy and Sarter, 1995). The task has proven extremely useful in assessing stimulus detection and attention, while being able to separate changes in responding from changes in accuracy. It has also helped support the role of the cholinergic system in sustained attention. To date, however, there has been limited evidence of drug-induced improvement in performance and assessment of animal models of schizophrenia (e.g. developmental or genetic models of schizophrenia). Although this area of research is improving, much still needs to be accomplished.

2.3. Lateralized Reaction-Time Task (LRT)

First described by Carli et al., (1985), the LRT exhibits similarities to the 5-CSR task. It is conducted in the same testing chambers but utilizes only 3 apertures - the central aperture and the two end apertures. For trial initiation the animal is required to maintain a nose-poke in the central aperture for a variable duration until a light stimulus appears in one of the end apertures. Thus to complete the task, the rodent must continuously scan the two lateral apertures while remaining fixated in the central aperture. The stimulus duration can be varied within a session, and the rodents can be cued to which side the stimulus will appear, normally through ns, normally using dim cue lights (Brown and Robbins, 1989). Consistent with the 5-CSR task, numerous measures are recorded including correct, incorrect, and anticipatory responses. Omission errors, total trials, as well as reaction time (RT; initial reaction, removing their nose from the central hole), movement time (MT; from removal of nose in central hole, to nose-poking at one of the cue stimuli), and reward latency can all be recorded. In fact, the latency measures taken in this task may provide a greater reflection of processing speed than either the 5-CSR task or the SAT, as performance is less confounded by possible locomotor effects. LRT training time is also faster than either the SAT or 5-CSR task..

2.3.1. Task Validity of the LRT as a Test of Attention or Vigilance—Initial reports on this task investigated its use in phenotyping an animal model of Parkinson's Disease. Carli et al, (Carli et al., 1985) infused 6-OHDA into the caudate nucleus of rats to determine whether attentional deficits would be observed as they are in Parkinson's Disease patients (Hart et al., 1998). Although no attentional deficits were observed, slowed reaction times (RT) were observed. Thus, while the animals could attend to the visual cue (no change in accuracy), and move as readily to the visual cue (no change in movement time), their ability to initiate movement was inhibited (increase in RT), possibly representing a speed/accuracy trade off, but more likely representing impaired movement initiation, as is observed in Parkinson's Disease (Simola et al., 2007). Frontal lobe abnormalities have been widely reported in schizophrenia patients (Robbins, 2005), while some thalamic abnormalities have also been observed (see (Magnotta et al., 2000) which may be linked to poor attentional performance (Laurens et al., 2005). Both of these regions have been evaluated to some degree in rats in the LRT. In rats, 6-OHDA infusion into the subthalamic nucleus (STN) reliably increased premature responses (Phillips and Brown, 1999) but has no effect on reaction time. In development of the task to model Posner's (1980) covert attention task, Weese et al, (1999) demonstrated that rats with lesions to the thalamic reticular nucleus (TRN) exhibited slowed RT of valid cued targets, to the extent that the RT in cued targets equaled that of invalidly cued targets, suggesting a covert orienting deficit. Following validation of the task, demonstrating increased RTs to invalid (misleading) cues compared to valid (beneficial) cues, as per attentional theory (Posner, 1980), Rosner and Mittleman (Rosner and Mittleman, 1996) lesioned the post-parietal cortex (PPC) of rats. Consistent with PPC lesions in the 5-CSR task however, no deficits in attentional performance were observed. Rats with medial forebrain bundle lesions exhibit impaired performance in the LRT with reduced trials, increased bias', reduced accuracy, and increased MT (Dowd and Dunnett, 2005; Dowd et al., 2005). It appears therefore that the LRT demonstrates some consistency with covert attention tasks in humans, although significant effects are often observed on RTs (processing speeds).

2.3.2. Perturbation of LRT performance—Other than the lesion studies discussed above, few studies have identified manipulations to perturb animal performance in the LRT. As with the SAT and 5-CSR task, scopolamine impaired performance in the LRT, slowing RT for both valid and invalid cues, and decreasing accuracy (Phillips et al., 2000). Jentsch (Jentsch, 2005) identified that spontaneously hypertensive rats appear to have naturally poorer performance in this task as measured by accuracy, when compared to normotensive Wistar-Kyoto rats.

2.3.3. Perturbations of task performance with relation to schizophrenia— Interestingly, this task appears to be sensitive to manipulations of cannabinoid receptors, which has some relevance as an environmental risk factor for schizophrenia (Hambrecht and Hafner, 2000). Activation of cannabinoid receptor 1 is reported to disrupt LRT acquisition and performance accuracy (Arguello and Jentsch, 2004; Verrico et al., 2004) The closest assessment of an animal model of schizophrenia in this task was the decreased accuracy, increased % omissions, increased premature responses, and faster RT induced by acute PCP treatment (Jentsch and Anzivino, 2004).

2.3.4. Effects of Established Antipsychotics on LRT performance—To date there have been no studies examining the effects of acute or chronic antipsychotics on LRT performance in normal animals or after perturbations with or without relevance to schizophrenia. This area needs to be addressed if this task is to be utilized in a preclinical battery.

2.3.5. Putative cognitive enhancers in the LRT—To date there have been few studies examining the effects of putative cognitive enhancers in the LRT, especially with regard to targets identified by the MATRICS program (Geyer and Tamminga, 2004). Some areas have been studied however. Arnsten (Arnsten, 2004) identified adrenergic receptors as a promising therapeutic target for the treatment of cognitive deficits in schizophrenia, with guanfacine, an α2A adrenergic demonstrating modest improvements in attention in schizophrenia patients (Friedman et al., 2001), although interpretation of the data has been debated (Mehta, 2002). Guanfacine did not improve spontaneously hypertensive rat performance in the LRT, nor alter performance in any way (Jentsch, 2005). While clonidine, an α2 adrenergic agonist, impaired LRT overall performance (reduction in accuracy, increased % omissions and RT) in normal rats, it attenuated PCP-induced deficits in LRT accuracy (Jentsch and Anzivino, 2004). More recently, Jentsch et al (2008) administered atomoxetine and methylphenidate to rats performing the LRT under two conditions, short and long preparatory periods. Methylphenidate did not alter performance under either condition. Atomoxetine reduced % correct under the short preparatory period, but increased % correct under the long preparatory period. MCL was slowed and % omissions increased by atomoxetine under both conditions. Although only single dose studies, these data highlight the need to examine varying test conditions and measures to evaluate the putative pro-cognitive effects of drugs. As described above however (secton 2.2.5), these effects may represent a new strategy used by the rats to perform the task (e.g. speed/accuracy trade-off), thus effects may not necessarily be attentive in nature. These data do highlight however that the challenges used in investigating putative pro-cognitive drugs may prove as important as the drug itself. In normal animals, nicotine administration reduces RT to both valid and invalid cues, suggestive of psychomotor speed enhancement, although no improvements in accuracy were observed (Phillips and Brown, 1999). Hence, to date, no drug tested has demonstrated efficacy in improving attentional performance as measured by accuracy in normal subjects.

2.2.6. Rat and Mouse Testing in the LRT—Given that the LRT uses the same apparatus as the 5-CSR task, requiring holepoking and not lever pressing, the LRT would not have the same difficulties training mice in the task compared to the SAT. Despite this fact, however, there appears to be only one mouse LRT publication, describing impaired performance of neurofibromatosis knockout compared to wildtype mice (Li et al, 2005). Thus more work is required in validating this task in mice, particularly assessing performance of different strains that may be used as background for genetically modified animals.

2.3.7. Conclusion and Future Studies for the LRT—In summary, the LRT certainly has promise for the assessment of sustained attention in rats and mice. The rapidity of training

(in comparison to the 5-CSR task and the SAT) may prove invaluable. The construct validity of this task for sustained attention however, has not yet been tested thoroughly, nor does it appear to probe all the relevant neural circuitry involved in attentional deficits in schizophrenia. While performance degradation with reduced signal intensity has been demonstrated, the effects of low and high event rate effects, distractors, and vigilance decrements have not yet been explored, and are considered prerequisites for validation of the sustained attention domain of the task. Moreover, prior to utilization of this task as a preclinical test for identifying cognitive enhancers for schizophrenia, drug-induced improvements in performance must be demonstrated that are not confounded by receptor tautology (Arguello and Jentsch, 2004). Characterizing improvements induced by nicotine, amphetamine, and caffeine would certainly prove beneficial, not only to demonstrate the predictive validity of the task, but also to confirm the extent to which drug-induced improvements can be observed.

3. Pre-attentional models

3.1. Prepulse Inhibition

3.1.1. Task Validity—Across species, presentation of a non-startling acoustic "prepulse" 30–300 ms before a startling stimulus reduces the magnitude of the startle reflex to the startling stimulus. This phenomenon is termed "Prepulse Inhibition" (PPI) of the startle response, and is used to measure sensorimotor gating. PPI of startle has been shown to be disrupted in a number of neuropsychiatric disorders, many of which are characterized by pathology in the corticostriatal loop, including schizophrenia, Huntington's disease, and obsessive compulsive disorder (for review see Braff et al., 2001; Swerdlow et al., 2001). Graham (1975) suggested that PPI can measure information processing, a construct of "automatic" attention in which an organism filters out extraneous stimuli during active stimulus processing. Indeed, PPI is extremely time dependent, there is a very short window (50–300 msec from onset of the prepulse to onset of the pulse) in which PPI occurs robustly, supporting the hypothesis that during active processing of the prepulse stimulus, other stimuli that are presented (in this case the startle pulse) are either not processed or responded to (i.e. "gated" or inhibited; (Graham, 1975; Hoffman and Ison, 1980; Norris and Blumenthal, 1996; Swerdlow et al., 1999). There is some support that PPI and other measures of sensorimotor or sensory gating reflect automatic or "pre-attentional" mechanisms, which may be orthogonal to controlled attention systems (Braff and Light, 2004). In humans, deficits in PPI also appear to be orthogonal to cognitive deficits as assessed by paper-pencil scales, however there may be some link between PPI and speed of processing or response time (see below).

In considering the use of PPI to probe systems relevant to cognition and schizophrenia, we briefly discuss the following questions: (1) what cognitive domains are orthogonal to and associated with PPI performance in healthy controls and schizophrenia patients; (2) is PPI predictive of known cognitive disrupters and enhancers; (3) can PPI probe the integrity of neural systems required for cognitive tasks?

3.1.2. PPI correlations to cognitive function in schizophrenia subjects and healthy controls—Thus far, studies of the link between PPI performance and cognition have been both relatively few and largely negative. In the early 1990s there were preliminary reports that negative priming, a measure of selective attention, and performance in the Wisconsin Card Sort Task (WCST), both of which are deficient in schizophrenia, may be correlated with PPI performance (Filion et al., 1999). These initial reports however were not followed by peer-reviewed publications and/or were not replicated by others (Swerdlow et al., 1995). Indeed a more recent study over a very large cohort of schizophrenia patients found no correlations between PPI and cognitive performance in a cognitive battery made up of the the WCST, California Verbal Learning Task, Wide Range Achievement Test, and Letter-Number Span (Swerdlow et al., 2006). These patients did show significant disruption in both the PPI and

neuropsychological scales. Hence, PPI is clearly not related to performance in these tasks, although the authors make the important point that these findings indicate PPI is not a redundant measure of functional disruption in schizophrenia patients. Indeed, low PPI was associated with poor Global Assessment of Function and Level of Independent Living scores, hence it appears to contribute to functioning via some other system than those subserving performance in the standard "pencil and paper" cognitive test battery (Swerdlow et al., 2006). Assessment of PPI and cognition in other patient groups with clear cognitive disruption reveals similar results, with patients with moderate Alzheimer's dementia, who largely have poor working or short-term memory, do not exhibit PPI deficits (Hejl et al., 2004; Ueki et al., 2006). PPI does not appear to decline with normal aging as traditional cognitive tasks are shown to do (Ellwanger et al., 2003), arguing that PPI performance is orthogonal to age-related cognitive dysfunction. Finally, PPI has been significantly linked to measures of thought disorder in schizophrenia patients (Perry et al., 1999), which supports the theory that deficient PPI in schizophrenia is indicative of core sensory processing, that when disrupted, results in cognitive fragmentation. Lower than "normal" PPI certainly does not always predict poor functioning in normal populations, for example women in the luteal phase of the menstrual cycle exhibit low PPI compared to other times in their cycle (Swerdlow et al., 1997), indicating that poor PPI alone does not predict cognitive fragmentation. In the CNTRICS consensus meetings, PPI was deemed to be an appropriate measure of the construct of "gain control" as a subset of the abnormalities in perception noted in schizophrenia. Together with mismatch negativity, PPI was seen to be an established task for use in the assessment of gain control in clinical studies of potential pro-cognitive treatments in schizophrenia (Green et al., 2009).

Recently, in healthy controls studied in independent laboratories, PPI has been reported to be positively correlated with strategy formation and execution time by selected tests from the Cambridge Neuropsychological Test Automated Battery (CANTAB; Bitsios et al., 2006; Csomor et al., 2008; Giakoumaki et al., 2006). Interestingly, the strongest correlations observed are with measures of planning speed, with subjects with low PPI exhibiting longer response times during cognitive testing. Schizophrenia patients exhibit similar deficits, with slower response time and poor strategy scores in the CANTAB battery (e.g. Tower of London-Stockings of Cambridge tasks; Pantelis et al., 1997), although there is no study to date specifically examining both PPI and CANTAB scores in schizophrenia patients. There is also a recent preliminary report of a significant positive correlation between working memory as measured by the Letter Number Span task in healthy women (Light et al., 2007). Treatment of healthy controls with tolcapone, a COMT inhibitor, increases PPI and LNS working memory in subjects with the Val polymorphism of the COMT gene (Giakoumaki et al., 2008). This finding suggests that working memory and PPI may have similar responses to indirect dopamine agonists. All of these studies have been in healthy controls however, thus future studies are required to determine if these measures are also related to schizophrenia-specific deficits in these tasks. Finally, there may be an association between PPI and some forms of attention in individuals with psychosis, such as distractibility and lateralized attention as assessed in the Posner test (Karper et al., 1996). These findings support the hypothesis that (at least in healthy controls) PPI is most relevant to attention, execution time, and/or "planning", domains that are not measured in the cognitive batteries discussed earlier. Thus, the data for PPI being linked specifically to a specific cognitive domain in normal or schizophrenia patients is weak for measures of cognitive errors, but may be relevant to attentional domains and planning speed. PPI is not currently in the MATRICS battery for cognition, and, like others (Hagan and Jones 2005), we would argue that its exclusion is unfortunate because of the availability of relatively predictive rodent models and its unique potential as a mechanism to bridge well described neural substrates and defined physiology (Geyer et al., 2001; Swerdlow et al., 2001) with cognitive constructs and global functions relevant to schizophrenia. As noted above, the CNTRICS group concluded that PPI should be used to assess the construct of abnormal perception in schizophrenia (Green et al., 2009).

3.1.3. Perturbations of task performance: Sensitivity to cognitive disruptors and enhancers—The cholinergic system has been widely shown to modulate cognitive processes, especially attentional components (Sarter and Parikh, 2005). In humans and animals, anticholinergic compounds have been shown to reduce PPI in normal subjects. For example, muscarinic receptor blockade reduces PPI in rodents, which may be specifically due to M3 and M4 receptor blockade (Geyer et al., 2001; Jones et al., 2005; Jones and Shannon, 2000a, 2000b; Ukai et al., 2004). Procyclidine has also been shown to disrupt PPI in healthy humans, although it is not yet known if anticholinergic drugs, which are commonly adjunctive therapy with typical antipsychotics to attenuate extrapyramidal side effects, also reduce PPI in schizophrenia patients (Kumari et al., 2001b). Pro-cholinergic drugs have also been shown to have the opposite effect, enhancing PPI in some contexts. Heavy smokers with schizophrenia exhibit higher PPI scores than non-smoking schizophrenia patients (these results are from a cross sectional design however) (Swerdlow et al. 2006). Smoking-induced enhancement of gating in schizophrenia is putatively due to the nicotine ingested during smoking, supported by recent data indicating mecamylamine blocks smoking-induced increases in PPI in schizophrenia subjects (George et al., 2006; Kumari et al., 2001a). Nicotine administration specifically increased PPI in a small sample of both healthy and schizophrenia subjects, which may be correlated to increases in hippocampal activity (Hong et al., 2007; Postma et al., 2006). In rodents, nicotine or selective nicotinic receptor agonist administration has also been shown to enhance PPI and block PCP- and apomorphine-induced disruptions of PPI under certain conditions (Andreasen et al., 2006; Ingram et al., 2005; Schreiber et al., 2002; Spielewoy and Markou, 2004; Suemaru et al., 2004). Similarly, AChEI have also been shown in rats to attenuate apomorphine-, scopolamine-, and MK-801-induced deficits in PPI (Hohnadel et al., 2007). Hence, it appears that PPI may be sensitive to the beneficial effects of nicotinic receptor agonists, which have been shown to have pro-attentional and pro-cognitive effects across many species, and may be particularly useful as a target for cognitive enhancement in schizophrenia (for review see Edward et al., 2006; Kumari and Postma, 2005).

NMDA receptor activation is a requirement for many forms of learning and memory (Castellano et al., 2001). In rodents, disruption of glutamate transmission in forebrain regions via competitive or non-competitive NMDA antagonist administration in the amygdala, hippocampus, and cortex also disrupts PPI (Bakshi and Geyer, 1998; for review see Swerdlow et al., 2001). A number of genes related to schizophrenia also appear to modulate PPI in rodents as shown by reverse genetic knockout mouse models, including neuregulin, secretin, and genetic models of 22q11 deletion syndromes (for review see Geyer et al., 2002; Swerdlow et al., 2008). However, it is not known if these mouse models will be useful in specifically testing for cognitive enhancers or antipsychotics. Unlike in humans, COMT mutations have not resulted in robust changes in PPI, COMT KO mice exhibit no change in PPI, while mice with increased COMT expression exhibit only small, non-significant decreases in PPI (Giakoumaki et al. 2008, Papaleo et al., 2008).

Developmental models of schizophrenia, including isolation rearing and immune challenge are also characterized by deficits in PPI, which are reversed by antipsychotic treatments (Powell and Geyer, 2002; Borrell et al 2002). Whether the PPI deficit produced via these manipulations is linked to cognitive deficits is unknown. The PPI deficits produced by these manipulations may be modeling the positive symptoms of schizophrenia, since they are reversed by both typical and atypical antipsychotic treatments. Isolation rearing has certainly been shown to perturb critical neural circuits involved in the cognitive domains selected by MATRICS however, such as hippocampal and prefrontal cortex abnormalities (Day-Wilson et al., 2006; Fone and Porkess, 2008; Lapiz et al., 2003; Schubert et al., 2008). Isolation-induced deficits have also been reversed by α7 nicotinic receptor agonism, a putative cognitive enhancer (Cilia et al., 2005). Thus, this question of antipsychotic efficacy as a predictive tool highlights the

difficulty faced by preclinical modeling of schizophrenia symptoms, as antipsychotic reversal of a cognitive deficit is not consistent with clinical observations, representing a false positive.

3.1.4. Effects of antipsychotics in PPI—The very abundant literature of antipsychotic effects on PPI is reviewed elsewhere (Geyer et al., 2001; Swerdlow et al., 2008). In humans, antipsychotic medication appears to improve PPI (Meincke et al., 2004; Minassian et al., 2007), with some suggesting that PPI may be a "disappearing" biomarker in the advent of improved treatment (Swerdlow et al., 2006). In mice, both typical and atypical antipsychotics can increase normal PPI, although this effect depends on the mouse strain and is often confounded by significant reductions in startle responding (e.g. Olivier et al., 2001; e.g. Ouagazzal et al., 2001). In rats, classic dopamine D_2 receptor antagonists are very effective in blocking direct and indirect dopamine agonist effects on PPI (for review, see Geyer et al., 2001). PPI disruptions induced by NMDA antagonists are partially but significantly attenuated by atypical, but not typical antipsychotic administration (Bakshi et al., 1994; for review see Geyer et al., 2001). Atypical antipsychotics may also be more effective in treating PPI in schizophrenia subjects (Kumari and Sharma, 2002; Swerdlow et al., 2006; Turetsky et al., 2007). Atypical but not typical antipsychotics are reported to have pro-cognitive effects in schizophrenia patients (Meltzer and McGurk, 1999; e.g. Sharma et al., 2003), although the effect size of atypical antipsychotic-induced improvements of cognition in schizophrenia is hotly debated (see final overall discussion). Hence, while dopamine agonist induced-disruptions of PPI cannot inform us about pro-cognitive treatments, it remains to be determined whether NMDA antagonist-induced disruptions of PPI would provide a valid screening tool for drugs that are efficacious for cognitive symptoms in schizophrenia (Geyer, 2006).

Alternatively, because antipsychotics do not completely (nor consistently) reverse NMDA-receptor agonist effects on PPI (see Geyer et al. 2001), this model may provide a window for improvement by other drugs. Given that clinical therapies for cognition will most likely be administered as adjuncts to antipsychotic medications, this type of model is most relevant to final clinical use. Groups using this strategy have reported synergistic or adjunctive effects of cognitive enhancers with antipsychotics in PPI (Wang et al., 2007). The practical difficulties of such a model (2 pretreatments and 1 treatment) however, may preclude it from common use.

It should also be noted that NMDA receptor antagonist effects on PPI have not been predictable from rodents and monkeys to man. Although NMDA antagonist administration produced PPI deficits in rats, mice, and monkeys, clinical studies using ketamine, a short acting NMDA receptor antagonist, have found either no effect or an increase in PPI (Abel et al., 2003; Duncan et al., 2001; Heekeren et al., 2007; Oranje et al., 2002; van Berckel et al., 1998). It has been suggested that the paradoxical ketamine effects in the clinic may be due to differential dosing regimens or pharmacokinetics in rodents and humans, and higher doses of ketamine may indeed produce the expected deficits (Abel et al. 2003). Serum glycine has also recently been shown to be negatively correlated with PPI performance in schizophrenia patients however; suggesting that *enhanced* glutamate transmission may be linked to PPI deficits in schizophrenia subjects (Heresco-Levy et al., 2007). Similarly, dopamine agonists such as amphetamine, which reliably disrupt PPI in rodents, appear to be surprisingly ineffective in parallel tests in healthy human volunteers (Swerdlow et al., 2002). Some similar paradoxical effects have been found with other serotonergic agonists (Heekeren et al., 2007; Vollenweider et al., 1999). Recent studies with the serotonergic hallucinogen psilocybin, however, have shown that PPI is disrupted or increased depending upon the specific temporal parameters used to elicit PPI in humans (Vollenweider et al., 2007). Further studies using a wider range of stimulus parameters may help to clarify and resolve such cross-species disparities in pharmacological models of disrupted PPI.

3.1.5 Mechanisms of PPI across mice and rats—There are species difference between rats and mice that are notable for modeling human PPI in rodents. Serotonergic manipulations in particular differ in their directional effect on PPI perfomormance across rats, mice and humans. Humans appear to exhibit increased PPI with MDMA treatment while mice and rats exhibit decreases in PPI (Vollenweider et al., 1999; Dulawa et al., 2000, Mansbach et al., 1989). Specific activation of the 5-HT_{1A} receptor appears to increase and decrease PPI in mice and rats respectively (Dulawa et al. 2000, Sipes and Geyer, 1995). In women, buspirone treatment reduces PPI, similar to the rat studies (Gogos et al., 2006). Hence mice and rats may differ in their predictive validity for specific neural systems for PPI in humans. Overall, the underlying circuity of PPI is much more well known and characterized in rats over mice (Swerdlow et al., 2001), however genetic effects on PPI are almost totally within the purview of mouse models (for review see Swerdlow et al. 2008). A note of caution in interpretation of increases in normal mouse PPI performance must also be given, as mouse PPI may be more sensitive to changes in baseline startle than those in rats (e.g. Ougazzal et al. 2001).

3.1.6. New Directions for PPI models—Although PPI is an unconscious form of behavior, it can be enhanced by conscious attention to detecting the prepulse, a phenomenon that is also disrupted in schizophrenia and schizotypal subjects (Dawson et al., 2000; Hazlett et al., 2003) and is significantly correlated with symptom severity (Hazlett et al., 2007). In animals, there are preliminary data suggesting that using a prepulse stimulus that has strong salience, either by training the animals that certain prepulse stimuli predict shock contingency or reducing the saliency of other competing contextual stimuli, results in increased PPI (Roskam and Koch, 2006; Plappert et al., 2006), These preclinical data are relatively new however, and further controls (e.g. across different prepulse modalities) and testing (e.g. correlations between other measures of salience, such as comparing amount of freezing to the prepulse when associated with shock and its efficacy as a prepulse) are required to determine if indeed these paradigms model attentional modulations of PPI per se. If so, these forms of PPI testing may refine the model towards probing the ability to detect salient and informative stimuli, a key theoretical deficit in schizophrenia subjects (Turetsky et al., 2007). In humans however, preliminary reports indicate that attentional modulation of PPI is not disrupted by glutamatergic or serotonergic hallucinogens (Heekeren et al., 2007), although the lack of effects may be confounded in part by reductions in baseline startle by these treatments. With further efforts to validate and explore how these models relate to cognitive deficits specifically in schizophrenia (versus positive or global symptoms as has been reported thus far), the addition of effortful attention may offer exciting advances in testing cognitive modulation of PPI.

3.1.6. Future Directions and Conclusions—Although correlations do not imply causation, it is generally implied that if there is a causal relationship between two variables a correlation should be measurable. Studies are now underway to determine if PPI performance is linked to other cognitive processes in animals, similar to those found in humans (possibly speed of processing). Evidence supporting a link between PPI performance under specific conditions putatively linked to schizophrenia (e.g. mPFC lesions, neurodevelopmental perturbations), and specific cognitive domains (e.g. gain control as an aspect of perception), will aid in our understanding of the potential of this measure to model both positive (e.g. sensitivity to antipsychotics) and cognitive symptoms. Preclinical disruptions of PPI by dopamine agonists and perhaps also NMDA antagonists in rats clearly provide probes of antipsychotic efficacy that have excellent predictive validity, however the utility of PPI in predicting cognitive enhancers remains to be clearly supported.

4. Speed of Processing

The speed of processing domain was one of the first discussed when identifying separable cognitive domains in schizophrenia because it represents one of the most basic domains of

cognition (Finkel et al., 2007; Nuechterlein et al., 2005). Assessment of processing speed is important because it may predict performance in other cognitive domains (Brebion et al., 1998; Brebion et al., 2008; Brebion et al., 2006; Finkel et al., 2007). The tasks chosen to represent this domain included category fluency, Brief Assessment of Cognition in Schizophrenia (BACS), Symbol-coding, and Trail-Making A tasks. Such tasks emphasize the speed at which target stimuli can be located, digit/symbol pairings made, and colors identified, etc. The use of these paper and pen tasks and their requirement of cognitive processing may result in difficulty in defining analogous preclinical tasks. The simplicity of these clinical tasks however, may allow the development of simple high throughput preclinical tasks.

Rodent models assessing processing speed could be numerous or limited, dependent upon the criteria set. For example, there are innumerable variations of reaction time (RT) tasks, wherein the presentation of a stimulus requires a response, whether it is a lever press, lever release, nose-poke, or removal of nose from an aperture. Such tasks are more typical in operant chambers and have been the subject of many studies. As the tasks utilized in humans (discussed above) do not equate to simple RT tasks however, such tasks in rodents will receive minimal discussion, thus limiting the scope of this section. The use of choice RT tasks allow for greater information regarding the manner in which responses are selected, and possibly delineating the putative effects on information processing (Blokland, 1998). As such, this section will focus on the LRT, both standard and cued detection versions, 5-CSR task, and olfactory discrimination.

4.1. Lateralized Reaction Time (LRT) Task

As described previously, the LRT has been described commonly as an animal model of attention whereby the rat is required to respond to visual cues located laterally. The separation of RT (reaction time; initial time taken to remove the rat's nose from the aperture after detection of a cue stimulus), and MT (movement time; time taken after RT to make a response at the cue stimulus), however, allows for more discrete measurement of processing speed as opposed to RT tasks where the RT measurements may be confounded by motoric effects. Because systems underlying performance in this task have been discussed (above), this section will concentrate on studies demonstrating this task's applicability to assessing processing speed.

When first described in the literature, as a test of visuo-spatial attention, the main effect of the first study was increased RT following 6-OHDA infused into the caudate nucleus of rats (Carli et al., 1985). Moreover, the only effects observed to date following nicotine administration were not on attention *per se* but a decrease in RT (Phillips and Brown, 1999). Acute administration of PCP had no effect on RT, and although PCP-induced reduction in accuracy was reversed by administration of the α2 noradrenergic agonist clonidine, the latter significantly slowed RT regardless of co-PCP or co-vehicle treatment (Jentsch and Anzivino, 2004). The cannabinoid 1 (CB1) receptor agonist WIN55,212, significantly slowed RT, which was subsequently reversed by administration of SR141716A, a CB1 receptor antagonist (Arguello and Jentsch, 2004). An adapted version of the LRT involves the rodents being cued to expect the stimulus in a specific location, normally using a dim cue light (Brown et al., 1991). This task, also known as the cued detection task, has been demonstrated using both 9-hole operant chambers (Brown et al., 1991) and classic Skinner boxes with levers (Dobrossy and Dunnett, 1997). However, similar to the varied procedures utilized in the 5-CSR task, caution must be exercised when comparing data from either test procedure. It was observed that despite striatal lesions causing impaired RT in the 9-hole box LRT (Brasted et al., 1998; Brown et al., 1991), such a lesion impaired MT in the Skinner box LRT, to the contralateral side only (Dobrossy and Dunnett, 1997). This difference raised questions as to whether the RT increases were reflective of motor deficits or true increases in processing time. A subsequent study by Brasted et al, (1998) explicitly comparing the two paradigms under the same

conditions as previously, concluded that the RT/MT effect differences were due to differences in the test chamber configuration. The greater distance required to complete a response in the Skinner box (as evidenced by significantly greater MT) involved a sequence of movements to execute, while the 9-hole box required only a single movement (Brasted et al., 1998). Thus, while both tasks effectively measure speed of processing, the 9-hole box LRT represents a more effective means of separating speed of processing (RT) and functional capabilities (MT).

4.2. 5-CSR task

As discussed previously, the 5-CSR task represents another operant-based choice reaction-time task. Since the response apertures are distributed in a wider array than the 9-hole box LRT, assessing processing speed in the 5-CSR task will retain the same RT confounds that are experienced in the Skinner box LRT, and is measured as MCL. Despite the confounds inherent in assessing MCL (time period between the stimulus presentation and the correct response) however, the presence of other measures assist in determining whether a drug effect on MCL is confounded by motoric or sedative effects (e.g. latency to collect food). Since the attention/vigilance section of this review discussed numerous studies conducted in the 5-CSR task, this section will highlight only studies that observed drug-related effects on MCL.

Grottick and Higgins (2002) found that, as in humans, nicotine, amphetamine, and caffeine reduced MCL in rats challenged by a reduced stimulus duration and increased session length. These effects were independent of speeding incorrect or reward latency measures (although amphetamine lowered incorrect latency at 8-fold higher doses than those affecting MCL; Grottick and Higgins, 2002). Such MCL speeding effects of amphetamine were also observed by Muir et al, (1995) and Bizzaro et al, (2004). Numerous studies also support Grottick and Higgins (Grottick and Higgins, 2002) observation of nicotine-induced reduction in MCL, both in rats (Grottick et al., 2000; Hahn et al., 2002a) and mice (Young et al., 2004), without affecting other latency measures. Other cholinergic agonists such as epibatidine (Hahn et al., 2003), SIB 1765F (Grottick and Higgins, 2000), and the AChEI donepezil (Balducci et al., 2003), reduced MCL. While other cholinergic manipulations mimic the psychostimulant effects of nicotine, the effects of caffeine have not been as consistent (Bizarro et al., 2004; Grottick and Higgins, 2002). Nevertheless, despite this discrepancy, there is evidence that classical psychostimulants can speed MCL in the 5-CSR task.

The dopamine D_1 receptor antagonist SCH23390 did not affect MCL, either alone or in combination with nicotine (Hahn et al., 2002a). Neither the dopamine D_2 antagonist sulpiride nor raclopride had any effect on the MCL of normal performing animals. While the former also did not alter the MCL in mPFC lesioned animals, the latter significantly reversed nicotine-induced reduction in MCL (Hahn et al., 2002a; Passetti et al., 2003). Effects of noradrenergic manipulations on MCL have been investigated, but the effects of α1 or α2 manipulation have been inconsistent (Hahn and Stolerman, 2005; Jakala et al., 1992; Puumala et al., 1997a; Puumala et al., 1997b; Sirvio et al., 1994). Non-selective antagonism of the 5-HT receptors via methiothepin or methysergide administration significantly slowed MCL of normal rats (Ruotsalainen et al., 1997). Considering that serotonin depletion in normal humans results in faster RT in the Trail-Making A task (Gallagher et al., 2003), suggests some discrepancy between MCL in the rat 5-CSR task and RT in the human Trails A task that should be further investigated. Selective antagonism of 5-HT_{2A} receptors via ketanserin administration was without effect on MCL, although reduced premature responding was observed, which in the version used could reflect reduced locomotor activation (Ruotsalainen et al., 1997). While the 5-HT_{1A} agonist 8-OHDPAT significantly reduced MCL in normal performing rats, to date this effect has only been observed in rats administered 8-OHDPAT intra-mPFC (Carli et al., 2006). Finally, and in line with animal modeling of the cognitive deficits in schizophrenia, NMDA receptor antagonism, administered intra-mPFC (Carli et al., 2006) or systemically (Le

Pen et al., 2003), significantly slows MCL, consistent with NMDA R antagonism-induced slowing of RT in humans (Micallef et al., 2004).

Greater details of the studies discussed above can be found in the attention/vigilance section. This brief summary provides support, however, that the 5-CSR task can be utilized to assess a form of speed of processing in animals. While the measures do not reflect processing speed alone, also perhaps less accurately than the LRT, the task does provide additional information on the pharmacological effects of drugs on cognition, further enhancing the profile of the 5-CSR task for use in preclinical modeling of the MATRICS battery.

4.3. Olfactory Discrimination

The assessment of choice RTs in response to odors may provide a novel yet invaluable method for studying processing speed in rodents. Olfactory choice RT performance has been demonstrated previously in mice (Bodyak and Slotnick, 1999) using the olfactometer apparatus developed by Slotnick (Slotnick and Risser, 1990). The task utilizes operant conditioning and requires very little training (Bodyak and Slotnick, 1999). Mice are required to nose poke in an aperture for a fixed period (1.5 s), during which time an odor is presented. After this time, the mouse needs to either lick at the water tube (within 2 s) or do nothing depending on the odor presented, whereas response to certain odors and non-response to others received reinforcement. Bodyak and Slotnick (1999) demonstrated that discriminatory accuracy levels were near perfect even when comparing no odor vs. 0.0001% ethyl acetate.

Rats exhibit a significant reduction in accuracy with increased odor similarity, with a strong negative correlation between the two (Uchida and Mainen, 2003). Surprisingly, the RT (sampling time) of the rats did not slow with increased odor similarity, with no correlation between the two variables, which is in stark contrast to increased complexity slowing human RT performance (Parasuraman, 1998). This finding is also in stark contrast with mouse performance, whereby increased task complexity, by increasing odor similarity, slows mouse RT performance (Abraham et al., 2004; Rinberg et al., 2006). It was proposed that these conflicting results may be a reflection of the task set-up (Abraham et al., 2004), since Uchida and Mainen (2003) used response holes that were located adjacent to the sample hole. Because Rinberg et al (2006) utilized a similar testing configuration in mice however, it appears that rats and mice use different strategies to complete the task. While rats learn an odor/response association, their accuracy increases following forced increased sampling time when the S- stimulus is presented (Slotnick and Risser, 1990). Thus it appears that the strategy employed by rats was being primed to react, but with a forced increase in sampling time they will utilize the chance of extra information (Slotnick and Risser, 1990). This strategy contrasts with mice whose strategy was to be primed to withhold from responding, thus as they learn the task they spend greater time sampling the S+ stimulus to ensure accurate responding (Bodyak and Slotnick, 1999). Such innate (primed) behavior is also in evidence when rats and mice are required to withhold from responding in a modified 5-CSR task, whereby withholding from response earns a reward in a no stimulus light condition, while a response was punished with a time-out phase. When challenged with such a paradigm, rats will respond 90% of the time in comparison with mice who will respond only 10% of the time (Spratt et al., 2000). These findings could also explain the differences observed between rat and mouse odor discriminatory performance when odor similarity is increased. While rats become less accurate as they still maintain their response speed (Uchida and Mainen, 2003), mice increase sampling time, and thus slow RT, to maintain accuracy (Abraham et al., 2004; Rinberg et al., 2006). Because increased RTs are observed in humans when task difficulty is increased (Parasuraman, 1998), perhaps it would prove more fruitful to utilize mice when investigating preclinical speed of processing when using this task.

Unfortunately there have been few studies conducted on rodents performing in the olfacotmeter. Thus there remains a paucity of studies demonstrating manipulation effects on task performance. While pharmacological effects have yet to be demonstrated, studies on genetic manipulation effects have been reported. Female estrogen synthetic enzyme KO mice exhibited significantly better performance on an olfactory discrimination (Wesson et al., 2006), and rats deficient of *n*-3 fatty acid exhibited poorer performance than their WT counterparts (Greiner et al., 2001). Although age-related effects have been examined, no deficit in accuracy or learning was observed with increased age (Kraemer and Apfelbach, 2004). The choice of odors utilized and the lack of RT information, however, highlights the need for further examination of this task. Perhaps pharmacological effects should be investigated in an attempt to validate this model for examining speed of processing in rodents.

5. Reasoning and Problem Solving

While the reasoning and problem solving domain can also be referred to as executive functioning, the terminology used here and in MATRICS assists in distinguishing it from the executive control involved in working memory (Baddeley, 1986). Therefore, here we are not referring to a control process that coordinates subsystems for working memory, but to a process by which problems are encountered and must be solved by abstract reasoning that may alter over time. The tests identified in the beta version of the cognitive battery devised by MATRICS included: Wechsler Adult Intelligence Scale (WAIS)-III Block Design; Brief Assessment of Cognition in Schizophrenia (BACS); Tower of London; and Neuropsychological Assessment Battery (NAB) – Mazes. When subsequently ranked according to the five ranking categories (described above), the NAB – mazes test was voted as the most representative test for this cognitive domain. This test involves seven paper and pencil mazes that must be completed as quickly and accurately as possible.

While the NAB-mazes test does not directly translate to a rodent paradigm, there are several rodent problem-solving tasks that also require good visuo-spatial scanning ability, visuo-motor control, processing speed, and learning. These tasks typically require rodents to acquire a new strategy while inhibiting the use of a previously reinforced strategy and could provide adequate tasks (Nuechterlein et al., 2005). Such tasks include: the Attentional Set-Shifting Task (ASST) developed by (Birrell and Brown, 2000) and based on the CANTAB intradimensional/extradimensional task (a computational version of the WCST; Owen et al., 1991); the cross-maze rule-shifting task (CMRST) characterized by Ragozzino and colleagues (Ragozzino et al., 1999); and various reversal learning paradigms utilizing both odors (Schoenbaum et al., 1999) and spatial cues (Widholm et al., 2001). The validity of these tasks to the reasoning and problem-solving domain will be discussed (Table 4). Although attempts have been made to develop touch screen technologies to assess problem solving abilities of both rats (Markham et al., 1996) and mice (Brigman et al., 2005; Bussey et al., 2001), these tasks have not been as well validated and can be difficult to implement, hence we will not focus on them here (Robbins, 1998, provides a species comparison). Interestingly, the WCST was integral to the decision of identifying the cognitive domain of reasoning and problem solving (Nuechterlein et al., 2004).

5.1. Attentional Set Shifting (ASST)

Birrell and Brown (Birrell and Brown, 2000) recently described a rodent analogue to the WCST, which they named the attentional set-shifting task (ASST). The WCST originated from extended observations in non-human primates (Eling et al., 2008) and requires the subject to identify target cards, where the only information guiding choice is the shapes that appear on the card, their color, their number, and the experimenter saying ‘correct’ or ‘wrong’, following the subject’s choice. Thus, while the subject sorts through the cards based on association rules using shape number or color as dimension, the appropriate rule may change, requiring the

subject to learn a novel rule, all within the same session. The rodent ASST differs from the WCST only by utilizing dimensions of odor (e.g. lemon vs. nutmeg), digging medium (e.g. sand vs. beads), and bowl texture (e.g. smooth vs. rough). Hence rats were trained to associate a specific cue (e.g. the odor nutmeg) with reinforcement. Rats were first trained on a simple discrimination (SD; one stimulus modality only; e.g. the odor lemon always predicts reward, the odor paprika is never reinforced), followed by compound discrimination (CD; two stimulus modalities, with only one relevant dimension consistent with SD, e.g. lemon scent still predicts reward and paprika never does, although two novel digging mediums are also now present), CD reversal (CDR; the previously irrelevant stimuli within the same modality now relevant, hence paprika is now always rewarded, while lemon is not, again irrespective of the digging medium), then an intra-dimensional (ID) shift (a novel stimulus within the same modality as previously used now relevant, so two novel odors now appear, parsley and cumin, with parsley always rewarded), ID reversal (IDR; the novel stimulus within the same modality is now relevant, cumin is now rewarded, parsley is not), extra-dimensional (ED) shift (ED; stimulus in a novel, previously irrelevant modality is now relevant, so that the digging medium tea leaves now predicts reinforcement, while plastic beads is never rewarded, irrespective of odor), and an ED reversal (EDR; the previously irrelevant stimulus within the same novel modality is now relevant, and plastic beads are rewarded while tea leaves are not), whereby six consecutively correct responses were required at each stage before moving onto the next, These manipulations would occur within the same test session. Importantly, Birrell and Brown (2000) demonstrated that the rats formed an attentional set as evidenced by the observation that the number of trials taken to perform the ED shifting was significantly greater than the number required for the ID shifting. Thus the rats took longer to acquire a rule that required a shift from one perceptual dimension to another, than when shifting within a dimension, providing predictive validity in comparison to the WCST in humans.

5.1.1. Task Validity of the ASST for the Reasoning and Problem Solving domain

—Rapid acquisition has been observed for the ASST, far quicker than when a rodent is required to respond to visual stimuli in a touch screen model, with rats displaying similar errors to criterion when compared to primates utilizing visual cues (Birrell and Brown, 2000; Markham et al., 1996; Robbins, 1998). This facileness is perhaps not surprising given that rodents attend preferentially to olfactory as opposed to visual cues (Jennings and Keefer, 1969), and the task capitalizes on natural foraging behavior. Despite the different modalities utilized (visual in the WCST and odors in the ASST), considerable homology has been exhibited for the systems supporting performance at each stage in this task. It has been demonstrated that despite the rodent mPFC not being anatomically analogous to the primate (including human) dorsolateral PFC, it was functionally homologous. Birrell and Brown (2000) observed deficient performance of the ED shifting section of the task after ibotenic acid lesions to the rat mPFC. Indeed the original description of a frontal deficit by Milner (1963) using the WCST was in patients with structural damage in mPFC. Consistent with rats, mPFC lesions in mice impair ED shifting (Bissonette et al, 2008). Lesions of the dorsolateral PFC impair ED shifting in humans and primates (Dias et al., 1996; Stuss and Alexander, 2000). Impaired ED shifting performance of schizophrenia patients has also been linked to hypofrontality in the dorsolateral PFC (Bunney and Bunney, 2000; Joyce et al., 2002; Weinberger et al., 1988; Weinberger et al., 1986). Moreover, reversal deficits (Pantelis et al., 1999; Pantelis et al., 2004) have been observed in OFC-lesioned rats (McAlonan and Brown, 2003) and mice (Bissonette et al, 2008) performing the ASST, and schizophrenia patients with OFC pathology performing the WCST (Shad et al., 2006). Thus, the rat and mouse ASST demonstrate construct and etiological validity for the IDED task used in humans. Furthermore, rats (Barense et al., 2002; Nicolle and Baxter, 2003), mice (Young et al, manuscript submitted), and humans (Owen et al., 1991) also exhibit age-related impairments in ASST performance, suggesting that the rodent ASST may model similar pathology and sensitivity to age as human set-shifting tasks.

5.1.2. Perturbation of ASST performance—As has been discussed, several manipulations that impair performance in this task have been reported. These manipulations include mPFC, orbitofrontal cortex (OFC), and frontal lesions, as well as aging (Barense et al., 2002; Birrell and Brown, 2000; McAlonan and Brown, 2003; Nicolle and Baxter, 2003). Pharmacologically induced impairments in performance, including putative models of schizophrenia, have also been examined. Chen *et al*. (2004) observed impaired ED shifting and Rev in rats treated with scopolamine. Interestingly, no effect was observed in ID shifting, however, suggesting that not only is it possible to dissociate ED shifts and reversals (mPFC and OFC lesions respectively; Birrell and Brown, 2000; McAlonan and Brown, 2003), but the neurochemical systems underlying ID are also separable (Chen et al., 2004). While no significant ID/ED difference was observed, the authors suggest that this result may be due to the injection protocol, resulting in a break during testing, as they had reliably demonstrated ID/ED differences in previous studies (Barense et al., 2002; Fox et al., 2003). Administration of the primary psychoactive constituent of marijuana, delta-9 tetrahydrocannabinol (Δ9-THC), impaired ID and reversal performance at each stage in the ASST without affecting ED shifting (Egerton et al., 2006), which the authors suggest reflect Δ9-THC-induced increase in perseveration without affecting strategy shifting. Δ9-THC administration could however, have disrupted the formation of an attentional set, so that the rats did not learn to focus on the original stimulus modality, thus performance following changes within the same modality was poorer, but ED shift performance did not differ from that of ID shift. The lower c-fos expression observed in the frontal cortex of these rats (Egerton et al., 2006) would support this latter explanation.

5.1.3. Perturbations of ASST performance with relevance to schizophrenia—Schizophrenia patients exhibit poorer ID/ED performance compared to healthy controls, both measured in more errors prior to ED shift, as well as more ED shift errors, and fewer subjects obtaining ED shift criteria (Tyson et al., 2004). Theoretically, a suitable animal model of schizophrenia would exhibit a similar phenotype compared to controls i.e. selective deficits in ED shift performance. Lovic and Fleming (2004) described a neurodevelopmentally induced deficit in ASST performance, in which artificially reared rats (rearing neonates without a mother), required more trials to attain criteria in CDR, ID shift, IDR, ED shift, and EDR, compared to maternally reared rats, demonstrating some consistency with schizophrenia patients. As they did not observe any effect on SD or CD, they suggest that the manipulation could have affected the rat's ability to perform complex learning (Lovic and Fleming, 2004). Impaired PPI was also observed in these animals, providing further support for this putative neurodevelopmental animal model of schizophrenia (see Lovic and Fleming, 2004; Van den Buuse et al., 2003). The sensitivity of the task to PCP-induced deficits has been inconsistent, however, which may be due to the use of different dose regimens across studies. Egerton et al. (2005) observed PCP-induced ED shift deficits after acute PCP administration (2.58 mg/kg, 22 hours prior to testing) that would mimic the psychotomimetic effects of PCP. Rodefer et al. (2005) also observed a significant PCP-induced ED shift deficit, although this dose regimen involved subchronic PCP treatment (5 mg/kg for 7 days followed by a 10-day washout period prior to testing), an NMDA antagonist regimen that is not psychotomimetic in humans. A subchronic PCP-induced deficit in ED shift was also observed by Goetghebeur and Diaz (2008). In contrast, subchronic administration of lower doses of PCP (3 mg/kg for 3 d/wk, for 5 weeks) did not affect ASST performance (Fletcher et al., 2005). While the reasons for the differences observed in these studies have yet to be elucidated, Fletcher et al., (2005) proposed that PCP-induced deficits in ED shift are a result of modulated dopaminergic activity, and that their PCP administration regimen was not sufficient to alter dopamine activity. Support for this theory came from their study demonstrating that PCP-treated rats exhibited normal locomotor responses to low doses of amphetamine (Fletcher et al., 2005). McLean et al. (2008a) observed a significant ED shifting deficit in rats treated with only 2 mg/kg PCP (2/

day, for 7 days) that was significantly reversed by clozapine and risperidone, but not by haloperidol. An ID/ED shift was not observed in these rats however, nor was there an effect of reversals – in fact vehicle-treated rats at most took 8 trials to criterion on average for any stage, with SD, CDD, and ID perfect performance (6 trials to criterion; McLean et al, 2008a). Thus it appears unlikely that these rats were performing the task appropriately, making it difficult to interpret the effects observed.

Fletcher et al., (2005) demonstrated that chronic amphetamine treatment (administered similarly to PCP though with an increased dosage as the weeks progressed) impaired ASST performance, in a similar fashion to scopolamine as measured by deficient reversals and ED shift yet normal ID shift (Chen et al., 2004). The finding that SKF38393, a dopamine D_1 receptor agonist, injected directly into the mPFC of amphetamine-treated rats significantly reversed the ED shift deficit, provides support for dopamine modulation of ED shifting behavior (Fletcher et al., 2005). Such a conclusion is further supported by human data demonstrating that the dopamine D_2 antagonist sulpiride impairs WCST performance in normal humans (Mehta et al., 2004). NMDA receptor contribution to ED shift cannot yet be ruled out, however, particularly with the finding that lower levels of [^{3}H]kainate binding in the cingulate cortex and higher levels of NMDA receptor binding in the dorsomedial striatum strongly correlated with poor ED shift performance in aged rats (Nicolle and Baxter, 2003). As these results relate to aged rats, however, their relation to impaired performance in schizophrenia patients remains unclear.

Finally, performance in neurodevelopmental rat models of schizophrenia has been assessed in the ASST, including NVHL and isolation rearing models (Marquis et al, 2008; McLean et al, 2008). The NVHL model significantly impaired ED shifting in rats that demonstrated an ID/ED shift and effects of reversal learning, thus it is likely that these rats genuinely demonstrated a deficit in shifting their attentional set (Birrell and Brown, 2000). Although the authors did not assess the performance of adult ventral hippocampal lesions on task performance to assess whether the deficit was neurodevelopmental in origin, the ED shifting does not depend on the temporal lobe (Chudasama and Robbins, 2006), thus it is unlikely the effects were not developmental in origin. The authors suggest that these deficits may relate to reduced density of dendritic spines in pyramidal neurons in layer 3 of the mPFC (Marquis et al, 2008), providing further links with schizophrenia. McLean et al, (2008b) assessed the effects of isolation rearing on ASST performance in rats, describing a specific ED deficit in isolation- compared to socially reared rats. Surprisingly however, the ED shifting performance of socially reared rats was actually better than their ID shifting performance, with no evident effect on reversals at any stage in either group (McLean et al, 2008b). Thus while the authors report an ED shifting deficit in socially reared rats, there was no evidence that an attentional-set had been formed, nor that the rats were performing the task appropriately given the lack of reversal effect.

5.1.4. Effects of Established Antipsychotics on ASST task performance—To the authors' knowledge, few studies have been conducted describing the effects of antipsychotic medication in the performance of the rodent ASST. Such information could prove invaluable, especially in further developing animal models of schizophrenia, as any cognitive enhancer produced would likely be used as an add-on to current antipsychotic treatment (Geyer and Tamminga, 2004). Goetghebeur and Dias, (2008) described sertindole-induced reversal and risperidone-induced amelioration of PCP-induced deficit in ED shifting in the task in rats. Haloperidol did not appear to improve performance in these rats however. These effects were also observed by McLean et al (2008) in subchronic PCP rats, where clozapine and risperidone reversed ED shifting deficits, while haloperidol did not. While Goetghebeur and Dias, (2008) demonstrated an ID/ED difference in their study, suggesting the PCP-induced ED shifting deficit was as a result of impaired shifting of an attentional set, McLean et al, (2008a) did not observe an ID/ED difference, nor any effects of reversals. Thus the data remain

open to interpretation. Moreover, given the lack of antipsychotic-induced improvement in ID/ED shifting in schizophrenia patients, the results in this model may be viewed as false positives. More research is required in this task, both on the effects of antipsychotics on normal animals and in models of schizophrenia.

5.1.5. Putative Targets for Cognitive Enhancement of ASST Performance—Few studies have examined the effects of putative pro-cognitive compounds in the ASST in animals. Tunbridge et al. (2004) demonstrated that tolcapone, a COMT (an enzyme involved in dopamine catabolism) inhibitor, significantly lowered trials to criterion performance in the ED shift only. Reduced activity of COMT via genetic polymorphism (Lachman et al., 1996) had previously been linked to improved WCST performance in humans (Egan et al., 2001), though this improvement was identified as a reduction in overall perseverative errors. Tunbridge et al. (2004) then demonstrated that tolcapone treatment significantly increased mPFC dopamine but not norepinephrine during stimulated conditions of catecholamine efflux only, suggesting that the improved ED shift performance observed in the tolcapone-treated rats could have been the result of enhanced dopamine neurotransmission, which may prove relevant to the dopamine hypofrontality hypothesis of cognitive deficits in schizophrenia (Goldman-Rakic et al., 2004). While the results presented were impressive, it must be noted that despite significant differences in ED shifting between the group means, the ED shift of the control rats did not significantly differ from their ID shift. Thus, it is unclear if the rats learned a perceptual attentional set, and hence demonstrated an attentional shift. As no other aspect of the task was improved however, it is unlikely that the tolcapone effect relates solely to simple learning. Therefore, the suggestion of Tunbridge et al. (2004) that a COMT inhibitor co-administered with an atypical antipsychotic may prove beneficial in the treatment of schizophrenia is plausible. Modafinil remains one of the few treatments to exert pro-cognitive effects on ED shift in schizophrenia patients (Turner et al., 2004). This pro-cognitive effect of modafinil was also observed in rats with subchronic PCP-induced ED shift deficits (Goetghebeur and Dias, 2008). The control group and PCP-treated group exhibited a difference in ID shift and ED shift, suggesting that a perceptual set was formed and thus the PCP and modafinil effects observed were likely to be executive in nature. These data by Goetghebeur and Dias (2008) may provide a model by which to assess putative reasoning and problem solving enhancers for the treatment of schizophrenia. More work is required to assess the reproducibility of the cognitive enhancing effects of modafinil in schizophrenia patients with chronic administration, and this animal model however, especially as antipsychotics also improved performance of PCP-treated rats in this study (Goetghebeur and Dias, 2008; see 5.1.4)

In their study in rats, Lapiz and Morilak (2006) investigated the effects of manipulating the noradrenergic system, another viable target for cognitive enhancement in schizophrenia (Arnsten, 2004). The effects of compounds including the α2-adrenoreceptor antagonist atipamezole and the α2-adrenoreceptor agonist clonidine on ASST performance were investigated (importantly, in this cohort rats exhibited a significant ED/ID difference; Lapiz and Morilak, 2006). Atipamezole, but not clonidine treatment, produced a significant improvement in ED shift (Lapiz and Morilak, 2006). The effects appeared to be mediated through cortical α1 adrenergic receptor activation because the improvement with atipamezole was blocked by the α1-receptor antagonist benoxathain administered intra-mPFC (Lapiz and Morilak, 2006). Serotonergic receptors may also modulate ASST performance. Since the discovery of the affinity of many atypical antipsychotics for the 5-HT_6 receptor, this receptor has been investigated for putative cognitive enhancing effects (Mitchell and Neumaier, 2005; Roth et al., 2004). Hatcher *et al*., (2005) recently demonstrated that the selective 5-HT_6 antagonists SB-271046-A and SB-399885-T significantly improved ASST performance in rats. Both 5-HT_6 antagonists improved reversal learning, while SB-271046-A moderately (vehicle-treated rats exhibited an ID/ED difference while SB-271046-A treated rats did not) and SB-399885-T significantly improved ED (Hatcher et al., 2005). A significant reduction in

total errors throughout the session was observed for both compounds in a task where the authors demonstrated that the rats underwent an attentional set-shift. As these 5-HT_6 antagonists significantly altered dopamine, acetylcholine, and norepinephrine levels in the mPFC (Hatcher et al., 2005; Riemer et al., 2003), they could theoretically provide remediation for the problem-solving deficits observed in schizophrenia patients. As yet, however, neither tolcapone, atipamezole, SB-271046-A, nor SB-399885-T have been administered in the context of animal models with putative construct validity for schizophrenia.

Perhaps due to its relative novelty and the expertise required to perform this task, there have been few reports to date on compounds that could reverse the ASST deficits observed in classic animal models of schizophrenia. As mentioned, the dopamine D_1 receptor agonist SKF38393 administered directly into the mPFC restored amphetamine-induced impairment in ED shifting (Rodefer et al., 2005). The COMT inhibitor tolcapone and the α2-adrenoreceptor antagonist atipamezole improved normal performance in otherwise untreated rats (Fletcher et al., 2005; Lapiz and Morilak, 2006). Rodefer et al. (2005) were, however, able to demonstrate reversal of the PCP-induced deficits they observed with systemic administration of papaverine, a phosphodiesterase (PDE) 10A inhibitor. Although papaverine has limited use as a therapeutic agent due to its undesirable side-effects (Brown et al., 1998; Smith et al., 2004), the reversal observed provides proof of principle for the viability of the PDE10A as a molecular target for cognitive enhancement (Rodefer et al., 2005).

5.1.6. Mouse versus Rat ASST testing—The ASST has also been configured for use with mice (Colacicco et al., 2002). To date, strain differences, subchronic PCP effects, lesions studies, and transgenic (D_2 and D_3 dopamine receptor KO and *Hdh*$^{CAG(150)}$ knock-ins) effects have all been described (Bissonette et al, 2008; Brooks et al., 2006; Colacicco et al., 2002; DeSteno and Schmauss, 2008; Glickstein et al., 2005; Laurent and Podhorna, 2004). In several studies, the procedures used differed from that used in rats insofar as testing of each stage was done on separate days (Brooks et al., 2006; Colacicco et al., 2002; Laurent and Podhorna, 2004). This strategy was chosen due to the apparent erratic behavior of mice after 1–2 hours of testing (Colacicco et al., 2002; Laurent and Podhorna, 2004). Other studies have however assessed mouse performance within a single session (DeSteno and Schmauss, 2008; Garner et al., 2006; Glickstein et al., 2005). Using a touch screen apparatus, Brigman et al. (2005) were able to show differences in performance with most manipulations, but did not demonstrate a significant ID/ED difference (Brigman et al., 2005). This lack of a significant difference between ID/ED shift performance suggests that the procedures used in these studies were not sufficient for mice to develop a perceptual attentional set (Brigman et al., 2005; Colacicco et al., 2002). This lack of an effect could be due to the multiple days of testing utilized as opposed to testing within the same test session. Some studies that used a single test session however, also did not report statistical analysis assessing ID/ED shift differences (Glickstein et al., 2005; Zhuo et al., 2007). Where ID/ED differences have been reported, the authors either used different stage criteria than rat and human studies (Garner et al, 2006; Bissonette et al, 2008), or they reported data that differed largely from previous reports in their same apparatus (DeSteno and Schmauss, 2008 vs. Glickstein et al., 2005). Thus, observable ID/ED differences in mice (Brigman et al., 2005; Colacicco et al., 2002; Laurent and Podhorna, 2004) remains an open question, although some methodological differences made to accommodate mouse behavior may prove beneficial, such as using platforms as opposed to digging medium as the second dimension (Young et al., manuscript submitted). Despite methodological differences however, ID/ED differences in mice have been observed (Bissonette et al, 2008; Garner et al, 2006). Moreover, consistent with human and rat literature, the mPFC and OFC appear to mediate ED shifting and reversal learning in mice (Bissonette et al, 2008). Furthermore, although a perceptual attentional set in mice was not verified, subchronic PCP administration in C57BL/6 mice produced a pattern of deficits similar to that reported in scopolamine- and amphetamine-treated rats, i.e. reversal and ED shift deficits (Chen et al., 2004; Fletcher et al.,

2005; Laurent and Podhorna, 2004), indicating that ED shift deficits can be dissociated in mice. Glickstein et al. (2005) also provided support for a dopaminergic involvement in the mouse version of this task when they described impaired CD in dopamine D_2 receptor KO mice, yet improved ED shift in dopamine D_3 receptor KO mice, albeit with slowed RT, suggesting a possible speed/accuracy trade-off. Thus, this study provides support for dopamine D_3 receptor antagonism as a therapeutic target for the treatment of cognitive deficits.

5.1.7. Conclusion and Future Studies for ASST—For a recently developed behavioral task, reports on the ASST have grown significantly in the past few years. The ASST has demonstrable face, predictive, and construct validity, suggesting that it could prove to be an invaluable preclinical tool in researching attentional set shifting deficits relevant to schizophrenia. Pharmacological predictive validation is limited however, and the replicability of findings has been questioned. Furthermore, improvement in ASST performance must be interpreted with care, for improved performance without an ID/ED difference may be indicative of the test animals not forming an attentional set, even if the saline control animals did. Methodological considerations may also limit the use of ASST in the drug discovery process given the low throughput and length of testing. While no training is required, it can take 3–5 hours to run a single rodent, thus most experimenters test 2 animals per day at maximum. Also, as the test length is variable, interpreting data based on pharmacokinetic profiles of drugs may prove difficult. A novel operant set-shifting task has been developed and is currently being validated that may prove more useful than the ASST (Floresco et al., 2008). Although his task requires greater validation, it shows promise for use in the drug discovery process. Finally, care must be taken in the interpretation of any data produced for the ASST, as a shift in attentional set can only be demonstrated by an ID/ED difference.

5.2. Cross Maze Rule-Shifting Task (CMRST)

Recently, another behavioral task has been described that requires rats to shift attention from one rule to another based upon task contingencies (this test has not yet been adapted for mice). Ragozzino et al. (1999) used a cross-maze apparatus to provide two modalities that rats could use to repeatedly select the arm that was baited. In the place version of the task, rats started in the east or south arm, and access to the west arm was always blocked. The north arm was always baited, and so regardless of starting position, the rat had to move into the north arm. Task acquisition was set at 10 consecutively correct responses and was verified by a probe trial in which the rats started in the west arm and were still required to move into the north arm. For the response version of the task, the rats always began in the east or west arms, but had a choice of moving left or right (north or south). The side opposite to the bias they had previously demonstrated was always rewarded, thus the rats learned to always move to the side contrary to their innate bias. It was later demonstrated that other task contingencies could be used. For example, Stefani and colleagues (Stefani et al., 2003; Stefani and Moghaddam, 2003) utilized the rats' ability to differentiate between bright or dimly lit arms and between rough and smooth textured arms, while Floresco and colleagues (Floresco and Ghods-Sharifi, 2007; Floresco et al., 2006a; Floresco et al., 2006b) also described the use of a visual cued arm. Thus, the task could assess extra-modal shifts (similar to the ED shift) by switching from the use of one set of contingent modalities to another. Similarly, an intra-modal shift (reversal learning) could be assessed by swapping the rewarded contingencies within a modality.

5.2.1. Task Validity for CMRST—In the first demonstration of this task, Ragozzino et al. (1999) investigated the requirement of the prelimbic-infralimbic (PL/IL) cortex for normal extra-modal shift performance (equivalent to human mPFC). They discovered that inactivation of this area did not impair learning or reversal learning, but did impair shifting from rules based in one modality to another. This pattern of deficits bears resemblance to the ED shifting deficits produced by PL/IL cortex lesions in the ASST, which spared every other aspect of ASST

performance (Birrell and Brown, 2000) and is similar to WCST deficits in monkeys and humans with dorsolateral PFC lesions (Dias et al., 1996; Stuss and Alexander, 2000). Further etiological validity for the ASST is supported by the finding that the OFC appears to mediate reversal learning selectively (Floresco et al., 2008; Ghods-Sharifi et al., 2008). Moreover, the dorsomedial striatum also appears to be important for reversal learning (Palencia and Ragozzino, 2004; Ragozzino and Choi, 2004; Ragozzino et al., 2002; Tzavos et al., 2004). Following direct administration into the dorsomedial striatum, Ragozzino and colleagues demonstrated that activation of AMPA receptors (Palencia and Ragozzino, 2004), muscarinic acetylcholine receptors (mAChRs; Ragozzino et al., 2002) though more specifically M1/4 nAChRs (Tzavos et al., 2004), but not nAChRs (Tzavos et al., 2004) is required in this area for normal reversal learning. When using brightness and texture of the arms as cues, Stefani and Moghaddam (Stefani and Moghaddam, 2003) suggested that blockade of AMPA receptors in the mPFC impaired every aspect of the task, whereas NMDA receptor blockade only affected the rats' ability to perform an extra-modal shift. Thus, similar to humans, the mPFC appears vital to measures of executive functioning in rats.

5.2.2. Perturbation of CMRST performance—One of the benefits of using this task over the ASST is that when looking at task perturbation, the type of errors made can be dissected for future analysis (Ragozzino et al., 2002). Thus, repeated entries into the previously rewarded arm can be measured as perseverative errors. Regressive errors are recorded when the rat made an error after making three correct responses. These errors were regarded as regressive because the rat was deemed to revert to responding in the previously correct arm even after receiving reinforcement elsewhere. Using the CMRST, revealed that the deficits produced by the non-selective mAChR antagonist scopolamine resulted from the rat being unable to learn a new rule (Ragozzino et al., 2002), while deficits caused by the NMDA receptor antagonist AP-5 or the selective M1 mAChR antagonist pirenzepine impaired the rats' ability to maintain a newly acquired rule (Palencia and Ragozzino, 2004; Tzavos et al., 2004). On the other hand, the non-selective nAChR antagonist mecamylamine did not impair the acquisition or maintenance of a new rule (Tzavos et al., 2004). It must be noted, however, that these drugs were administered directly to the dorsomedial striatum, and their systemic actions have yet to be assessed. Ragozzino and Choi (Ragozzino and Choi, 2004) did, however, describe supporting evidence that mAChRs may provide a crucial role in the avoidance of returning to a previously learned strategy (committing regressive errors). They measured medial striatal acetylcholine (ACh) output of rats performing a reversal of the place version task and observed that while output remained stable during performance of the learned task, and for the first 6 min into the reversal, it rose by 250% between 6 and 12 min as the rat was learning the reversal, and progressively decreased back to baseline by 24–30 min (Ragozzino and Choi, 2004). This result bears both resemblance and contradiction to microdialysis studies completed in rats performing the 5-CSR task.

Using the response version and visual cued tasks, Floresco et al. (Floresco et al., 2006a) investigated the role of Nucleus Accumbens (NAcc) subregions in CMRST performance. They hypothesized that the NAcc core and shell may also mediate rule-shifting behavior as the mPFC projects to both the NAcc core and shell, while the OFC projects primarily to the core (Brog et al., 1993; Reynolds and Zahm, 2005). They demonstrated that inactivation of the NAcc core through GABA-A/B agonist (muscimol and baclofen) treatment disrupted extra-modal shifts, with increased regressive errors (returning to previously learned strategies), while leaving the initial reversal learning intact (Floresco et al., 2006a). However, inactivation of the NAcc shell significantly improved rule-shifting performance, but only when inactivated during training in the initial contingency (Floresco et al., 2006a). It appeared that inactivation of the NAcc shell resulted in the rats failing to encode as irrelevant the stimuli that did not predict the reward. This result is consistent with the finding that rats with NAcc inactivation do not display latent

inhibition, where task acquisition is retarded if the stimuli used were previously presented yet meaningless (Jongen-Relo et al., 2002).

The importance of the NAcc in CMRST performance was supported in a series of elegant experiments by Goto and Grace (2005). They investigated the behavioral effects of tonic and phasic dopamine release on mPFC and hippocampal synaptic inputs in the NAcc. Tonic dopamine release and D_2 receptor stimulation within the NAcc after unilateral PFC inactivation impaired extra-modal shifting performance by increasing perseverative responses (Goto and Grace, 2005). Dopamine D_1 receptor antagonism in the NAcc following PFC inactivation had no effect on performance however, while both D_2 receptor stimulation and D_1 antagonism in the NAcc after hippocampal inactivation impaired both initial learning and rule-shifting performance without increasing perseverative responses (Goto and Grace, 2005). Thus, it appears that dopamine receptors in the NAcc, dependent upon their innervation, mediate both learning and rule-shift performance, and that manipulation of these receptors can significantly alter baseline performance. The information gleaned from these studies supports the hypothesis of dopamine-mediated executive function and may provide targets for putative cognitive enhancers (Goldman-Rakic et al., 2004). Floresco et al. (2006b) investigated what effect modulation of dopamine D_1, D_2, and D_4 receptors located in the mPFC had on rule-shifting performance. While no effect of infusion of the D_1 receptor agonist SKF 81297 was observed, the D_2 antagonist eticlopride and the D_4 agonist PD168,077 significantly impaired rule-shifting performance by increasing perseverative errors.

Such studies provide useful information on ways in which to perturb performance and on the neurotransmitter/neuroanatomy underlying CMRST behavior. In order to assess putative cognitive enhancers as a part of a preclinical MATRICS test battery, more schizophrenia-relevant perturbations are required.

5.2.3. Perturbations of CMRST performance with Relevance to Schizophrenia— As mentioned above, the D_4 agonist PD168,077 impaired performance in the CMRST (Floresco et al., 2006b). This effect, however, could be NMDA receptor-mediated because PD-168,077 attenuates NMDA-mediated synaptic transmission in PFC pyramidal neurons by reducing NMDA-mediated currents and increasing the internalization of these receptors (Wang et al., 2003). This premise is supported by the finding that the NMDA non-competitive antagonist MK-801 administered intra-mPFC can impair attentional set-shifting performance in a similar manner to PD-168,077 (Stefani et al., 2003). Interestingly, while infusion of a D_2 agonist quinpirole into the NAcc following mPFC inactivation impaired rule-shifting (Goto and Grace, 2005), the same agonist infused directly into the mPFC did not affect performance (Floresco et al., 2006b). Thus, infusion of a D_2 agonist and antagonist do not necessarily exhibit opposite effects on performance because the effects can be site-specific.

The use of cannabis, of which the psychoactive ingredient Δ9-THC acts as an agonist on cannabinoid receptors, is a known risk factor for schizophrenia and cognitive dysfunction in schizophrenia patients (D'Souza et al., 2005). Hill et al. (2006) demonstrated that systemic administration of the CB1 receptor agonist HU-210 at high enough doses significantly impairs the ability of rats to rule shift, causing increases in perseverative errors. Reversal of this impairment may have some relevance to the perseverative deficits observed in schizophrenia patients, although these deficits do appear after acute CB1 receptor agonism, as opposed to chronic use observed in schizophrenia patients (D'Souza et al., 2005).

5.2.4. Effects of Established Antipsychotics on CMRST task performance—To date, no studies have been published addressing the effects of established antipsychotics in the CMRST. The intra-mPFC infusion of the dopamine D_2-selective antagonist eticlopride impairs performance (Floresco et al., 2006b). While this study does not provide information on the

effects of systemically administered antipsychotics on CMRST performance, it does provide some insight as to the putative effects in such studies.

5.2.5. Putative Targets for Cognitive Enhancement in the CMRST—There have been few examples of systemically administered compounds affecting performance in the CMRST. Infusion of the D_4 antagonist L745-870 into the mPFC of normal rats significantly improved rule-shifting performance (Floresco et al., 2006b), consistent with studies demonstrating pro-cognitive effects of systemic D_4 antagonists (Arnsten et al., 2000; Jentsch et al., 1999; Zhang et al., 2004). Although cannabinoid pharmacological manipulation was not identified in the MATRICS meeting as a therapeutic target (http://www.matrics.ucla.edu/matrics-meetings-frame.htm), the fact that high doses of a CB1 agonist impair CMRST performance (Hill et al., 2006) suggests that manipulation of the cannabinoid system may prove to be a useful target for cognitive enhancers. Indeed, Hill et al. (2006) also demonstrated that a CB1 receptor antagonist APU-25 can significantly improve CMRST performance by reducing perseverative errors in normal rats. The observation that administration of the CB1 receptor agonist HU-210 at low doses can also improve performance, similar to the CB1 receptor antagonist APU-25, complicates the interpretation of the CB1 receptor as a target for cognitive enhancement.

5.2.6. Rat versus Mouse Testing in CMRST—To date, no studies have reported mouse behavior in the CMRST, thus comparing performance between species is not possible. Given that mice can perform the radial arm maze (see 7.1) would suggest however, that they can use intra-maze cues to perform tasks.

5.2.7. Conclusion and Future Studies for the CMRST—The CMSRT supplies psychopharmacologists with another potentially useful tool with which to assess rule learning and shifting behavior. Similar to the ED shift performance in the ASST, the IL/PL frontal cortex appears essential for extra-modal rule shifting performance in the CMSRT. However, while it has been demonstrated that rats performing the ASST form an attentional set and that the ED shift measures their ability to shift from that attentional set (Birrell and Brown, 2000), it has yet to be demonstrated that rats performing the CMSRT form such an attentional set shift. In fact, it is common for rats to take the same number of trials for initial acquisition for both intra-modal (reversal learning) and extra-modal shifts (Floresco et al., 2006a; Floresco et al., 2006b; Palencia and Ragozzino, 2004; Ragozzino and Choi, 2004; Ragozzino et al., 2002; Ragozzino et al., 1999; Tzavos et al., 2004), although rats appeared to take more trials when shifting from visual cue to response learning but not vice-versa (Floresco et al., 2006a; Floresco et al., 2006b; Goto and Grace, 2005). While the importance of the dorsomedial striatum and the PFC, as well as several receptors therein, have been demonstrated for performance of this task, there have yet to be many studies investigating the effects of systemically administered drugs, including established antipsychotics. Moreover, there has been little investigation into the effects of the manipulations related to schizophrenia described elsewhere, such as NMDA receptor antagonism or neurodevelopmental perturbations, on performance in this task. It would be very interesting to note whether a perseverative-like phenotype can be observed after such manipulations, as is seen in schizophrenia patients. As no studies have demonstrated the latter and there has yet to be a report on mouse performance of the task, more has to be done to validate its use, especially with regard to schizophrenia.

5.3. Skinner box reversal learning

While the first two reasoning and problem solving tasks described involve a great deal of observation time, a reversal learning task has been described using an operant chamber. Widholm *et al*., (2001) used a two-lever operant box to assess reversal learning in Long-Evans rats. In the initial task, rats were reinforced for responses on one lever and not the other. Once

responding reliably on that lever (>85% on two consecutive days), the active lever would be switched the following day, requiring the rat to reverse the learned response from one cue lever to the other, based solely on the spatial location of the levers (i.e., spatial reversal learning; SRL). The rats would then be subjected to four additional reversals during which performance could be manipulated with drug challenges.

5.3.1. Task validity of Skinner Box Reversal Learning to Problem Solving Domain—To date, there have been very few studies exploring the neuroanatomy underlying performance of this task. Recently, however, in a similar operant task, Boulouqouris et al, (2007) demonstrated that OFC lesions significantly impaired reversal learning in the task while leaving initial learning intact. The authors observed increased perseverative errors with OFC lesions, but no effect of IL/PL cortex lesions (Boulougouris et al., 2007). Thus, although the IL/PL region is required for attentional shifting performance (Birrell and Brown, 2000; Ragozzino et al., 1999), it is not required to perform this reversal learning task, which may be consistent with studies of the human mechanism for reversal learning (Remijnse et al., 2006).

5.3.2. Perturbation of Skinner box Reversal Learning Performance—In their first description of the task, Widholm et al, (2001) identified SRL deficits in the first reversal in male, and the fourth and fifth reversals in female rats that had undergone prenatal exposure to Arocolar 1254 (a polychlorinated biphenyl environmental contaminant administered to pregnant Long-Evans rats from gestational day 6 to post-natal day 21). Rats prenatally exposed to another contaminant, 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (a halogenated aromatic hydrocarbon environmental contaminant; administered to pregnant Sprague-Dawley rats from gestational days 10 to 16), however, exhibited no deficits in the SRL (Widholm et al., 2003). Dioxin exposure did, however, improve both original learning in males and reversal learning in females when tested in a more difficult reversal task. In this visual reversal learning (VRL) task, the active lever was indicated by the presence (or absence) of a cue light above the lever, and hence the lever the rats were required to respond to varied within a session, unlike the SRL (Widholm et al., 2003). Although the cause for this dioxin exposure-induced improvement remains unknown, these studies support the sensitivity of this task to developmental and environmental insults, important risk factors for schizophrenia. As discussed above, performance can be impaired by OFC lesions (Boulougouris et al., 2007), indicating etiological validity for neural substrates underlying reversal learning in humans. More recently, Neill's group has created a hybrid of these two tasks (Abdul-Monim et al., 2003; Idris et al., 2005) working in female rats. Their version resembles the SRL task since the active lever is always on the same side within a training session, but the active lever is also cued by the presence or absence of a light source located above the lever, thereby assessing cued reversal learning. Assessment of reversal learning occurred within a session whereby the active lever was located at the same side for 25 trials or 5 min, and then following a 2 min time out phase the active lever was switched to the opposite side for a further 25 trials or 5 min (see below). This time-out phase appears to cue the upcoming reversal and probably explains both the very rapid nature of the reversal and the lack of a clear adaptation or re-learning phase in the data. Hence, the task should properly be viewed as a cued-reversal task.

5.3.3. Perturbations of Skinner box Reversal Learning with relevance to schizophrenia—Few studies have examined the effects of neurodevelopmental models of relevance to schizophrenia on performance of operant reversal learning. The only known study to date was performed in isolation-reared rats, a putative model related to schizophrenia (Fone and Porkess, 2008; Powell and Geyer, 2002), in which no effects on performance were observed, nor were the animals hypersensitive to PCP administration (Abdul-Monim et al., 2003). It has been demonstrated, however, that both acute (Abdul-Monim et al., 2003; Idris et al., 2005) and subchronic PCP (Abdul-Monim et al., 2006) induced deficits in reversal learning

performance while leaving initial learning intact. Impaired reversal but intact initial learning is also observed after administration of the NMDA receptor antagonist MK-801 (van der Meulen et al., 2003). These findings are consistent with a study demonstrating that antagonism of NMDA receptors in the OFC significantly impairs reversal learning in intact rats (Bohn et al., 2003). Acute amphetamine also leads to reversal learning deficits (Idris et al., 2005) that may differ qualitatively from those produced by subchronic PCP, insofar as amphetamine increased perseverative responses and PCP increased regressive errors (Neill et al., personal communication). PCP and amphetamine both brought performance to chance levels when the active lever was switched (reversal), however, and the rats appeared incapable of performing the reversal within the 25 permitted trials.

5.3.4. Effects of Established Antipsychotics on Skinner box Reversal Learning—There have been several studies investigating the effects of antipsychotics both in normal rats and in models related to schizophrenia. The typical antipsychotic haloperidol impaired both initial and reversal learning in normal rats, while the atypical antipsychotics ziprasidone and clozapine had no effect in normal animals (Abdul-Monim et al., 2003). Haloperidol, but not chlorpromazine, exhibited moderate effects at reversing acute PCP-induced deficits (Abdul-Monim et al., 2003), while ziprasidone, clozapine, and olanzapine all fully reversed PCP-induced impairments in reversal learning (Abdul-Monim et al., 2003, 2006; Idris et al., 2005). Haloperidol successfully reversed d-amphetamine-induced reversal learning deficits while clozapine did not (Idris et al., 2005). The interpretation of these data must be examined in light of clinical observations of antipsychotics lacking the ability to fully reverse cognitive deficits in schizophrenia.

5.3.5. Putative Targets for Cognitive Enhancement in Skinner box Reversal Learning—As yet there have been no publications examining the effects of compounds that act on the targets laid out by the MATRICS group (Geyer and Tamminga, 2004). There have been several publications describing positive effects of atypical antipsychotics on task performance (see above). Since it is recognized that these drugs do not sufficiently improve cognitive functioning or the quality of life of schizophrenia patients, however, these positive effects must be interpreted with caution.

5.3.6. Conclusions and Future Studies for Skinner Box Reversal Learning—As might be expected, this task requires greater validation in its specificity to target systems relevant to schizophrenia. First the task requires further refinement, whether to utilize the SRL, the VRL, or the cued task developed by Neill's group. The task requires further validation with regard to its cross-species translatability for human tests of reasoning and problem solving, the NAB maze task in particular. Then, perturbations of task performance with relevance to schizophrenia require development, as do the effects of putative cognition-enhancing compounds in these perturbations and in normal animals. This task has only been used with rats to date; since lever pressing is required, it is unlikely to be practical for development in mice, although nose-poking could be used in future tasks. Despite the need for further study, this task provides an opportunity to assess one component of problem solving, reversal learning, using automated operant techniques, and although the detail of data collected is not as rich as the ASST or CMRST, operant techniques allow a larger number of animals to be tested simultaneously. A more complex operant task involving multiple cue modalities, and that requires the prefrontal cortex, has been developed (Haddon and Killcross, 2005). This task has yet to be widely used however but may prove to be useful in the operant assessment of reasoning and problem solving.

5.4. Overall Conclusions for Preclinical Tasks in the Reasoning and Problem-Solving Domain

The three tasks discussed – ASST, CMRST, and Skinner box reversal learning – all display similar etiological validity with respect to the brain regions that subserve performance, with shifting attention between modalities being served by the IL/PL cortex in the ASST and CMRST, while the OFC appears to mediate reversal learning in all three tasks. Knowledge of the systems that subserve NAB mazes performance would prove extremely useful in validating the three tasks as appropriate preclinical tests for this domain. The ability of the ASST to identify whether an attentional set was formed and reliably assess set shifting perhaps provides the best opportunity with which to model reasoning and problem solving in rodents. Each study must be carefully conducted to ensure construct validity (such as ensuring an ED/ID difference to demonstrate attentional-set-shifting), however, which will greatly facilitate accurate interpretation of results. The labor intensive work for the ASST and CMRST may limit their use, although Skinner box reversal learning does not provide a measure of set-shifting. The novel automated task by Floresco et al. (2008) may provide an opportunity for high throughput automated testing, though more work is required. Given the use of levers however, limits the possibility of assessing the performance of mice in this task. Mice testing in the other tasks have also been limited however, and perhaps efforts should be made to address this issue as well as attempts to develop a mouse version of the CMRST.

6. Visual Learning and Memory

Visual learning and memory deficits have been observed in patients with schizophrenia (Aleman et al., 1999; Heinrichs and Zakzanis, 1998; Nuechterlein et al., 2004; Wood et al., 2002; Yoo et al., 2006) and in people at ultra-high risk for psychosis (Brewer et al., 2005). For their clinical test battery, MATRICS identified the Brief Visual Memory Test – Revised (BVMT-R) (Benedict and Groninger, 1995; Benedict et al., 1996) to assess visual learning and memory in schizophrenia patients. The BVMT-R consists of 6 geometric designs on an 8 × 11 inch piece of paper. The subject is shown the paper with the designs for 10 sec and then asked immediately to reproduce the drawings in the same location (“recall trial”). This procedure is repeated for a total of 3 trials. After a 30 min delay, the subject is asked to reproduce the drawings for a fourth time (“delayed recall”). After this delayed recall, there is a recognition test in which the subject is asked whether or not he/she has seen the image previously (simple “yes” or “no” response). Thus, there is a spatial and a non-spatial (recognition) aspect to the task. Because the task has six alternate forms, it can be administered repeatedly to the same subjects without “practice effects,” while maintaining good test-retest reliability (Benedict, 2005). Recent studies have used the BVMT-R or the BVMT were used to describe deficits in visual learning and memory in schizophrenia patients (Schretlen et al., 2007; Woodward et al., 2004). Schizophrenia patients showed deficits in the immediate recall, delayed recall, and the recognition components of the task (Schretlen et al., 2007). Additionally, epilepsy patients show impairments in the BVMT-R (Barr et al., 2004). Improvements on the BVMT-R have been observed with Aricept treatment in patients with traumatic brain injury, suggesting that it is sensitive to drug effects (although see Freedman et al., 2008; Morey et al., 2003). Additionally, similar tests include a visual memory component and have shown improvement with clozapine (Meltzer and McGurk, 1999).

There are several learning and memory tasks that are appropriate for study in rodents. Learning and memory tasks that involve a visuo-spatial component such as maze-based tasks (e.g., Morris water maze, Barnes maze) are certainly relevant to the visual learning and memory domain. Another non-maze-based learning and memory test in rodents is the Novel Object Recognition Test (NORT; Ennaceur and Delacour, 1988), which relies on the rodents’ tendency to explore novel objects encountered in its environment. We will focus primarily on the NORT and the Morris water maze and briefly review the Barnes maze.

6.1. Novel Object Recognition Test (NORT)

The NORT is widely used in rats and mice as a test of recognition memory, and has also been referred to as 'spontaneous object recognition' or 'visual paired-comparison' (Clark and Martin, 2005; Van Meer and Raber, 2005). The test involves exposing the rodent to two identical objects for a brief period of time (e.g., 3–10 min). After a delay (ranging from a few minutes to a few days), the rodent is placed back in the chamber with one of the familiar objects it encountered in the first phase and an additional novel object (Bevins & Besheer 2006). Rodents typically spend more time exploring the novel object over the familiar object, which is interpreted as reflecting the rodent's memory for the familiar object and its desire to explore a novel object (Dere et al., 2007). Because the task relies on the rodent's preference for novelty, it does not require any rule learning and hence no pre-training (Clark and Martin, 2005). Task difficulty can be increased by increasing the delay or increasing the number of objects presented. A more extensive review of one-trial object recognition tasks, including the pharmacology and neuroanatomy of the NORT and assessment in genetic mutants can be found in Dere et al. (2007).

6.1.1 Validity of the Task—Numerous studies have been performed evaluating the mechanism underlying NORT performance which can be compared to what is known in humans (Table 5). The weight of the evidence suggests the involvement of the perirhinal cortex, rather than the hippocampus, in NORT performance. Specifically, lesions of the peri-postrhinal cortex impair performance in the NORT at short (15 min) and long (24 h) delays but leave intact spatial memory as assessed in the radial arm maze (RAM; Winters et al., 2004). In this same set of experiments, rats with hippocampal lesions showed no impairment in the NORT but did show deficits in the RAM (Winters et al., 2004). Forwood et al, (2005) also showed that rats with hippocampal lesions showed intact NORT performance (in an apparatus minimizing spatial cues – e.g., raised walls) after a 48 h delay. Similarly, acute inactivation of the perirhinal cortex at all three stages of object recognition testing (encoding, consolidation, and retrieval) also impaired performance in the NORT (Winters and Bussey, 2005). As with delays used in working memory tasks (see above), there appears to be a delay-dependent role of the hippocampus in performance on the NORT, with impairment at 24 h delay but not 5 min delay after acute inactivation of the hippocampus (Hammond et al., 2004). Rats with hippocampal lesions have shown impairments in object recognition memory at delays of 10 min, 1 h, and 24 h but not at 10 sec or 1 min (Clark et al., 2000). Other studies have failed to show a difference in the NORT in rats with hippocampal lesions (Mumby et al., 2002;Winters et al., 2004). Recent studies have suggested that some of these disparities may be due to differences in encoding during the object sampling (or acquisition) phase and the size of the lesion (Ainge et al., 2006) – a problem that will be discussed more in depth later in this section – as well as the degree of spatial and contextual cues (Winters et al., 2004). Human studies also point to a functional distinction between regions of the medial temporal lobe and recognition of novel objects versus novel spatial arrangements of objects (Pihlajamaki et al., 2004). Specifically, Pihlajamaki et al, (2004) showed that the perirhinal cortex was activated with the presentation of contextually novel objects whereas the hippocampus was activated with the presentation of objects in a novel spatial configuration. It is thought that the perirhinal cortex is the final stage in visual information processing (Bussey and Saksida, 2005). Indeed, Bussey, Saksida, Cowell, and colleagues propose that the perirhinal cortex stores "representations" of visual features of complex objects and have outlined this theory in several recent papers (Bussey and Saksida, 2002,2005;Cowell et al., 2006 for review), with support from rat and human cognitive testing elsewhere (Eichenbaum et al., 2007 for review). Interestingly, schizophrenia patients show decreased volumes in anterior ventromedial temporal lobe, including the perirhinal cortex (Turetsky et al., 2003), suggesting that the NORT has some etiological validity for probing brain regions indicated in the pathophysiology of schizophrenia (Turetsky et al., 2003). Hence, the NORT in rodents is sensitive to selective

lesions of the medial temporal lobe, which has become increasingly important in theories of visual learning and memory in human studies. In contrast, cytotoxic lesions of the frontal cortex do not produce deficits in the NORT in rats (Yee, 2000). However, administration of the MEK inhibitor PD98059 (Kamei et al., 2006) or a D_1 antagonist (Nagai et al., 2007) into the prefrontal cortex before training impaired object recognition memory when mice were tested at a 24 h delay, suggesting that the prefrontal cortex does play a role in object recognition memory particularly at long delays. The role of the hippocampus/perirhinal cortex in NORT performance parallels studies in humans suggesting the key role of medial temporal lobe in declarative memory (Squire and Zola-Morgan, 1991). Specifically, right hippocampal volume is related to visual learning (Exner et al., 2008). In a study directly comparing schizophrenia patients and patients with temporal lobe epilepsy (either right or left), schizophrenia patients showed similar deficits in a visual memory task as those observed in right temporal lobe epilepsy patients (Yoo et al., 2006).

More recently, there has been an effort to use the NORT to screen for putative antipsychotic compounds. Important for the validity of the task for use in preclinical studies of schizophrenia, schizophrenia patients show deficits in 2-D object recognition tasks very similar to the NORT (Aleman et al., 1999; Clare et al., 1993; Heckers et al., 2000; Tek et al., 2002) and display a different pattern of thalamic and prefrontal brain activation compared to control subjects when performing the task (Heckers et al., 2000). However, as noted above, lesions of the frontal cortex do not impair performance in the NORT in rats (Yee, 2000). One problem in the interpretation of animal lesion data as it relates to human neuroimaging data is that the lesion studies do not mimic the putative connectivity problems in schizophrenia patients, e.g., fronto-temporal circuits (Ragland et al., 2007; Weiss and Heckers, 2001). To our knowledge, no imaging studies have been performed in schizophrenia patients performing the BVMT-R.

6.1.2. Perturbation of NORT performance with relevance to schizophrenia—The NORT is often used to evaluate rodent models of memory dysfunction and screen for memory-enhancing or memory-disrupting compounds, for which several procedures exist. For example, performance in the NORT decreases with increasing delays. Thus, compounds can be administered to rats during these times of poor performance (e.g., 24 h delay) to assess memory-enhancing capabilities (e.g., Pichat et al., 2006). Historically, the NORT has been used to screen for compounds in aging and Alzheimer's disease research. For example, old rats show deficits in object recognition when compared to young rats (Scali et al., 1997a; Scali et al., 1997b; Vannucchi et al., 1997), and mutant mouse models of Alzheimer's disease also show deficits in the NORT (Dewachter et al., 2002; Peister et al., 2006; Pfankuch et al., 2005). Sleep deprivation during the consolidation phase impairs performance in the NORT in mice (Palchykova et al., 2006b) and Djungarian hamsters (Palchykova et al., 2006a), lending further support to the validity of the task for cross-species comparisons with humans (for review Walker and Stickgold, 2004).

6.1.2.1. Pharmacological disruption of performance: Evidence regarding the role of ACh in NORT performance has been mixed. For example, the muscarinic acetylcholine receptor antagonist scopolamine disrupts performance in the NORT at short delays (1–15 min) (Ennaceur and Meliani, 1992; Vannucchi et al., 1997; Woolley et al., 2003). Physostigmine, an AChEI, has been shown to disrupt performance at the 1-min delay but not at longer delays (Ennaceur and Meliani, 1992). Other studies have suggested that increasing ACh with AChEI improved performance in the NORT. For example, the AChEI metrifonate and tacrine improved NORT performance in old (22–24 months) rats (Scali et al., 1997a; Scali et al., 1997b). Along these same lines, decreasing ACh release through stimulation of histamine H_3 receptors also disrupted performance in the NORT (Blandina et al., 1996).

Due to the need to identify pro-cognitive targets for schizophrenia, pharmacological disruptions of novel object recognition by compounds having relevance to schizophrenia have been examined. Acute and chronic exposures to psychotomimetic compounds such as PCP, which have proven useful in the identification of antipsychotic medications in other rodent behavioral models, have been examined to explore the effects on recognition memory. During short delays (1 h; when vehicle-treated rats perform well on the task), acute administration of the NMDA antagonists MK-801 and PCP impair performance (Pichat et al., 2006). Repeated PCP treatment (10 mg/kg/day for 10 days) followed by a washout period (3 days and 6 weeks after the last dose of PCP), a treatment regimen that is not associated with psychotomimetic or impaired cognition effects in humans, impairs NORT performance during the retention phase while having no effect during the training phase (Hashimoto et al. 2005). One day of repeated methamphetamine exposure (4 injections of 4 mg/kg, 2 h apart) in rats results in NORT deficits 1 and 3 weeks later (Schröder, 2003). Similar impairments have been observed with repeated methamphetamine (7 days) in ICR mice (Kamei et al., 2006) and MDMA in rats (Camarasa et al., 2008). Intracerebral administration of dopamine ligands into the PFC support a role of D_1 receptors and the PFC in recognition memory at a long (24 h) delay. Specifically, a dopamine D_1 antagonist injected into the PFC impaired long term recognition memory in the NORT whereas a D_2 antagonist injected into the PFC had no effect (Nagai et al., 2007).

6.1.2.2. Developmental Models of Schizophrenia: In a developmental model of prenatal immune activation in rats, adult offspring exposed to poly I:C prenatally showed deficits in the NORT after 1- or 24-h delays, which were improved with subchronic clozapine but not haloperidol administration (Ozawa et al., 2006). Based on the observation of deficits in glutathione levels in the medial prefrontal cortex of schizophrenia patients, Castagne et al. (2004a; b) have shown that osteogenic disorder-Shiongi rats show deficits in object recognition when given the glutathione synthesis inhibitor BSO and the dopamine uptake inhibitor GBR12909 during early postnatal development (Castagne et al., 2004a; b). Rats reared from weaning in isolation have been considered to model some of the symptomatology and pathophysiology of schizophrenia (Fone and Porkess, 2008; Powell and Geyer, 2002). Isolation-reared rats show impaired performance in the NORT at delays of 1 h, which are accompanied by cytoskeletal alterations in the hippocampus (Bianchi et al., 2006), and at longer delays (3.5 – 4 h; McLean et al. 2008).

6.1.2.3. Mutant mouse models: NORT deficits have been reported in several lines of mutant mice (Dai et al., 2007; Dewachter et al., 2002; Peister et al., 2006; Rampon et al., 2000; Redrobe et al., 2004). Some of these mouse models have direct relevance to schizophrenia and could be used as screens for putative pro-cognitive treatments for the treatment of schizophrenia. Mice heterozygous for deletion of the vesicular glutamate transporter-1 (VGluT-1) show normal memory at short delays but impaired memory at longer delays in the NORT (Tordera et al., 2007). Similarly, deletion of either the H_1 or H_2 histamine receptor produces deficits in NORT (Dai et al., 2007). Hippocampal-specific deletion of BDNF in adult mice impairs NORT performance (Heldt et al., 2007). Mice with a truncated form of cAMP-responsive element binding protein (CREB)-binding protein (CBP) show impaired long term memory in NORT and these impairments are reversed with a PDE4 inhibitor (Bourtchouladze et al., 2003). Interestingly, environmental enrichment improved performance in CA1-specific NMDAR1 KO mice (Rampon et al., 2000). Several lines of mutant mice have shown improved performance in the NORT. For example, mice with a specific deletion of forebrain neuronal glycine transporter 1 (GlyT1) show improved performance in the NORT (Singer et al., 2007). Similarly, cannabinoid CB1 KO mice show a longer retention time (48 h) in the NORT compared to their WT counterparts (Maccarrone et al., 2002; Reibaud et al., 1999).

6.1.3. Effect of established antipsychotics on NORT task performance—Current antipsychotic drugs have had mixed effects in the NORT. On their own, antipsychotics either impair performance or have no effect. For example, chronic administration of olanzapine (0.5 mg/kg/day) disrupted novel object recognition and failed to reverse NORT deficits produced by chronic mild stress (CMS; Orsetti et al., 2006). Similarly, chronic haloperidol was not effective in preventing object discrimination deficits induced by CMS, and although haloperidol produced deficits in spatial memory in a place recognition task, it had no effect on object discrimination in the NORT (Orsetti et al., 2006). Raclopride, another D_2 dopamine antagonist, impaired performance in the NORT when the delay was 1 min (Woolley et al., 2003). Chronic oral administration of risperidone and haloperidol impaired NORT performance (Terry et al., 2007a). In other studies, antipsychotic drugs were able to block drug-induced impairments in NORT. Subchronic clozapine (5 mg/kg) but not haloperidol (0.1 mg/kg), attenuated the cognitive impairment in the NORT produced by prior exposure to chronic PCP in mice; whereas, acute clozapine and haloperidol had no effect (Hashimoto et al., 2005). Other studies have shown that acute clozapine (1 and 5 mg/kg) and risperidone (0.2 mg/kg) but not haloperidol do reverse the lasting effects of subchronic PCP regimens (Grayson et al., 2007) as well as the deficits produced by acute psychotomimetic treatments with MK-801 (Karasawa et al., 2008) in NORT. Another atypical antipsychotic aripiprazole also reversed a subchronic PCP-induced deficit in recognition memory when administered either acutely or repeatedly (Nagai et al. 2008). Clozapine (3 mg/kg, 7 days) reduced methamphetamine-induced deficits in NORT, but haloperidol (1 mg/kg, 7 days) had no effect (Kamei et al., 2006). In this experiment, neither clozapine nor haloperidol affected novel object preference on their own (Kamei et al., 2006). SCH23390 (0.3 mg/kg), a D_1 receptor antagonist, administered immediately before methamphetamine every day prevented methamphetamine-induced impairments in NORT; whereas, the D_2 antagonist raclopride (8 mg/kg) failed to prevent methamphetamine-induced NORT impairments (Kamei et al., 2006). Taken together, the data on antipsychotic effects on NORT performance suggest that atypical antipsychotics improve while typical antipsychotics fail to improve performance in the context of pharmacologically induced NORT deficits. Given that antipsychotic treatment appears to improve cognitive performance in schizophrenia only modestly and at low doses, irrespective of typicality, these data must be interpreted with caution.

6.1.4. Effects of putative cognitive enhancers on performance in the NORT—Although most human studies of stimulants such as nicotine, caffeine, and amphetamine suggest improved performance on attentional and speed of processing tasks with less data on visual learning and memory tasks, there is some preclinical evidence of stimulants improving performance in the NORT. When administered either immediately before or immediately after the sample phase or immediately prior to the choice phase, nicotine improved performance in the NORT in normal rats following a 24 hour delay (Puma et al., 1999). Both chronic (12 months) and subchronic (4 days) caffeine improved performance in the NORT (Costa et al., 2008a; Costa et al., 2008b). Amphetamine (2 mg/kg) reversed a NORT deficit in Fmr1 KO mice while disrupting performance in WT mice (Ventura et al., 2004).

The potential pro-cognitive effects of α7 nAChR agonists for the treatment of schizophrenia have been assessed preclinically in animal models including the NORT. For example, the selective α7 nAChR partial agonist SSR180711 improved performance in the NORT in rats and mice after a long delay (24 h in rats and 48 h in mice; Pichat et al., 2006). The effects of SSR180711 were blocked by the α7 nAChR antagonist methyllycaconitine (MLA) in rats and were absent in α7 nAChR KO mice (Pichat et al., 2006), supporting a critical role for the α7 nAChR in object recognition memory. Impairments in NORT performance induced by acute MK-801 or acute PCP in PCP-sensitized rats are reversed by SSR180711 (Pichat et al., 2006). In the first published clinical trial of an adjunctive treatment for schizophrenia using

the MATRICS test battery, however, the α7 nAChR partial agonist DMXB-A did not improve performance on the BVMT-R (Freedman et al., 2008).

Several molecular targets of the second-generation antipsychotics have been studied in terms of their efficacy in animal models relevant to schizophrenia. For example, CP-809,101, a full agonist at the 5-HT_{2C} receptor, improved performance on the NORT in CD-1 mice after a 24 h delay when performance in vehicle-treated mice was low (Siuciak et al., 2007). CP-809,101 also showed efficacy in animal models with predictive validity for antipsychotics, namely antagonism of apomorphine-induced deficits in PPI, antagonism of amphetamine- and PCP-induced hyperactivity, and suppression of conditioned avoidance responding (Siuciak et al., 2007). Recent evidence suggests that the 5-HT_6 receptor may be involved in learning and memory processes (Hirst et al., 2006; King et al., 2004; Lieben et al., 2005; Mitchell et al., 2006; Woolley et al., 2003). The 5-HT_6 antagonist RO 04-6790, while having no effect on its own, blocked the disruptive effects of scopolamine but not raclopride, suggesting that the drug is interacting with the cholinergic but not the dopaminergic system (Woolley et al., 2003). Subsequent studies supported the efficacy of 5-HT_6 antagonists in reversing a scopolamine-induced deficit (Hirst et al., 2006; Lieben et al., 2005), delay-dependent deficits (King et al., 2004), and tryptophan depletion-induced deficits (Lieben et al., 2005) in the NORT. The dopamine D_1 receptor has been a putative target for improving cognition in schizophrenia patients (Goldman-Rakic et al., 2004; Tamminga, 2006). The dopamine D_1 agonist SKF 81297 impaired performance after a short delay (15 min) but improved performance at the 0.3 mg/kg dose after a 4 h delay (Hotte et al., 2005), an effect confirmed with subsequent experiments and shown to be associated with increased phosphorylation of CREB and DARP-32 (Hotte et al., 2006).

Modulating glutamate receptor function has been examined in regards to object recognition performance. For example, the glycine site of the NMDA receptor has received increased attention as a potential site for antipsychotic activity and, as such, has been assessed in the NORT. D-serine and a glycine transporter inhibitor were shown to reverse MK-801-induced deficits in NORT in rats (Karasawa et al., 2008). The metabotropic glutamate receptor 5 (mgluR5) positive allosteric modulator increased novel object recognition in rats under experimental conditions of poor performance (48 h delay interval) (Liu et al., 2008). Combined treatment with the metabotropic glutamate receptor (mGluR) 5 antagonist MPEP and the mGluR2/3 antagonist LY341495 impaired performance in the NORT at a 24 h delay but not a 15 min delay (Barker et al., 2006). In a model of neurotoxicity, memantine, a moderate to low affinity NMDA antagonist, blocked a NORT deficit induced by subchronic MDMA (bid, 4 days, 72 hours before testing) (Camarasa et al., 2008). Hence, increasing evidence suggests that modulations of glutamate function may improve performance in the NORT both acutely and in the context of neurotoxicity models.

Along these same lines, PDE inhibitors (2, 4, 5, 9) are beginning to be tested for their effects in preclinical cognitive models and as adjunctive treatments to antipsychotics for the treatment of schizophrenia because they elevate levels of cyclic nucleotides (cAMP, cGMP), which play an important role in long term potentiation (LTP). The PDE5 inhibitors sildenafil and vardenafil improved performance in the NORT in rats and mice at long (24 h) delays (Prickaerts et al., 2005; Prickaerts et al., 2004; Rutten et al., 2005) by improving consolidation of memory as opposed to AChE inhibitors, which improve acquisition of object memory (Prickaerts et al., 2005). The effects of PDE5 inhibitors, however, may be an example of a false positive in the NORT. In a recent clinical trial, sildenafil did not improve cognitive symptoms in schizophrenia as assessed using an extensive cognitive test battery; however the BVMT-R was not included (Goff et al., 2008). One of the more extensively studied PDE inhibitors is the PDE4 inhibitor rolipram. Rolipram improved NORT performance in various models of impairment including iron loading or aging (de Lima et al., 2008), tryptophan depletion (Rutten

et al., 2007), scopolamine or time (Rutten et al., 2006), and in the context of a genetic mutation (Rubinstein-Taybi syndrome; Bourtchouladze et al., 2003). Sub-chronic rolipram improved NORT performance at a long delay (24 h) when the last dose was administered up to 24 h before training (Rutten et al., 2008). The PDE2 inhibitor Bay 60–7550 (Boess et al., 2004) and the PDE9 inhibitor BAY 73–6691 (van der Staay et al., 2008) have also been shown to improve performance in the NORT.

The antidepressant fluvoxamine, which has been used as an adjunct treatment for schizophrenia, reversed a NORT deficit induced by prior exposure to subchronic PCP in mice. The reversal appeared to be dependent on activation of sigma receptors, as a similar effect was produced with sigma agonists and blocked by sigma antagonists (Kenji Hashimoto et al., 2006). Kamei et al. (2006) observed an increase in phosphorylation of ERK1/2 in the prefrontal cortex of mice when exposed to the novel objects on training day. In support of this observation, administration of the MEK inhibitor PD98059 into the prefrontal cortex before training impaired object recognition memory when mice were tested at 24 h (Kamei et al., 2006). These effects may be fairly ubiquitous as the MAP kinase ERK1/2 pathway has been implicated in neural plasticity and memory across multiple paradigms (Giovannini, 2006).

6.1.5. Object recognition across rats and mice—In general, the protocol for assessing object recognition across mice and rats is similar, however, there may be some adjustments needed in arena size and object size to equate levels of exploration and reduce use of objects for arena exploration (e.g. sitting or standing on top of object) (Bevins and Besheer, 2006). Mice also tend to exhibit less exploration than rats, possibly due to neophobia (Dere et al. 2007). A recent study comparing forgetting curves across the most commonly used strains of each species, Sprague Dawley rats and C57BL/6J mice, indicated that mice have a steeper forgetting curve compared to rats, with performance reaching chance levels in mice after only 2 hours delay compared to 4 hours in rats (Bertaina-Anglade et al., 2006). Unlike in other cognitive tasks, there appears to be little variation in the forgetting curve across inbred mouse strains, however there are large differences in exploration and sample time (Sik et al. 2003). Both rat and mouse species have similar responses to amnesic effects of scopolamine and benzodiazepine treaments (Bertaina-Anglade et al., 2006). Some reports agree across rats and mice that the hippocampus may be involved in NORT over longer delay periods, (Hammond et al., 2004, Clark et al., 2000). However, more refined neural circuit mechanisms of novel object recognition is more well described in the rat, especially using procedures that make the protocol more or less hippocampal dependent (for review see Dere et al., 2007). As with most of the other cognitive task, pharmacology and neuroanatomy are more represented by rat studies while genetic manipulations are represented by mouse studies.

6.1.6. Conclusions on the NORT—There are several reasons that the NORT has become a useful tool in translational studies of cognitive enhancers in schizophrenia and is particularly well suited for preclinical studies of the visual learning and memory domain outlined by MATRICS (Green et al., 2004; Nuechterlein et al., 2004). First, the test is brief with a relatively fast throughput. Not to discount the utility of other more complex cognitive tasks that require extensive training, high-throughput tasks provide a practical way to screen novel compounds. Second, task performance varies with the delay interval (i.e., retention interval) and complexity of the task (e.g., number of objects). This feature of the NORT allows for the parametric assessment of pharmacological compounds and provides windows of “good” performance with which to assess cognitive disruptors and “poor” performance with which to assess cognitive enhancers. Third, psychotomimetic drugs impair performance and at least some antipsychotics and putative cognitive-enhancers improve performance in the NORT, suggesting that the task has a certain degree of predictive validity for the treatment of schizophrenia. Fourth, very similar aspects of recognition memory can be assessed in humans using the BVMT-R, which

makes it increasingly useful as a preclinical tool to screen potential pharmacological treatments for schizophrenia.

The NORT, however, is not without its limitations. There are several reasons that people have argued against its use as a cognitive assessment tool in preclinical rodent studies (Sarter 2004). First, although the task does rely on the rodents' natural tendency to explore novely (and thus has some degree of ethological validity), it is difficult to determine what type of memory the task is measuring (e.g., declarative). It is not clear whether or not the rodent is remembering discrete features of the objects, which is a common feature of declarative memory in humans (Sarter 2004). Along these same lines there is no way of determining whether the task is measuring attention, motivation, encoding, retrieval, etc. Second, and perhaps the most relevant for this review, is the problem with the predictive validity of the task. From our review of the literature, NORT has become increasingly common as a drug screen for putative cognitive enhancers for schizophrenia. Most of the published studies have indicated that almost all targets tested to date have shown efficacy in NORT. At least two such targets, the α7 nAChR agonists (Freedman et al., 2008) and the PDE 5 inhibitor sildenafil (Goff et al., 2008) produced a positive signal in the NORT but failed to improve cognition in schizophrenia patients in clinical trials. As reviewed here, the preclinical pharmacology in the NORT is rapidly expanding. The extent to which NORT offers a useful preclinical screen for cognitive enhancers will in part depend on the knowledge gained from clinical trials in schizophrenia.

6.2. Morris Water Maze

One of the most widely used mazes for assessment of spatial memory in rodents has been the Water Maze (Morris, 1984; Morris et al., 1982). The water maze involves a rodent learning to locate an escape platform from various starting positions within the maze. Maze-based tasks such as the Morris water maze offer the assessment of learning (acquisition) and memory (retention) and have been well characterized in rodents in terms of drug and lesion effects. For a more extensive review of the water maze see (D'Hooge and De Deyn, 2001; Hodges, 1996; Morris, 1984; Sweatt, 2003) and for the dissection of learning and memory processes see (Morris et al. 2003). Briefly, the task involves a few trials in which the rodent is placed in an arena filled with opaque water in which there is a small hidden platform available for the animal to escape the water. Following the trials in which the platform is hidden (e.g., 2 blocks of 4 training trials per day for a 5 day period), there are probe trials in which there is no platform, allowing reference memory and perseveration to be assessed. The interval between training and probe trials can be within the same day or over months. There is a "reversal" form of the task where once trained to one location, the platform moves randomly to a different location either each day or even each trial. A "visible platform" version of the task is often performed to assess sensory and motor abilities and motivational factors. A recent modification of the water maze involves beacons suspended above the maze to indicate the specific location of the hidden platform within the quadrant, which offers the ability to measure spatial memory by limiting the involvement of spatial navigation in the task (Clark et al., 2007). Another variation of the water maze includes the use of a submerged platform (Atlantis platform) that is activated after a pre-determined amount of time spent swimming in the location of the platform (Riedel et al. 1999; Day & Langston 2006; Hirst et al. 2008). For example, the rat or mouse is trained to swim within a certain area (e.g., 20 cm radius) around the submerged Atlantis platform at which point the platform rises out of the water automatically. This paradigm ensures the animal doesn't find the platform fortuitously and encourages focused searching, and has been used successfully in both rats and mice. The task can also be used to increase cognitive load on the mice whereby they must learn five successive platform locations (Chen et al, 2000). This task resembles more the span capacity of the mice, and impairments have been observed that correlate to levels of Aβ deposition in PDAPP mouse model of Alzheimer's disease (Chen et al, 2000).

There is also a delayed matching to place or sample version of the water maze (Frielingsdorf et al., 2006; Hodges, 1996; Hodges et al., 1995; Morris, 1984; Steele and Morris, 1999), which some have described as working memory. However, this task is unlikely to measure working memory in a manner consistent with human testing, especially with the tasks chosen for the MATRICS test battery (see working memory Section 7.1). In the matching to place task, the latency to find the hidden platform on trial 2 is compared to the latency to find the platform on the first exposure (Trial 1) (Frielingsdorf et al., 2006; Morris, 1984; Steele and Morris, 1999). On each day the location of the platform is changed. Matching or non-matching to sample tasks involve a sample trial in which the invisible platform is cued with a stimulus (e.g., bright light; white or black cylinder). On subsequent test trials the same stimulus is presented along with a new stimulus-cued platform and the rat is required to swim to either the previously cued platform (matching to sample; MTS) or the new stimulus (non-matching to sample; NMTS) (Means et al., 1996; Winocur and Hasher, 2004). While data in primates suggests that delayed matching or non-matching to position or sample are dependent on the frontal cortex, there is evidence that performance on the delayed matching to place (DMTP) task in the water maze in rodents is hippocampally mediated (Steele and Morris, 1999); however, other studies suggests that the task is not dependent on the septohippocampal cholinergic system (Frielingsdorf et al., 2006). For a discussion of the validity of rodent tasks for assessing working memory see Section 7.1.

6.2.1. Validity of the Morris water maze—The hippocampus has probably been the most extensive brain region studied for its role in learning and memory in the water maze (Silva et al., 1998; Ferbinteanu et al., 1999; Morris et al., 1982; Sutherland et al., 1983). The dorsal hippocampus in rats appears to be more important for spatial learning in the water maze compared to the ventral hippocampus (Moser et al., 1993), with selective CA1 and CA3 lesions impairing acquisition in the water maze (Stubley-Weatherly et al., 1996). Although the water maze relies heavily on spatial cues, with training, rats with hippocampal lesions can use non-spatial cues to learn the task (Pouzet et al., 2002). A human analogue of the water maze has been developed as a virtual maze in which hippocampal activation occurs when the subject is using allocentric cues to solve the task but not egocentric cues (Parslow et al., 2005), similar to findings in animals in which the hippocampus is involved in spatial cues (Ferbinteanu et al., 1999; Morris et al., 1982; Silva et al., 1998; Sutherland et al., 1983). Rats with lesions of the habenula also exhibit impaired performance in the water maze, providing additional support for the construct validity of the task for schizophrenia, since habenula dysfunction may contribute to the cognitive deficits in schizophrenia (Lecourtier et al., 2004). In regard to face and construct validity, the water maze is a visuo-spatial task that probes recognition memory similar to the BVMT-R in humans. The BVMT-R has a spatial component, similar to the water maze. There is an age-associated decline in performance on the water maze (Carrasco et al., 2006; Connor et al., 2006; Richter-Levin and Segal, 1996) similar to the cognitive decline in a human analogue of the task (Parslow et al., 2005), as well as decrements in performance following sleep deprivation (Guan et al., 2004; Tartar et al., 2006). Perhpas the most compelling aspect of task validity are the recent cross-species studies of spatial navigation in virtual mazes. There have been several recent reports of the performance of schizophrenia patients in virtual mazes which require the subject to navigate through a multimodal environment (Hanlon et al. 2006; Ku et al. 2003; Kurtz et al. 2007; Weniger & Irle 2008; Sorkin et al. 2006; Sorkin et al. 2005). There is some evidence from these virtual maze tasks that performance parameters predicted those with schizophrenia and correlated with some clinical symptoms (Sorkin et al. 2005; 2006). In a comparison of a virtual park measuring allocentric memory and a virtual maze measuring egocentric memory, schizophrenia patients performed poorly on the allocentric version of the task but displayed intact performance on the egocentric version of the task, and preliminary analyses indicated that errors in the virtual park correlated with both disorganized symptoms and performance on the WMS-R (Weniger & Irle 2008). In a task very

similar to the rodent Morris water maze, the virtual Water Maze Task (WMT), schizophrenia patients had difficulty in the hippocampus-dependent (i.e., hidden platform) version (Hanlon et al. 2006). Like the water maze in rodents, there are most likely several aspects of sensory integration and cognition being measured in these virtual mazes. It is the hope, however, that these tasks will be amenable to neuroimaging experiments and potentially useful in diagnosis and/or genetic studies (Sorkin et al. 2006), which may make data usedul without the need to specify the cognitive construct being assessed. Another encouraging aspect of the virtual maze tasks in humans is the possibility of producing cross-species tasks in humans that can better match the preclinical tasks (e.g., similarity between the virtual Water Maze Task in humans and the Morris Water Maze in rodents; Hanlon et al. 2006). Taken together, there is evidence that the water maze demonstrates a certain degree of validity as a task of visual learning and memory in schizophrenia (Table 5).

6.2.2. Perturbation of water maze performance with relevance to schizophrenia

—The water maze has been used since the early 1980s as a task to probe learning and memory function in rodents,(D'Hooge and De Deyn, 2001; Myhrer, 2003 for review). Hence, the overview provided here is a brief review of the manipulations and drugs most relevant to schizophrenia and is in no way meant to be an exhaustive review of the water maze. Similar to the NORT, performance in the water maze decreases with an increase in the interval between training and probe trials. As reviewed in Table 5, there is an age related decline in performance in the water maze (Carrasco et al., 2006; Connor et al., 1992; Richter-Levin & Segal, 1996), as well as a decreased level of performance with sleep deprivation (Guan et al., 2004; Tartar et al., 2006)

6.2.2.1. Pharmacological disruption of performance: For a more complete review of the literature on the pharmacology of the water maze, the readers are referred to reviews by Myhrer (2003) and D'Hooge and De Deyn (2001). The two neurotransmitter systems most extensively shown to affect water maze performance are the glutamatergic and cholinergic systems (D'Hooge and De Deyn, 2001). PCP disrupts performance in the water maze when administered during acquisition and recall (Didriksen et al., 2007; Podhorna and Didriksen, 2005; Wass et al., 2006) but does not interfere with consolidation in C57BL/6J mice and Wistar rats (Podhorna and Didriksen, 2005). Subchronic PCP (2 mg/kg, 7 days, 24 h washout) produced specific deficits in spatial learning and memory in C57 mice while not affecting performance in the visible platform variations, ruling out general effects on sensorimotor function (Beraki et al., 2008a). A similar regimen of MDMA (b.i.d., 4 days; 72 h washout) also impaired learning and memory in the water maze (Camarasa et al., 2008). The mGluR1 antagonist JNJ16259685 impaired spatial acquisition performance but not retention in mice tested in the water maze (Steckler et al., 2005) as did the non-competitive mGluR1 antagonist BAY36–7620 (Schröder et al. 2008). In contrast, the mGluR5 antagonist MPEP did not affect performance in the water maze at doses that did produce anxiolytic effects (Ballard et al. 2005; Car et al. 2007). While post-training AMPA/kainite antagonists have been shown to disrupt consolidation in rats (Riedel et al. 1999), NMDA antagonists post-training did not impair memory consolidation in either rats or mice using the Atlantis version of the task (Day & Langston 2006).

6.2.2.2. Developmental models of schizophrenia in the Water Maze: Several developmental animal models of relevance to schizophrenia have been examined for their effects on learning and memory in the water maze. For example, perinatal and early postnatal PCP administration impairs water maze performance in rats (Andersen and Pouzet, 2004; Sircar, 2003; Secher et al. 2008). Rats with neonatal ventral hippocampal lesions show impairments in the water maze when tested as adults (Le Pen et al., 2000; Silva-Gomez et al., 2003). On the other hand, rats exposed to an immune challenge in utero (PolyI:C administration to pregnant dams) do not

show impairments in water maze performance (Zuckerman and Weiner, 2005). Rats that had been exposed to a mitosis inhibitor methylazoxymethanol (MAM) during gestation show reversal learning deficits but not reference memory deficits in the Morris water maze (Flagstad et al., 2004). Maternal deprivation of rats during postnatal days 9 and 11 also impairs performance in the water maze in adulthood (Garner et al., 2007). ICR mice reared in social isolation for 4 weeks post-weaning showed similar deficits in learning (acquisition) and memory (performance during the probe trial) in the water maze (Ibi et al., 2008). Hence, several but not all neurodevelopmental models of schizophrenia have shown deficits in learning and memory in the water maze in both rats and mice.

6.2.2.3. Mutant mouse model performance in the water maze: The Morris water maze is one of the most commonly studied tests of learning and memory in mutant mice. Several groups have used the water maze to elegantly dissect the molecular pathways of learning and memory. For example, alpha-calcium-calmodulin kinase II (αCaMKII) mice show specific impairments in water maze performance (Silva et al. 1992). Parsing out which cell types and connections within the hippocampus are important for learning and memory in the water maze. Nakazawa et al. (2002) showed that mice lacking NMDA NR1 receptors in the pyramidal cells in CA3 generated using Cre/loxP recombinase system did not show memory deficits for the hidden platform when the full complement of extra-maze cues were present; however, the mice did have impaired performance in the task during a partial cue version of the task (Nakazawa et al. 2002) and in a delayed matching to posisiton version of the task (Nakazawa et al. 2003). While these are just a few examples of the growing literature on mutant mouse models of the cellular and molecular aspects of water maze performance, other mutant mouse models haver been created based on models of disease. In addition to the large number of mutant mice used in the study of aging, Alzheimer's disease, and other neurodegenerative disorders, there are several mutant mouse lines modeling certain aspects of schizophrenia that have been assessed in the Morris water maze. Mice carrying point mutations of the glycine binding site, which results in pronounced NMDA receptor hypofunction, were unable to perform a cued learning paradigm in the water maze (Ballard et al., 2002). Along these same lines, mice with a mutation of D-amino acid oxidase (DAO) - which increases D-serine levels in brain - showed improved performance on the reversal phase of the task (Labrie et al. 2008). mGluR5 KO mice showed deficits in acquisition and hidden platform trials of the water maze, however, they also showed longer latencies in the first block of trials during the visual platform, which calls into question the specificity of the learning deficits (Lu et al. 1997). In regard to susceptibility genes for schizophrenia, several lines of mutant mice have impaired performance in the water maze. Female mice with inducible forebrain expression of a humanized mutant DISC1 gene demonstrate deficits in spatial memory when trying to find the hidden platform (Pletnikov et al., 2007). ErbB4 (a tyrosine kinase transmembrane receptor that binds neuregulin) heterozygous mice also show disruptions in spatial learning and memory in the Morris water maze (Golub et al., 2004); whereas, regulator of G protein signaling 4 (RGS4) homozygous KO mice do not differ on spatial learning and memory in the water maze (Grillet et al., 2005). Calcineurin is involved in synaptic plasticity and is decreased specifically in the hippocampus of patients with schizophrenia (Eastwood et al. 2005). Forebrain specific calcineurin KO mice show impairments in a delayed matching to position version of the water maze (Zeng et al. 2001) as well as impairments in other behaviors of relevance to schizophrenia (e.g., PPI, locomotor hyperactivity, decreased social interaction; Miyakawa et al. 2003). Finally, Galphas mRNA has been linked to schizophrenia and its overexpression in the forebrain of C57 mice resulted in impairments in the water maze as well as decreased PPI and locomotor hyperactivity (Kelly et al. 2008).

6.2.3. Effects of existing antipsychotics on water maze performance—Several antipsychotic drugs have been tested in the water maze for their effects on acquisition and

retention of spatial learning, with varying degrees of improvement or impairment being observed (for review see Hagan and Jones, 2005). Most antipsychotics tested in the water maze, using both acute and chronic dosing regimens, disrupt both acquisition and retention (Didriksen et al., 2006; Skarsfeldt, 1996; Terry, Jr. et al., 2007a; 2002a; 2003) with the exception of sertindole, which showed no effect (Didriksen et al., 2006), and risperidone, which slightly improved performance (Terry, Jr. et al., 2003). Follow-up studies have shown, however, that longer-term treatments (6 months) with either risperidone or haloperidol impair performance in the water maze (Terry, Jr. et al., 2007b). When administered at low doses, atypical antipsychotics such as sertindole, risperidone, and clozapine reverse PCP-induced deficits in performance (Didriksen et al., 2007). Along these same lines, a study in mice showed that low dose clozapine (0.5 mg/kg) but not haloperidol (0.05 mg/kg) blocked subchronic plus acute PCP-induced deficits in acquisition and retention (Simret Beraki et al., 2008b). In contrast, the putative antipsychotic with 5-HT_{1A} agonist and D_2 antagonist properties, SSR181507, had no effect in the water maze (Depoortere et al., 2003).

6.2.4. Effects of putative cognitive enhancers on water maze performance— Several putative cognitive enhancers such as glycine site agonists, which are either being tested or proposed for the cognitive symptoms of schizophrenia, have been shown to improve performance in the water maze in various models of impaired performance (Baxter et al., 1994; Lelong et al., 2001; Sirvio et al., 1992). Chronic nicotine (0.35 mg/kg, b.i.d.; 14 days) improved performance in the water maze in rats during both the hidden platform trials and the probe trial (Hernandez and Terry, 2005). Similar improvements in performance have been observed with the 5-HT_6 receptor antagonist SB-399885 (Hirst et al., 2006) and the 5-HT1A antagonist WAY-101405 under conditions of task difficulty (Hirst et al. 2008). AC-260584, a muscarinic M_1 receptor agonist showing an antipsychotic profile in a several rodent paradigms, improved performance during the probe trials of the water maze (Vanover et al., 2008). The selective alpha-7 nAChR allosteric modulator NS1738 attenuated a scopolamine-induced deficit during acquisition of the water maze task (Timmermann et al. 2007), although these data could be interpreted in terms of receptor tautology. PCP-induced deficits in acquisition of spatial learning in rats were reversed with the nitric oxide synthase inhibitor L-NAME, whereas, deficits in reference memory during the probe trial were not fully restored (Wass et al., 2006). Memantine, a low to moderate affinity NMDA antagonist, prevented MDMA-induced learning and memory deficits when administered immediately before MDMA in a subchronic dosing regimen (b.i.d., 4 days, 72 h washout prior to testing; Camarasa et al., 2008). Based on their wide distribution in the brain including the cortex and hippocampus, H3 histamine receptors have been posited as targets of pro-cogntive compounds (Brown et al. 2001). Whereas the initial imidazole-based H3 antagonists showed some efficacy in preclinical cognitive tasks, due to side effects they could not be developed clinically. More selective, potent, non-imidazole compounds are being developed and have shown efficacy in aged rats tested in the water maze and in other cognitive tasks such as NORT (at a 24h and 48 h delay) and ASST (both ED shift and Reversal) (Medhurst et al. 2007). Thus, several drugs that have been suggested as either putative cognitive enhancers or neuroprotective compounds have shown efficacy in models of disrupted water maze performance.

6.2.5. Water maze across rats and mice—Several studies have reported differing strategies used by mice and rats when performing the variations in the water maze. In comparison to rats, mice tend to engage in more floating and thigmotaxis when performing the water maze task. Lipp and Wofer (1998) suggested that the superior performance of rats may be attributable to better swimming abilities and more consistent performance across trials rather than superior cognitive abilities. For example, in land based versions of the task, rats and mice do not differ in performance, suggesting that the species differences are not merely due to spatial abilities (Whishaw and Tomie 1996). There are arguments suggesting that there are

cellular and molecular differences between rats and mice in memory, which may account for some of the species differences (Lipp & Wofer 1998). Although there are clear species differences in water maze performance, both rats and mice are consistently used in neurobiological studies of the water maze. As with most other tasks, the majority of the lesion and pharmacological studies have focused on rats and the molecular genetic studies have focused on mice. Of all of the rodent tasks reviewed here, however, the water maze probably has the most extensive neuroanatomical and pharmacological data available in mice. As reviewed above, many of the same pharmacological agents (e.g., PCP, MDMA, mGluR1 antagonist) and lesions disrupt performance in mice similar to the effects observed in rats. Some differences in the effects of lesions do exist between the two species, however. For example, while lesions of the hippocampus produce rather specific effects on hidden platform trials and spare performance on visual platform trials in rats, hippocampal lesions in C57BL/6J mice impair performance on the visual platform trials as well (Cho et al. 1999). The required size of the hippocampal lesion also appears to differ between rats and mice, with rats requiring close to 80% and mice only 50% reduction in dorsal hippocampus to impair performance in the water maze task (reviewed in Silva et al. 1998). Similar to rats, mouse hippocampal pyramidal cells show place-specific firing (Cho et al. 1998; McHugh et al. 1996; Rotenberg et al. 1996; Silva et al. 1998 for review), lending further evidence for the involvement of the hippocampus to spatial navigation.

6.2.6. Conclusions and future directions of the water maze—The Morris water maze has shown utility as a model of cognitive deficits associated with schizophrenia based on several lines of evidence. First, some neuroanatomical substrates underlying the task (e.g., hippocampus, habenula) have been shown to be altered in schizophrenia. Second, performance on the task can be disrupted with psychotomimetic drugs such as PCP, gene deletions of relevance to schizophrenia (e.g., DISC1 mutant), and neurodevelopmental manipulations (e.g., neonatal ventral hippocampal lesions). Third, the water maze is a fairly high-throughput measure of learning in rodents, with acquisition of task achieved within a few days. Fourth, the water maze also allows for the measurement of several aspects of learning and memory – acquisition, recall, reversal, spatial – with the ability to evaluate performance across several dependent measures. Although there are several advantages to the use of the water maze task in the evaluation of mutant mouse lines, developmental models, or putative cognitive enhancers, there are also some disadvantages. Performance in the maze is very much dependent on motor ability, with drug effects often producing non-specific effects on swim speed. Additionally, researchers are becoming increasingly aware of the confounds of apparatus, training procedure, species, strain, water temperature, innate thigmotaxis, floating behavior, non-spatial cues, gender and even bodyweight on performance of the animals tested (D'Hooge and De Deyn, 2001; Lindner, 1997; Selden et al., 1990). The MWM can also be very stressful for the rodent, which often confounds the manipulation with stress (Holscher, 1999). The "stress" of water maze testing, however, can be minimized by habituating the mice to the pool and using a visual cued test to assess any difficulties with swimming or vision. With the proper attention to apparatus set-up, testing parameters, animal handling, and habituation procedures, fairly consistent data can be reproduced across laboratories (D'Hooge and De Deyn, 2001 for review).

Similar to the NORT, the issue of false positives also arises with the water maze. Data from one of the first MATRICS clinical trials, the alpha-7 nAChR agonist failed to show efficacy on the learning and memory domain (BVMT-R; Freedman et al. 2008), suggesting that there are also some problems with false positives when using the water maze as a screen for cogntivie enhancers for schizophrenia. Also similar to the NORT, some argue that it is difficult to assess which aspect of cogntion is being tested with the water maze (Sarter 2004). Perhaps the most exciting aspect of the water maze as a test of learning and memory in preclinical screens for cognitive enhancers, however, is the ability to dissect cell-specific aspects of learning and

memory using molecular genetic tools, as illustrated by the work of Tonegawa and colleagues (Nakazawa et al. 2002; 2003) and Silva and colleagues (Silva et al. 1998). No other task described in this review has such an extensive wealth of data on the neuroanatomical, cellular, molecular and pharmacological mechanism for performance.

6.3 Barnes Maze

A very similar test to the water maze that was developed to avoid the highly stressful experience of water swim is the Barnes Maze (Barnes, 1979). Similar to the water maze, the Barnes maze is a circular platform maze that was constructed originally for rats (Barnes, 1979) and has been adapted for mice (Holmes et al., 2002; Paylor et al., 2001). The maze generally consists of an elevated platform that contains 36–40 holes around the perimeter of the platform. Similar to the water maze, there is an escape route located under one of the holes. The rodent is first habituated to the maze and shown the location of the escape route. Trials involve allowing the rodent to explore the maze and find the escape tunnel. Similar to the water maze, spatial vs. non-spatial memory can be distinguished by rotating the position of the escape route relative to spatial cues in the room and by using visual cue trials in which an object is placed by the escape route. The Barnes maze can be useful in certain mutant mice that have difficulty swimming or when the experimenter wishes to remove the potentially stressful experience of being placed in the water in the water maze (Paylor et al., 2001). Additionally, mice use alternative strategies in the water maze, such as floating and thigmotaxis, which can confound interpretation of the data from the water maze (see above).

To date very few studies with relevance to schizophrenia have been performed on rodents in the Barnes maze. O'Tuathaigh et al (2007) found increased escape latencies and error rates in male but not female NRG1 KO mice and acknowledged that further work is required before activity and or anxiogenic confounds can be discounted. Sex differences were also observed in Barnes maze performance in mice whose dams were subjected to chronic variable stress (CVS; Mueller and Bale, 2007). Male mice subjected to CVS exhibited poorer learning and memory in the Barnes maze, while CVS females exhibited significantly better performance (Mueller and Bale, 2007), demonstrating that environmental insult models can alter Barnes maze performance in adult rodents, but that such models may exhibit sex differences. Further studies are required to characterize animal models of schizophrenia in the Barnes maze and to assess whether pharmacological intervention can improve performance.

7. Working Memory

Tasks most commonly used to assess working memory in humans assess the span capacity of working memory (Baddeley, 1986). This trend is reflected in the two tasks chosen to assess working memory for the MATRICS test battery, the University of Maryland Letter-Number Span Task (UMLNST) and Wechsler Memory Scale-III Spatial Span Task (WMS-III SST). While for many years the digit span task has been used to assess working memory in humans, the WMS-III SST is regarded as a 'visual analogue of the Digit Span subset' (The Psychological Corporation, 2002). Although this assumption has been contested (Wilde et al., 2004), in part due to the recognition component available in the WMS-III SST, it still remains a valuable task for identifying age and neuropsychiatric effects on working memory performance (Wilde et al., 2004). In fact, the recognition component available for use in this task should provide a better analogy for the development of animal models of working memory as they will invariably assess recognition and not recall (Dudchenko, 2004). Given that the human tests in the MATRICS test battery assess working memory span capacity, any valid rodent test must therefore also assess working memory span capacity, for both spatial and non-spatial information.

Nuechterlein et al. (2005) warn of the difficulty in assessing working memory in rodent paradigms. They note that while the human letter number span task involves a substantial demand on the manipulation of numerous pieces of information online, putative animal paradigms of working memory such as the delayed match to sample tasks often mainly require the short-term maintenance of one item of information. Such discrepancies are likely to lead to the assessment of different cognitive constructs, a hypothesis that receives support from neuroanatomical studies. In the assessment of human performance of spatial span working memory, PET, fMRI, and lesion studies concur that the frontal lobes, including the mPFC and parietal regions are activated (Bor et al., 2006; Bor et al., 2001; Curtis, 2006; Reeves et al., 2005). Frontal lobe mediation of spatial working memory in humans contrasts with many proposed animal tests of spatial working memory that include delays, whereby performance is often hippocampally dependent and discrete mPFC lesions do not impair performance (Lee and Kesner, 2003b; Steele and Morris, 1999). Moreover, human tests of spatial short-term memory that do not include delays do not require an intact hippocampus (Cave and Squire, 1992), while the inclusion of delays leads to performance being mediated by the hippocampus (Carrozzo et al., 2005). The evidence suggests, therefore, that hippocampal-dependent tasks may not sufficiently assess working memory span. Such discrepancies in measurement of a cognitive construct, working memory span vs. temporal short-term memory, could be the cause of a lack of predictive validity of some animal paradigms (Sarter et al., 2003). Jentsch (2003) concurs with the doubts raised by Nuechterlein et al., (2005) regarding rodent tests of working memory, and points out that most tests assess an animal's ability to express behavioral flexibility (avoid repeating earlier behavior), inhibit proactive interference, or exhibit resistance to delay. In fact, labeling such tasks as working memory remains questionable (Baddeley, 1996). Thus, few tasks address the issue of assessing working memory span capacity, as is common in the human tests of working memory described above (Jentsch, 2003). One reason such discrepancies may have occurred has been due to differing definitions of working memory (Dudchenko, 2004; Gisquet-Verrier and Delatour, 2006; Jentsch, 2003). In human research, working memory was defined as the capacity to simultaneously store, process, and manipulate information (Baddeley, 1996; 1986). For animal testing, it is widely acknowledged that 'working memory' tasks are most commonly defined as tests of 'short term memory for an object, stimulus, or location that is used within a testing session, but not typically between sessions' (pp. 700; Dudchenko, 2004). Such a definition for animals therefore includes tasks that incur up to a 2 hour delay between stimulus presentation and testing, far outside of the testing duration of human working memory span capacity (measured in seconds). Here we will focus on rodent tasks that measure working memory span capacity (and avoid discussion of tasks using extended delays) in an attempt to focus only on the most cross-species tests that are translatable to the human working memory construct (Baddeley, 1996). The Radial Arm Maze (RAM; Olton and Werz, 1978), Odor Span Task (OST; Dudchenko et al., 2000; Turchi and Sarter, 2000; Young et al., 2007b), and Spatial Span Task (SST; Dudchenko et al., 2000) represent animal tests of memory that require the storage, maintenance, and manipulation of information. They may offer the greatest opportunity for modeling the WMS-III SST and UMLNST as each requires the maintenance of multiple pieces of information 'online' in order to determine a response. Moreover, the RAM, SST, and OST are not subject to the same levels of proactive interference that may confound results obtained in the operant delayed-match to place paradigm (DNMTP; Dunnett and Martel, 1990) or delayed T-maze alternation (Levin et al., 1997), thus reducing the possibility of complex explanations/interpretations of drug effects. Moreover, the DNMTP and the T-maze require the maintenance of one piece of information at any one time to determine an appropriate response, and as such do not measure the capacity of working memory span.

7.1. The Radial Arm Maze (RAM)

The RAM is one of the longest established tests of spatial working memory in rodents (Olton and Werz, 1978). The RAM has been used to assess spatial working memory in a variety of species including rats (Addy et al., 2003; Bettany and Levin, 2001; Levin et al., 1996; Rezvani and Levin, 2002), rabbits, birds (Lipp et al., 2001), and even man (Aadland et al., 1985). A review of the apparatus, use, and procedures available in the RAM is provided by Olton (1987). In brief, the RAM typically uses an octagonal central chamber with eight attached arms. Each arm is baited and the animal is required to enter each arm and retrieve the reward therein. Thus to complete the task with minimal effort, the animal must not re-enter a previously visited arm, adopting a win-shift foraging strategy. The spatial working memory of the animal is often measured by the number of baited arms entered prior to re-entering a previously visited arm, thus the maximum number obtainable is 8. Unfortunately, the ease with which this task is completed by rodents makes this task susceptible to ceiling effects, limiting its sensitivity to group differences in basic spatial working memory (Lipp et al., 2001), although 12 and 16 arm mazes have been developed in an attempt to overcome this confound (Ingram et al., 1981; Levin et al., 1996). Another procedure, whereby certain arms are never baited, simultaneously allows the assessment of spatial reference memory. This procedure however, lowers the maximum span capacity assessed to 4. Individual search strategies are evident in the performance of this task, for example with the animal visiting the opposite arm after it re-enters the hub, or the adjacent arm, especially when the animal is hungrier (Hodges and Green, 1986). The assessment of these strategies may be the focus of the study (Olton, 1987). For this review however, focus will be placed on studies that highlight effects on working memory, and as such reference memory, strategies, and task acquisition effects will not be covered in this section.

7.1.1. Task Validity for RAM to assess Working Memory—As discussed previously, for etiological validity to the cognitive domain the task discussed should be mediated by similar neural substrates as those in man (Table 6). In the RAM, both the mPFC and the hippocampus are important for optimal performance (Lee and Kesner, 2003a,2003b;Taylor et al., 2003). It appears however, that the hippocampus mediates performance primarily when extended delays are in place (Lee and Kesner, 2003a,2003b), supporting work suggesting that the hippocampus primarily mediates temporal but not span capacity of working memory. When investigating the contribution of the PL/IL area of the PFC to RAM performance, Gisquet-Verrier and Delatour (2006) found that PL/IL lesions did not impair the performance of rats in the standard RAM. When distracting events were introduced during task performance however, rats with PL/IL lesions displayed significantly more errors than sham-operated controls. This finding suggests an important role for the PL/IL area not in working memory capacity, but in maintaining information online or attentional focus during task completion. The medial septal nucleus (Hepler et al., 1985), nucleus basalis (Wang et al., 2006), parietal cortices (Ammassari-Teule et al., 1998), and fimbria-fornix region (Cassel and Kelche, 1989;Addy et al, 2005), are also important for the maintenance of working memory. Levin (1988) provides an excellent review of the basic psychopharmacology underlying the RAM, but highlights the importance of the cholinergic system in mediating performance, as well as its interaction with the dopaminergic system. At the time, there appeared to be little evidence supporting a role for the noradrenergic system, though there was some for the serotonergic system. Overall, the data demonstrate some validity for the brain regions required during human performance of working memory tasks, with the frontal lobes mediating working memory span.

Also consistent with cognition in humans, the cognitive performance of animals in the RAM is subject to impairment through natural processes. For example, aged animals exhibit significantly poorer performance than their younger counterparts (Ingram et al., 1981; Kadar et al., 1990a; Kadar et al., 1990b). Although contradictory evidence does exist (Beatty et al.,

1985), these latter findings may have been a result of ceiling effects, since Ingram et al. (1981) utilized a 12-arm RAM, while Beatty et al. (1985) utilized only an 8-arm RAM. Ceiling effects continue to be problematic in this task due to the limited number of items to be stored online. Ceiling effects may also account for why sleep deprivation did not appear to significantly impair working memory performance in rats as it does in humans (Kim et al., 2001), since the maximum span of arms to remember was only four (Smith et al, 1998). Further research is required to ascertain the effects of sleep deprivation on performance in the task.

7.1.2. Perturbations of RAM task Performance—Due to the ceiling effects observed in the RAM, significantly improving performance in normal animals proves extremely difficult. Numerous studies have first induced a performance deficit through a variety of means and then attempted to reverse the impairment. For example the mAChR antagonist scopolamine has often been used to impair performance in this task (Braida et al., 1998; Cassel and Kelche, 1989; Lichtman and Martin, 1996; Lindner et al., 2006).

As was discussed previously, there are no proven treatments for the cognitive symptoms of schizophrenia against which to benchmark putative cognitive enhancement. Licensed pharmacological treatments for the progressive cognitive decline seen in Alzheimer's disease do exist and are mostly found in the form of AChEIs. Numerous studies have been performed assessing the effects of AChEIs in the task. Improvements on normal performance have not been observed due to ceiling effects, thus AChEIs are tested following an experimentally induced deficit.

Early work predominantly assessed the effects of AChEIs following the disruptive effects of scopolamine (Braida et al., 1998; Cassel and Kelche, 1989; Lichtman and Martin, 1996; Lindner et al., 2006). While such studies proved informative, there remains the confounding effect of receptor tautology as demonstrated by Lichtman and Martin (Lichtman and Martin, 1996). Work by Braida and Sala (Braida et al., 1998) however, provides an example of an induced deficit reversal without this confound. Performance was impaired by administration of a cannabinoid agonist (CP 55,940), which was subsequently reversed by an AChEI (eptastigmine).

7.1.3. Perturbations of RAM Task Performance with Relevance to Schizophrenia —PCP administration has often been used to impair cognitive performance in animals as a putative model of schizophrenia. Neither acute nor chronic doses of PCP impair rat or mouse working memory performance in the RAM however (He et al., 2006; Li et al., 2003). MK-801, another NMDA receptor antagonist, does impair working memory as measured by the RAM in both rats and mice (Carboni et al., 2004; Huang et al., 2004; Marcus et al., 2005). Interestingly, heterozygous reeler mice, a putative model of schizophrenia (Costa et al., 2002), do not exhibit impaired baseline performance in the task, possibly due to ceiling effects (described above), but exhibit an increased sensitivity to MK-801-induced deficits in performance (Carboni et al., 2004). Treatment with the cannabinoid agonist CP 55,940 impairs performance (Braida and Sala, 2000), which bears some relevance to schizophrenia, as discussed above. The NVHL model of schizophrenia has been assessed in the RAM. Rats with NVHL exhibit significantly lower working memory performance than sham-operated controls (Levin and Christopher, 2006). Based on the observation that kynurenic acid (KYNA) levels are elevated in schizophrenia patients (Erhardt et al., 2001), the effects of KYNA have begun to be evaluated in preclinical animal models of schizophrenia. Elevating levels of KYNA in rats through acute administration of its precursor kynurenine led to impaired RAM performance (Chess et al., 2007), possibly mediated via the α7 nAChR since KYNA acts as an antagonist to this receptor leading to reductions in dopamine levels (Wu et al., 2007). The effect on RAM performance was characterized primarily as an increase in omissions, not visiting novel arms,

and was only observed once a 30 s delay was imposed between arm entries, suggesting a deficit in short-term as opposed to working memory.

7.1.4. Effects of Established Antipsychotics on RAM performance—There have been numerous studies examining the effects of antipsychotic treatment on RAM performance. Some studies report significant impairments in RAM performance in rats following acute antipsychotic treatment such as haloperidol, olanzapine, and clozapine (Addy and Levin, 2002; Addy et al., 2005; Levin et al., 2005b; Ortega-Alvaro et al., 2006), although other studies report no impairment following acute clozapine or raclopride treatment, or chronic clozapine or olanzapine administration in normal animals (Marcus et al., 2005; Ortega-Alvaro et al., 2006). A lack of positive or detrimental effects on normal performance may have been masked by ceiling effects due to task simplicity. Clozapine did not reverse impairments in the RAM induced by the NVHL model of schizophrenia (Levin and Christopher, 2006). In fact the NVHL-induced impairment was exacerbated following clozapine treatment in male rats, corroborating the clozapine-induced deficits in performance observed in normal rats (Addy and Levin, 2002). Clozapine did, however, reverse fimbria-fornix lesion-induced deficits in performance (Addy et al., 2005), another putative model of schizophrenia (Pouzet et al., 1999). Both clozapine and raclopride also significantly reversed MK-801-induced working memory deficits, the former more completely than the latter (Marcus et al., 2005). As discussed previously, it is arguable whether clozapine appreciably reverses the cognitive deficits of schizophrenia patients. Thus, it is arguable whether a cognitive deficit model of schizophrenia should be reversed by clozapine, and if not, it would be questionable whether the fimbria-fornix lesion- or MK-801-induced deficits in RAM performance would be regarded as a reliable model.

7.1.5. Putative Targets for Cognitive Enhancement in the RAM—MK-801-induced deficits in RAM performance have been reversed by treatment with the histaminergic H_3 antagonist clobenpropit (Huang et al., 2004). As discussed above, the MK-801-induced impairment in performance was also partially attenuated by raclopride but was fully reversed when the animals were administered a combination of raclopride and idazoxan, an α2A+C adrenoreceptor antagonist (Marcus et al., 2005). The authors elegantly demonstrated that the combination of raclopride and idazoxan displayed a similar affinity for D_2 and α2A+C receptors as clozapine, suggesting that these receptors mediated the clozapine reversal of MK-801 induced deficits (Marcus et al., 2005).

There have been numerous studies investigating the effects of cholinergic agonists in the task, particularly nicotine. Much of this work is reviewed elsewhere, but to summarize, nicotine can improve performance in the task following fimbria-fornix lesions, atypical antipsychotic treatment such as olanzapine or clozapine (Addy and Levin, 2002; Levin et al., 2005b), though not 5-HT_2 antagonist treatment (Levin et al., 2005a). It has been suggested that the pro-cognitive effects of nicotine are mediated by the α7 nAChR (Bancroft and Levin, 2000; Bettany and Levin, 2001; Levin, 2002; Levin et al., 2002).

7.1.6. Rat and Mouse Testing in the RAM—The majority of RAM testing has been conducted in rats. While initial reports suggested that mice could not perform the RAM (Mizumori et al, 1982), these were likely to be as a result of technical differences. When utilizing appropriate tools to minimize response strategies, mice readily perform the RAM to a high level, consistent with rats (Pico and Davies, 1984; Roullet and Lassalle, 1992). Little work has been accomplished however in schizophrenia research testing mice in the RAM. In fact further predictive and construct validation of this task is required in mice, prior to the assessment of transgenic models of schizophrenia in the RAM.

7.1.7. Conclusions and Future Studies for the RAM—The RAM represents one of the oldest tests of working memory in the rodent and this section certainly is not sufficient to cover all the research that has been conducted in this working memory task. Requiring the rodent to maintain several pieces of information online in order to complete the task provides one of the closest tests of working memory in rodents and there are numerous similarities between rodent and human performance following manipulations. Moreover, as the task requires the rodents to adopt a win-shift strategy in a foraging environment, the RAM has ethological validity. Greater research is required in raising the ceiling that exists in the task, and perhaps using perturbations in task performance that are relevant to schizophrenia. Numerous genetic mouse models of schizophrenia exist and it would be fruitful to assess their performance in the task.

7.2. Odor Span Task (OST)

The OST is a recently developed task originally designed to assess the contribution of the hippocampus to non-spatial working memory (Dudchenko et al., 2000). The OST has been conducted in both rats (Dudchenko et al., 2000; Turchi and Sarter, 2000) and mice (Young et al., 2007a; Young et al., 2007b; Young et al., 2008), with the differences between the rat and mouse versions being minor, as discussed elsewhere (Young et al., 2007b). The task requires the rodent to dig in a scented bowl for a food reward. After retrieval of the reward, the rodent is then presented with two scented bowls, the first they encountered previously, and a novel scent. The novel scent is baited, and thus the rodent must ignore the previously baited bowl and dig only in the novel scented bowl. Next, three scented bowls are presented, the first two previously presented, the third novel, and again the rodent must remember the first two scents in order to avoid digging in those bowls (i.e. digging only in the novel scent). Up to (so far) 24 different scents can be presented and the rodent must always remember the previously encountered odors (23 in this case), digging only in the novel scent. The locations of the bowls are always random, thus the rodent cannot utilize visual cues in selecting the novel odor. Hence, the task assesses non-spatial working memory span capacity (Dudchenko et al., 2000).

In contrast to many ‘working memory tasks’ mentioned above, performance does not rely on an intact hippocampus (Dudchenko et al., 2000). In fact, similar to human working non-spatial working memory tasks, performance was impaired following lesions to basal forebrain region in rats (Turchi and Sarter, 2000). Lesions to the basal forebrain have been consistently shown to impair attentional performance across a range of animal models of attention (McGaughy and Sarter, 1998; Risbrough et al., 2002). Thus, Turchi and Sarter (Turchi and Sarter, 2000) proposed that the poor performance of basal forebrain lesioned rats may have been due to poor attentional processing (Turchi and Sarter, 2000).

This hypothesis is consistent with human working memory performance where impaired attention can result in impaired working memory performance (Healey and Miyake, 2008). The attentional component in this task was further emphasized by the different pattern of impaired performance displayed by α7 nAChR KO (Young et al., 2007a) and caspase-3 over-expressing mice (Young et al., 2007b). The former exhibited attentional-mediated impaired performance, characterized by lower spans completed and increased latency, but similar motivation levels (hence increased distractibility during task performance) while the latter’s poor performance was likely to reflect impaired olfactory working memory span capacity, characterized by a lower span length and increased error rate (Young et al., 2007a; Young et al., 2007b). To date, besides identifying the hippocampus as unlikely to mediate performance (Dudchenko et al., 2000) and the basal forebrain identified as important for performance (Turchi and Sarter, 2000), the neuroanatomy underlying this task has yet to be fully elucidated. It would be beneficial to identify whether areas that subserve human non-spatial working memory contribute to performance in this task; similarly it would be of benefit to assess various animal models of schizophrenia in this task. Improved performance after administration of a

cognitive enhancer has been demonstrated, since nicotine reversed the working memory deficit exhibited by caspase-3 over-expressing mice (Young et al., 2007b). While modafinil improved non-spatial working memory in humans (Randall et al., 2005; Turner et al., 2003), modafinil has yet to be assessed in rodents in the OST. Performance in the OST can be impaired following NMDA receptor antagonism as MK-801 impaired mouse performance (Finlayson et al, personal communication). Other schizophrenia-relevant compounds have yet to be tested however, including assessing the effects of antipsychotic administration.

7.3. Spatial Span Task

The Spatial Span Task (SST) was developed originally to mimic the context of the OST but to assess spatial as opposed to non-spatial working memory span capacity (Dudchenko et al., 2000). The cues used were not distinguished by odor but by spatial location. Similar to the RAM, good performance has been reported to be achieved by adopting a win-shift strategy. However, unlike the RAM with 8, 12, or 16 (rarely) locations, the SST utilizes a board with 24 differing locations. This number provides the task with greater resolution in detecting performance impairments associated with increased load placed on spatial working memory capacity. As mentioned, the task was designed similarly to the OST, using the same bowls and testing table. For the SST, bowls are placed at specific locations, with a novel baited bowl added to a new location after every correct response. Thus, the rat is required to remember previously visited locations (bowls) to avoid revisits. As with the WMS-III SST, the subject can use visual recognition while attempting to remember what locations to visit (or avoid). It is therefore our view that this task may prove beneficial in assessing the spatial working memory span capacity of animals in a fashion similar to that of humans in the WMS-III SST. It is acknowledged however, that a great deal of work must first be conducted with the SST to ensure that it displays predictive and construct validity, in addition to its face validity. Furthermore, mouse testing in the SST has not yet been reported yet but would be useful given the increasing generation of transgenic models of schizophrenia.

7.4 Conclusions for Preclinical Working Memory Tasks

The conflict of definitions of working memory between human and animal testing will continue to create difficulties when attempting to assess putative cognitive enhancers for this cognitive domain. The task of modeling this cognitive domain in animals is more challenging when attempting to assess working memory span capacity as opposed to temporal capacity (delay memory). However, the RAM, OST, and SST represent three rodent tasks that may accurately test this construct. The RAM represents a model of working memory span that has been well studied in terms of both procedural guidelines and relevant neuropsychopharmacology. Nevertheless, the well-documented ceiling effects may limit its potential when only 8 arms are used. The OST and the SST represent two relatively novel and lesser-known paradigms. They do, however, appear to fulfill the criteria required as tests of non-spatial and spatial working memory span capacity, although animals may utilize relative familiarity when completing these tasks also. Moreover, because of the layout of the paradigms, a far greater span capacity can be assessed, reducing confounding ceiling effects. Both tasks require greater validation prior to the testing of putative cognitive enhancers. One form of validation that may prove useful in these tasks would be attempting to mimic the tolcapone-induced improvement in working memory in humans (Apud et al., 2007). A novel working memory task, modeled on the human n-back task has recently been created (Ko and Evenden, 2009). This task attempts to mimic the human n-back task by provividing levers in an operant chamber as opposed to numbers in the human version. The rat has to press these levers in a given sequence, then following poking in the reward area, the rat must press either the last (1-back) or penultimate (2-back) lever (Ko and Evenden, 2009). Although in its infancy, this task may prove useful in assessing working memory span capacity in a manner consistent with human testing. Future studies may further

explore the OST, SST and n-back task to determine the effects of prefrontal lesions on the OST and SST without the confounding influences of delays.

8. Social cognition

Social cognition represents a specific domain of cognition that involves the evaluation of and appropriate responding to social cues (Penn et al., 1997). Patients with schizophrenia exhibit deficits in social cognition as reflected by difficulties in utilizing context when processing social cues (Penn et al., 2002), interpreting the facial affect and emotion of others (Mandal et al., 1998), and anticipating social sequences (Corrigan and Addis, 1995). Although social cognition was not one of the factors identified by factor analysis of cognitive domain deficits, it was added to the MATRICS battery as a domain because it is a prominent deficit in schizophrenia diagnosis and its successful treatment would significantly benefit functional outcome (Choi and Kwon, 2006; Nuechterlein et al., 2004). The more general symptom of "social withdrawal" is included among the negative symptoms of schizophrenia and is often one of the earliest symptoms to occur (Johnstone et al., 2005; McClellan et al., 2003; Miller et al., 2002). Deficits involving withdrawal or isolation in at-risk populations may also be predictive for development of schizophrenia (Johnstone et al., 2005; Miller et al., 2002), although this construct is more difficult to measure experimentally. As with other cognitive deficits, disorders in social cognition are not treated adequately by existing antipsychotic medications, and represent a pressing unmet need in schizophrenia treatments. The "managing emotions" component of the Mayer-Salovey-Caruso Emotional Intelligence Test was selected for the MATRICS consensus cognitive battery (Nuechterlein et al., 2008). This paper-pencil test asks the subject to problem solve different situations involving emotions, for example how to best retain feelings of contentment after a vacation. Although this type of test is obviously not easily modeled in rodents, Green et al. (2005) argued that preclinical research can contribute to our basic understanding of the neural substrates behind social cue processing and behavior.

At present, animal models of social behavior relevant to schizophrenia have focused largely on two separate models, social interaction (e.g. the interest level and repertoire of social behavior exhibited by the subject when exposed to a non-aggressive conspecific) and social memory (the subject's memory of a previous exposure to a conspecific; Ellenbroek and Cools, 2000). Other models of social communication (e.g. ultrasonic vocalizations between pup and dam or by adults in a social situation) and motivation (e.g. working for access to a conspecific) have been less studied but may provide tools to explore neural substrates for social behavior.

8.1 Social Interaction Task

8.1.1. Validity of the Social Interaction Task—Social interaction models have been studied across species in both non-human primates (Ellenbroek et al., 1996; Goosen, 1981) and rodents (e.g. Nadler et al., 2004; e.g. Sams-Dodd, 1996). In rodents, a number of variants of social interaction tests are being used, including giving the subject a choice between maze regions that contain a caged conspecific and empty regions (termed a measure of "sociability" or social avoidance) (Moy et al., 2004). The validity of social interaction tests for the social symptoms in schizophrenia is difficult to assess as the tests for social deficits vary widely in schizophrenia research (Green et al., 2004). Social interaction appears to have face validity for symptoms of social withdrawal in schizophrenia subjects, although most current human social cognition tasks are centered around the processing of emotional and social cues from others (see Theory of Mind, Frith, 1992; Green et al., 2004). In humans, conscious facial affect recognition, which is reported to be deficient in schizophrenia (Edwards et al., 2002; Mandal and Palchoudhury, 1989), appears to drive bilateral amygdala activation (Habel et al., 2007). Other tasks have implicated the prefrontal cortex in normal and schizophrenia subjects during a mental state attribution task (Russell et al., 2000). The medial frontal cortex has been highlighted recently as a critical area for social stimulus processing and responding (Amodio

and Frith, 2006). In rodents, forebrain (including, amygdala, hippocampus, and frontal cortex) and hindbrain neural circuits appear to modulate social interaction, suggesting that some analogous neural circuitry exists for social function across humans and rodents (for review of the task File and Seth, 2003). In terms of predictive validity, there appears to be growing evidence that the vasopressin/oxytocin system modulation of rodent social behavior is translatable to some human social behaviors (e.g. “trust” and face recognition) (for review see Heinrichs and Gaab, 2007; Lim et al., 2005). It is not clear, however, that these are valid models for deficits in schizophrenia. A direct involvement of oxytocin in the pathophysiology of schizophrenia appears to be debatable, with evidence for and against alterations in oxytocin in schizophrenia subjects (Beckmann et al., 1985; Bujanow, 1974; Glovinsky et al., 1994; Goldman et al., 2007). The effects of oxytocin on social behavior and PPI however (e.g. Feifel and Reza, 1999; Lee et al., 2005), are the basis for ongoing clinical trials for this hormone as an adjunctive therapy for schizophrenia (Feifel et al. clinicaltrials.gov ID#NCT00506909). These studies will be critical in examining the predictive validity of rodent social behavior models for schizophrenia. It is also unclear whether or not antipsychotic medication improves facial affect recognition (Fakra et al., 2007; Gaebel and Wölwer, 1992; Kee et al., 1998; Lewis and Garver, 1995).

8.1.2. Perturbation of Social Interaction Task performance—Models of perturbations of social interaction have predominantly focused on schizophrenia-relevant (see below) and autism-relevant biological perturbations. For recent reviews of autism-related perturbations see Moy et al. 2008 and Crawley 2007. New genetic models that may also have bearing on schizophrenia related pathology will be discussed below. Deficits in social interaction can be induced by administration of the psychotomimetics ketamine, PCP, and dizocilpine (MK-801) (Becker and Grecksch, 2004; Sams-Dodd, 1998; Weike et al., 2005) as well as by blockade of mGluR5 (Koros et al., 2007). Since there is little information on the effects of NMDA receptor antagonists or dopamine agonists on emotional cognition in humans, the predictive validity of these pharmacological models remains to be assessed (Micallef et al., 2003). Dopamine $D_{2/3}$ receptor agonists may also reduce social interaction. It is unclear, however, if this effect is specific to social interaction or is due to increases in motor activation (Gendreau et al., 2000). Exposure to a non-selective cannabinoid receptor agonist either during development or adulthood also robustly reduces social interaction (O’Shea et al., 2006), indicating that this model may be useful in modeling the putative effects of marijuana exposure during development in humans. Social withdrawal has also been reported to be produced by developmental manipulations of relevance to schizophrenia, including neonatal asphyxia (Laviola et al., 2004), immune challenge (Tohmi et al., 2004), prenatal MAM exposure (Flagstad et al., 2004; Le Pen et al., 2006), neonatal PCP treatment (Harich et al., 2007), and NVHL (Flores et al., 2005; Sams-Dodd et al., 1997).

There are several potential genetic mutations related to schizophrenia that exhibit social behavior abnormalities. For example, secretin KO mice exhibit reduced social exploration and other cognitive deficits, which supports the preliminary reports of transient efficacy of secretin for negative symptoms in schizophrenia (Nishijima et al., 2006; Sheitman et al., 2004). Additionally, KO mice lacking calcineurin, which has been linked to schizophrenia risk, exhibit a number of social and cognitive deficits as well as reduced PPI (Miyakawa et al., 2003; Yamada et al., 2007). Mice carrying the mutant human DISC1 gene exhibit alterations in social interaction (Pletnikov et al., 2007). A recent report describes mice carrying a SRE2b gene overexpression transgene encoding a G-protein coupled-receptor which exhibit reduced social interaction and barbering behaviors, and the same report found a SRE2b gene SNP association with schizophrenia (Matsumoto et al., 2008). These mutant mice, in particular those carrying the specific human genes found to be mutated, may be valuable novel screens for detecting pro-cognitive drugs relevant to schizophrenia pathology.

8.1.3. Effect of established antipsychotics on social interaction—Both haloperidol and clozapine ameliorate PCP- and amphetamine-induced disruptions of social interaction (Sams-Dodd, 1998, 1999). Atypical antipsychotic treatments with 5-HT_{1A} agonist properties attenuate PCP-induced deficits in social interaction (e.g., Bruins Slot et al., 2005). Olanzapine enhances social interactions in normal animals as well (Frye and Seliga, 2003). There are also recent reports that galantamine may facilitate antipsychotic efficacy in the social interaction test (Wang et al., 2007). Although ketamine-induced disruptions in social interaction are reversed by clozapine and haloperidol, the anxiolytic diazepam also reduced ketamine-induced increases in aggression (Becker and Grecksch, 2004). This efficacy of diazepam may indicate that this model is sensitive to false positives, unless one considers the possible efficacy of benzodiazepines in treating schizophrenia (Volz et al., 2007). Recently, F15063, a compound with mixed D_2/D_3 antagonist and 5-HT_{1A}/D_4 agonist properties which has been argued may provide antipsychotic efficacy with fewer sedative side effects, reverses PCP-induced deficits in social interaction (Depoortere et al., 2007a). Finally, $mGluR_{2/3}$ agonist treatment also reversed social interaction deficits produced by neonatal PCP (Harich et al., 2007), suggesting that this model is sensitive to new (i.e. not directly active at dopamine receptors) putative classes of antipsychotics (Patil et al., 2007).

8.1.4. Effects of putative cognitive enhancers on performance in social interaction—Cognitive enhancers have generally not been studied in the rodent social interaction test, since it is based predominantly on social interaction and not learned behavior (see social recognition below). It is likely that this test predicts anxiolytic activity of many compounds as opposed to enhancing cognitive processes. Oxytocin and vasopressin agonists appear to increase social interaction (most specifically pair bonding) in normal rodents and in models of disruption (Heinrichs and Gaab, 2007; Insel and Winslow, 1998; Lee et al., 2005). A number of new compounds targeted for the treatment of schizophrenia have also been reported to facilitate social interaction, including the mixed dopamine D_2/D_3 receptor antagonist and 5-HT_{1A} agonist F15063 (Depoortere et al., 2007b). CB1 receptor KO mice are insensitive to MK-801-induced deficits in social interaction (Haller et al. 2005), indicating that antagonists at this receptor may be worth further inquiry. Moreover, given the increased risk of schizophrenia with cannabis use, studies investigating the interaction of the CB_1 receptor and animal models of schizophrenia in this paradigm may prove informative.

8.2. Social Recognition

Social recognition (also called “social novelty”) models in rodents have received increased interest in part due to their potential in revealing new systems that may be relevant to social disturbances found in autism (Lim et al., 2005). Social recognition tests in rodents (rats, mice, voles, etc.) involve assessing the time spent investigating a novel, unfamiliar conspecific in the presence of a familiar conspecific (Engelmann et al., 1995; Ferguson et al., 2002; Thor and Holloway, 1982; Winslow and Camacho, 1995). For example, during the first phase a mouse is exposed to a juvenile mouse. After a delay (typically 30–60 min), the mouse is then exposed to the same “familiar” mouse plus a “novel” mouse. The time spent investigating the juvenile is recorded and mice typically show an increased preference for the novel juvenile mouse. A rat variant of this test involves a simple procedure in which a rat is exposed to a juvenile rat for 5 min on the first trial, and then after a 30-min delay the rat is exposed to the same juvenile. The amount of time spent in olfactory investigation is reduced from the first trial to the second trial (Thor and Holloway, 1982), indicating habituation. Another variant involves repeated exposure of the rat to a juvenile rat for four trials separated by 10 min. On the fifth trial, the rat is then exposed to a novel juvenile rat. While the investigation time decreases over the first 4 trials (habituation), investigation time increases on the fifth trial (Winslow and Camacho, 1995).

8.2.1. Task Validity for the Social Recognition Task—As with social interaction, oxytocin and vasopressin systems appear to play a role in social recognition (Ferguson et al., 2002). Social recognition appears to involve olfactory neural circuits, the amygdala, hippocampus, and septum (for review see Ferguson et al., 2002; Insel and Fernald, 2004; Squires et al., 2006). In terms of predictive validity, genetic manipulations relevant to schizophrenia indicate that some genes that may be risk factors for schizophrenia also may contribute specifically to social cognition (see below).

8.2.2. Perturbations of the Social Recognition Task—Reviews of task perturbations relevant to drug abuse (McGregor et al., 2008) and autism (Hammock and Young, 2006) are available. Here, we will focus our attention on schizophrenia-related perturbations. As with other memory tasks, acute treatment with NMDA antagonists decrease social recognition (Hlinak and Krejci, 1994). Neonatal PCP treatment is reported to exert lasting effects on social recognition in adult rats (Harich et al., 2007). Recently, the vasopressin 1a receptor has been shown to be required for intact social recognition in mice (Bielsky et al., 2005), and vasopressin deficient rats exhibit social recognition deficits as well as other schizophrenia-related cognitive and sensorimotor gating deficits (Engelmann et al., 1994; Feifel and Priebe, 2001). Cannabinoid receptor agonism also reduces social recognition (Schneider and Koch, 2002). L-methionine-induced down regulation of reelin and GAD67 may be a promising new pharmacological model of both social and some cognitive disruptions seen in schizophrenia. Methionine treatment is reported to exacerbate schizophrenia symptoms (Wyatt et al., 1971) and in rodents chronic methionine treatment produces deficits in social recognition and increased aggression, as well as reductions in PPI (Tremolizzo et al., 2005). A fairly selective genetic model for schizophrenia-related social recognition may be neuregulin mutant mice, which show specific deficits in social recognition and sensorimotor gating but no deficits in social interaction, spatial memory, or anosmia (O'Tuathaigh et al., 2007). Mutations in the neuregulin gene are among the more consistent findings in studies of genetic risk for schizophrenia vulnerability (for review see Norton et al., 2006).

8.2.3. Effects of established antipsychotics on social recognition—Although the effects of antipsychotics on social recognition memory have not been studied extensively, initial reports indicate that amisulpride and clozapine block acute PCP-induced deficits in social recognition (Terranova et al., 2005), as well as the deficits produced by neonatal PCP treatment (Harich et al., 2007).

8.2.4. Effects of putative cognitive enhancers on social cognition—The neuropeptides oxytocin and vasopressin have been shown to increase social recognition (Ferguson et al., 2002), enhancing acquisition and consolidation, respectively. As indicated above, it is not yet clear if these systems have similar effects in humans on social cognition. Modulation of the cholinergic system can also improve social recognition performance in rodents. Both nicotine and physostigmine administration improve social recognition in normal rats (Perio et al., 1989; Timmermann et al., 2007). Moreover, galantamine significantly reverses scopolamine-induced deficit in social recognition performance (Di Cara et al., 2007). Given that enhancement of performance can be observed, studies are being conducted for receptor targets for cognitive enhancement in schizophrenia. For example, several studies now demonstrate significant improvement in social recognition at varying time-points after selective α7 nAChR agonist administration in rats (Boess et al., 2007; Timmermann et al., 2007; Van Kampen et al., 2004). Moreover, similar to galantamine, the D_1 receptor agonists SKF 82958 and SKF 82197 improved scopolamine-induced deficits in social recognition performance in rats (Di Cara et al., 2007). Thus, there is a growing interest in using this technique to assess putative cognition enhancers.

8.3. Conclusions and Future Directions for preclinical social cognition

Animal models of deficient social interaction must be carefully evaluated for confounds including reduced volition, memory deficits, and/or sensory processing deficits. In many paradigms, it is important to distinguish between a specific social deficit versus a deficit in short term memory (but see below). When testing the effects of pharmacological manipulations or gene deletion on social behaviors in rodents, it is important to rule out olfactory processing deficits as olfaction is the primary cue used for social recognition (Ferguson et al., 2002). Although schizophrenia patients show deficits in processing of both visual and verbal social information (Kohler et al., 2003), the importance of language in human social interactions and the importance of odor processing in rodents limits the direct comparisons that can be made across species. Another possible limitation of these models is that social cognition in humans is measured as processing and fine discrimination of emotional or social cues (e.g. facial and verbal emotion identification tasks), not simple recognition or interaction tasks. Measures of behavioral responses to ultrasonic vocalizations with putatively different meanings (e.g. 22 and 50-kHz alarms to negative and positive cues, Brudzynski, 2007) or specific to social play (Panksepp, 2007) could provide improved ways to assess recognition of and appropriate responding to social cues in rodents. It may also be of use to explore other animal species that also have explicit social cues (e.g. darkened eye spots or social vocalizations) and consequent social behaviors to examine the neurobiology of social cue recognition (e.g. Binz et al., 1990; e.g. Korzan et al., 2006) Non-human primates may be, in the end, the most valid models of social cognition found in humans, due to the complexity and strong social bonds found in primate social behaviors that are not replicable in other species (Dunbar and Shultz, 2007).

One of the more difficult questions for all models of social cognition is how orthogonal is social cognition from non-social cognition? Should a valid model only reflect social deficits (as generally has been the case for vasopressin and oxytocin neuropeptide system manipulations)? This distinction may be particularly difficult since object recognition, the inanimate equivalent to social recognition, is becoming widely used in the assessment of visual learning and memory deficits in animal models of schizophrenia (see Visual Learning and Memory section). The distinction between social and cognitive deficits is not clear in schizophrenia as some studies have shown a high correlation between social and nonsocial cognition measures in schizophrenia populations (Sergi et al., 2007; Vauth et al., 2004). The new work initiated in response to the MATRICS program will help us identify the independent constructs contributing to these symptoms. The field of social cognition in schizophrenia is relatively new, and the next few years should yield important advancements towards a greater understanding of the pathology specifically linked to social deficits in schizophrenia (e.g. putative reductions in orbito/frontal or amygdala processing of social cues; Abdi and Sharma, 2004; Brunet-Gouet and Decety, 2006; Coccaro et al. in press). These advancements will aid in refining and testing the translatability of the current rodent models for social cognition disruptions in schizophrenia.

9. Verbal Learning and Memory

One of the principal MATRICS domains has been identified as verbal learning and memory. As a high order function it can be argued that several others domains can be operationally influenced by the capacity of verbal ideation. For instance it is far more difficult to memorize visual patterns if they cannot be verbally tagged, it is easier to memorize a picture of blue ball on a green grass than a random blue and green pattern. This very capability though makes this domain a uniquely difficult challenge to preclinical scientists as speech is not a capacity yet to be observed in rats, mice, or even, arguably, higher primates. Is it therefore impossible to propose that there may be exact preclinical homologs to the clinical procedures used to probe this domain? The Hopkins Verbal Learning Task (HVLT) is the preferred MATRICS instrument. A number of other commonly used tasks also map well to this domain including:

Logical Memory‘ Verbal Pairs‘ CVLT battery‘ Story Learning‘ Digit Span‘ Distractibility‘ Verbal Memory; and Digit Sequencing. As it is impossible to use speech in a rodent protocol, the challenge is to determine if there is an ethological equivalent that requires a similar level and type of processing. Only a clear argument of the basis for a proposed homology can allow some degree of useful translation between the preclinical and clinical settings for this domain.

Man uses several sensory modalities for communication. Over very short distances, olfaction is used to a limited extent for interpersonal communication. Sight is used more extensively, again principally for one to one communication often of emotion, or mood, by facial expression for instance. Sight and in particular facial recognition is also the primary means by which individuals are recognized. The vast bulk of inter-human communication is oral which in turn is principally verbal in nature and hence often language based. These verbal systems have then evolved into written and other forms of language-based communication. The other principal component resulting from language is the ability to internally represent information in verbal terms. The fact that most of us “think” verbally and often categorize and cue recall with verbal tags may again be a unique human capability. There are certainly other species that use “verbal” communication even if it cannot be defined as language based, such as the higher primates and birds. In rodent species, though there is evidence of oral communication between pups and dams, or in playful behavior (see above), it appears that many of the functions that we use oral, or visual, communication for are achieved in the olfactory domain (Vosshall, 2005). To be properly classed as “verbal” communication not only does the appropriate sensory detection capability need to be present but also the means to control the content of the message being transmitted. In this regard, the understanding of the role of pheromones in rodent communication has advanced from the seminal paper of Buck and Axel in 1991 (Buck and Axel, 1991). The genetic and molecular mechanisms associated with pheromone production and detection is now well understood. Similarly, significant strides have been made in the understanding of the “language” (Restrepo et al., 2004; Yamaguchi et al., 1981) and how it can be used to communicate information ranging from the sexuality to the presence of a parasitic infection in an individual (Beauchamp and Yamazaki, 2005; Kavaliers et al., 2004). The lexicon of the “language” now emerging is built up from a complex mix of volatile pheromones which can be controlled in their release through binding to non-volatile major urinary proteins (MUPs) (Hurst and Beynon, 2004; Hurst et al., 2005) which are then sensed by the highly polymorphic V1 and V2 receptors in the olfactory mucosa (Karunadasa et al., 2006).

This evidence supports the contention that rodents have a complex and effective olfactory communication capability. If this contention is accepted, then it can be surmised that the information thus communicated should also be processed at a high level. The evidence to support this assumption is less extensive, but recently Lin et al, (2006) have performed an elegant series of studies illustrating a clear topographic mapping of individual odors onto specific glomeruli in the main olfactory bulb (MOB) using a combination of intrinsic imaging and gas chromatography techniques. As would be expected, a number of the odors that produced representation in the dorsal MOB were associated with strong naturalistic cues, fox urine and bobcat urine, for instance. However, many of the positives came with odors with a less obvious ethological relevance but also a clear concordance with odors that have been used successfully in laboratory protocols, cloves, peanut butter, onion, cumin, cardamom, banana, and nutmeg to name a few. There would appear therefore to be some evidence to suggest that rodents are able to process specific odors through the olfactory cortex in a way that bears a resemblance to that for verbal information in the auditory cortex. The final step in the argument can only at present be supported by logic, the premise being that higher centers responsible for learning and memory will utilize these similar types of information in similar ways.

A number of olfactory-based protocols have been developed for use with rodents. The closest, at face value, to those listed in the clinical category is the odor-span task described above (working memory section; Dudchenko et al., 2000). The task requires a rat to learn an ever-lengthening “list” of odors against which a novel odor presented on each successive trial must be discriminated. The odors are presented in small containers positioned randomly around an arena, the novel exemplar being baited with a small buried reward. The task is carefully controlled to ensure that no spatial strategy can be used to solve it, nor can scent marking. Dudchenko et al. demonstrated that the task was not dependent upon hippocampal competence for it to be acquired and performed accurately. This demonstration clearly indicates that the task cannot be classified as a spatial task. If the arguments above can be accepted, then this task could be viewed to be a rodent equivalent of the tasks such as a word list or digit span, both of which have been classified within the MATRICS “verbal learning and memory” domain. This task has recently been developed further to allow testing in mice (Young et al., 2007b), with a putative contribution of alpha 7 nAChR to performance (Young et al., 2007a), and progressive impairment in Tg2576 mice, a transgenic model of Alzheimer’s disease (Young et al., 2008).

A similar task requiring animals to dig for rewards in baited bowls was developed by Birrell and Brown (Birrell and Brown, 2000) in order to probe the capacity for intra- and extra-dimensional set shifting (the ASST, described in reasoning and problem solving above). Though the task is not exclusively olfactory, as it also requires animals to take into account the texture of the digging medium, it does clearly demonstrate that odor information can be readily incorporated into complex high order processing in rodents. In their work, Birrell and Brown demonstrated that the task during an extra-dimensional shift was sensitive to focal frontal cortical lesions. This finding allows the task and the anatomical substrate to be paralleled with similar data from non-human primates and frontally damaged human patients. The deficits in these types of task exhibited by frontal patients exhibit many similarities to those of schizophrenics and in part leading to the hypo-frontal function hypothesis.

It must be accepted that no absolute homolog of the verbal information handling seen in man, and impaired in schizophrenics, can be recapitulated in rodents. However, the main principal in current animal models of psychiatric disease is the modeling as far as possible a sub-set of processes that are affected by the disease. By looking at what language is used for and the relative level of specialized processing in man, perhaps the closest analogue in rodents is the handling of olfactory information. Certainly rodents are able to learn tasks dependent on this modality quickly, in some cases as quickly as the clinical equivalent, and with a similar degree of information content. Therefore assessment of results from these protocols may prove valuable in translating from the preclinical to clinical domains.

10. Discussion

MATRICS galvanized efforts from academia, industry, and governmental bodies to develop pro-cognitive compounds for the treatment of schizophrenia. MATRICS initiated the development of mechanisms by which putative therapeutics can be assessed in schizophrenia patients, including a cognitive test battery encompassing seven cognitive domains. MATRICS only took the first step, however, and much more work is needed before we can effectively ameliorate the cognitive deficits that appear to be such key impediments to the successful functional recovery of patients with schizophrenia. This work is being continued on several fronts, including TURNS and CNTRICS in the U.S. and emerging programs in Europe (see Markou et al., 2009). The CNTRICS program has begun to use information from cognitive neuroscience research to specify more precisely the critical constructs and to refine the relevant tasks. The work of CNTRICS is continuing and will now extend to explicit considerations of developing and validating cross-species tests. To date, however, a thorough review of the

potential for a preclinical cognitive test battery has been largely missing from the literature. Given the large increase in cognitive testing in rodents, and the availability of an increasing list of cognitive tests, the present review identified those tests that would provide some relevance to each of the cognitive domains identified by MATRICS, while leaving the constructs identified by CNTRICS for further discussion.

The major concern for the tests discussed here was that of cross-species translatability and construct validity. Like CNTRICS, we deemed it most important that the tasks measure accurately the cognitive construct that is assessed in the MATRICS battery. Such a focus is particularly relevant given the lack of any known compound that is effective in treating cognitive deficits in schizophrenia. In the absence of a positive control or gold standard compound, one must focus on construct rather than predictive validity (Floresco et al., 2005; Geyer, 2006; Markou et al., 2009). Hence, in most instances, we have focused on the cognitive constructs being assessed by the specific measures included in the MATRICS test battery rather than only the general names for the seven cognitive domains. Some tests have received greater attention than others, largely due to the availability of data on these tests that have relevance to cross-species comparability, opinions expressed in the TURNS preclinical subcommittee survey (Young et al., 2006; http://www.turns.ucla.edu/preclinical-TURNS-report-2006b.pdf), and our collective opinion on the strengths and weaknesses of each task. Some tests listed here are in their infancy, and others are still being developed. In contrast to the CNTRICS effort to focus on tests that are in need of further development to make them appropriate for use in clinical settings, we have focused more on established tests. Brief mentions of the newer tests were included because they may offer further opportunities to identify pro-cognitive compounds that could prove to be efficacious in the clinic. As was highlighted in several sections, the need for greater clarity in the methods used and in the labelling of constructs and tasks is required. Furthermore, the identification of pharmacological effects in normal animals as well as in normal humans would greatly improve the assessment of cross-species comparability and predictive validity of these tasks.

A number of issues that warrant thoughtful discussion were not adequately addressed here. For example, the modal treatment program discussed in MATRICS was to identify drugs that would be used as co-treatments in patients already treated on stable regimens of antipsychotics. Such a co-treatment model would prompt additional concerns regarding pharmacodynamic or pharmacokinetic interactions between the pro-cognitive agent and the on-board antipsychotic. Although such interactions may be important in future preclinical studies, they have not been considered here. Another complexity is the likelihood that the direct mechanisms of pro-cognitive treatments will have selective effects on specific aspects of cognition, given the separable neurobiological substrates of different cognitive functions. As discussed elsewhere (Nuechterlein et al., 2005), improvements in one core cognitive function due to the direct actions of a drug on a key neurochemical system may have secondary benefits on other interdepent cognitive functions, especially as reflected in tasks in which performance is sensitive to multiple factors. Similalry, the meager improvements in some cognitive measures that accompany treatment with some atypical antipsychotics, primarily at low doses, may reflect performance improvements due to the lack of competing influences of psychotic symptoms. Another complexity is the need for preclinical (and clinical) development programs to focus on the specific goals of the clinical treatment. Although an ideal pro-cognitive compound might improve all aspects of cognition in all psychiatric disorders, such a goal is clearly unrealistic. If a treatment is specific to reversing an abnormality that is unique to schizophrenia, it might be both effective and specific to schizophrenia patients, or even a subset of schizophrenia patients. Of somewhat lesser value, though still useful, would be a compound that was efficacious in any disorder in which the relevant cognitive function is impaired. Additional complexities that have only been introduced here in passing include the need for adequate dose-response assessments in pharmacological studies and the similar need for

examination of chronic drug treatments to better mimic the standard clinical practice. When evidence was available, consideration of whether the use of mice or rats has been discussed. Fewer comments have addressed the potential importance of strains within species. In both contexts, there is likely to be no general answer to the question of which animal is most valuable for preclinical studies. Rather, the determination of the optimal species and strain for a given cognitive task remains an empirical question that must be addressed specifically in each case.

The present review is intended to further the work begun in MATRICS, with the overall goal of identifying new compounds that will have efficacy in the treatment of cognitive deficits in schizophrenia. Although there is a rich literature regarding the psychological constructs included within the broad domain of cognition, complemented by considerable understanding of the neurobiological substrates of at least some of these cognitive functions, our knowledge of pharmacological effects on specific cognitive constructs is relatively limited. Given the opportunity for clinical applications of new knowledge in this area, further research regarding the pharmacology of cognition has begun and will no doubt increase. As noted above, additional programs, such CNTRICS, are also working toward translational cognitive tests for humans and animals, which should complement the existing data from preclinical cognitive tests and provide an avenue for drug discovery across human and animal experimental paradigms. Future studies should assess how well these cognitive tests in animals correlate with each other and represent discrete cognitive domains, similar to what was done in the MATRICS and what was done with the discussion of PPI in this review. The field should also continue investigating developmental, pharmacological, and genetic manipulations relevant to schizophrenia (e.g., prenatal immune challenge, psychotomimetics, mutant mouse lines) in some of the tests that show particular promise for their relevance to schizophrenia. Preclinical scientists should pay particularly close attention to the clinical debate on the effectiveness of antipsychotics for cognitive symptoms in schizophrenia and design experiments that better model the dosing and class of antipsychotics found to be the most effective. As the clinical data on pro-cognitive therapies in schizophrenia emerge, the preclinical field should try to design experiments that offer the best predictive validity (i.e., increasing true positives and decreasing false positives) for effective therapeutics.

Acknowledgments

This work was supported by the National Institute of Mental Health (R01 MH071916; R01 MH52885; MATRICS; TURNS), the Veterans Affairs VISN 22 Mental Illness Research, Education, and Clinical Center, a NARSAD Young Investigators Award (JWY), as well as current support from a Stein Institute for Research in Aging Fellowship (JWY).

Abbreviations

Δ9-THC
: delta-9 tetrahydrocannabinol

5C-CPT
: 5-choice CPT

5-CSR
: 5-choice serial reaction

6-OHDA
: 6-hydroxy-dopamine

ACh
: acetylcholine

AChEI

acetylcholinesterase inhibitor

ADHD
attention deficit hyperactivity disorder

ASST
Attentional Set-Shifting Task

BACS
Brief Assessment of Cognition in Schizophrenia

BVMT-R
Brief Visual Memory Test – Revised

CANTAB
Cambridge Neuropsychological Test Automated Battery

CB1
cannabinoid 1

CD
compound discrimination

CDR
CD reversal

CNTRICS
Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia

CMRST
cross-maze rule-shifting task

CMS
chronic mild stress

COMT
catechol-O-methyltransferase

CPP
3-(R)-2-carboxypiperazin-4-propyl-1-phosphonic acid

CPT
continuous performance test

CPTIP
CPT-identical pairs

CVS
chronic variable stress

DISC1
Disrupted in schizophrenia 1

DNAB
dorsal noradrenergic bundle

DNMTP
delayed-match to place

ED
extradimensional

EDR
ED reversal

fMRI
Functional magnetic resonance imaging

GlyT1
glycine transporter 1

HLVT
Hopkins Verbal Learning Task

ID
intradimensional

IDR
ID reversal, ITI, inter-trial interval

KO
knockout

KYNA
kynurenic acid

LRT
lateralized reaction-time

LSD
lysergic acid diethylamide

mAChRs
muscarinic acetylcholine receptors

MAM
methylazoxymethanol

MATRICS
Measurement and Treatment Research to Improve Cognition in Schizophrenia

MCL
mean correct latency

mGluR
metabotropic glutamate receptor

MIL
mean incorrect latency

MLA
methyllycaconitine

MOB
main olfactory bulb

mPFC
medial prefrontal cortex

MRL
mean reward latency

MT
movement time

MUPs
major urinary proteins

NAB
Neuropsychological Assessment Battery

NAcc
Nucleus Accumbens

nAChR
nicotinic acetylcholine receptor

NIMH
National Institute for Mental Health

NORT
Novel Object Recognition Test

NRG1
neuregulin-1

NVHL
neonatal ventral hippocampal lesion

OFC
orbitofrontal cortex

OST
Odor Span Task

PCP
phencyclidine

PDE
phosphodiesterase

PET
Positron Emission Tomography

PL/IL
prelimbic-infralimbic

PPC
post-parietal cortex

PPI
Prepulse Inhibition

PRODH
proline dehydrogenase

RAM
radial arm maze

RGS4
regulator of G-protein signaling 4

RT
reaction times

SAT
sustained attention task

SD
simple discrimination

SRL
spatial reversal learning

SST
spatial span task

STN
subthalamic nucleus

TRN
thalamic reticular nucleus

TURNS
Treatment Units for Research on Neurocognition in Schizophrenia

UMLNST
University of Maryland Letter-Number Span Task

VGluT-1
vesicular glutamate transporter-1

vITI
variable ITI

VRL
visual reversal learning

WCST
Wisconsin Card Sort Task

WMS-III SST
Wechsler Memory Scale-III Spatial Span Task

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Table 1

Overview of preclinical rodent tasks which map onto the MATRICS test battery.

MATRICS Domain	Task	Species	Motivation	Pros	Cons	References
Attention + Speed of processing	5-choice serial reaction task	Rats & mice	Appetitive	Automated. High face, predictive, & construct validity for CPT	Extensive training & special equipment required	Carli et al., 1983; Young et al., 2004
	Sarter's Sustained Attention Task	Rats	Appetitive	Automated. High face, predictive, & construct validity for CPT	Difficult to test in mice. Extensive training & special equipment required	McGaughy & Sarter 1995
	Lateralized reaction-time task	Rats & mice	Appetitive	Automated. Some face & predictive validity. Fairly rapid training	Specialized equipment needed-not widely established, better as a test of processing speed	Carli et al, 1985; Jentsch 2003
Speed of Processing	Olfactory Discrimination	Rats & mice	Appetitive	Automated. Has ethological validity. Limited training	Specialized equipment required. Few pharmacology studies.	Slotnick 2000, Uchida & Mainen, 2003
Sensorimotor gating - pre-attention?	Prepulse inhibition	Rats & mice	N/A	Simple, High face, predictive, & construct validity for parallel human tests.	Special equipment required & relationship to cognition unknown	Swerdlow et al, 1994; Geyer et al, 2002
Reasoning & Problem Solving	Attentional set-shifting	Rats & mice	Appetitive	Simple design with high analogy for WCST	Labor intensive & low throughput	Birrel & Brown, 2000; Colacicco et al., 2002
	Cross Maze Set-Shifting Task	Rats	Appetitive	Simple design, no training required	Labor intensive & low throughput	Ragozzino et al 1999
	Serial reversal acquisition paradigm	Rats	Appetitive	Simple design, can be automated, with face validity	Not widely established, construct validity unknown	Widholm et al, 2001
Visual Learning & Memory	Novel Object Recognition	Rats & mice	Innate	Simple design, high throughput, well characterized	Not goal oriented task so changes may reflect processes other than cognition	Ennaceur & Delacour, 1988; Dere et al. 2007
	Barnes maze	Rats & mice	Aversive	Simple, quick design, well characterized	Confound innate responses to task	Barnes, 1979; Paylor et al., 2001
	Morris water maze	Rats & mice	Aversive	Simple, quick design, well characterized	Confound of stress & innate responses to task	Morris et al., 1981; Chen et al., 2000

MATRICS Domain	Task	Species	Motivation	Pros	Cons	References
Working Memory – spatial	Radial arm maze	Rats & mice	Appetitive	Can be automated, simple design, high predictive & face validity	Ceiling effects	Levin et al., 1996; Sigurdsson et al., 2004
	Spatial Span Task	Rats	Appetitive	Simple design, no proactive interference, ethologically relevant stimuli	Not widely established, predictive validity unknown	Dudchenko et al., 2000
Working Memory– non-spatial	Odor span task	Rats & mice	Appetitive	Simple design, no proactive interference, ethologically relevant stimuli	Not widely established, limited publications	Dudchenko et al., 2000; Young et al., 2007b
Social Cognition	Social Interaction Task	Rats & mice	Innate	Simple design, no training required, face validity	Also used as a model for negative symptoms	Sams-Dodd et al. 1996; Nadler et al., 2004
	Social Recognition Task	Rats & mice	Innate	Simple design, no training required, face validity	Hard to specify “recognition” memory vs. specific social deficit	Ferguson et al. 2002

Table 2

Measures and their interpretation from the 5CSR task.

5-CSR task measures	Also referred to as:	Domain linked to:
Accuracy	Proportion Correct, % Correct, %C	Attention – selective and sustained
% Omissions	%O	Sustained Attention, Motivation, Motoric effects
Premature Responses	Anticipatory responses	Impulsivity, Motivation
Perseverative responses	Divided into correct and incorrect	Impulsivity, cognitive flexibility
Incorrect errors	Errors of commission	Attention
Mean Correct Latency	MCL	Processing speed
Mean Reward Latency	MRL	Motivation, Cognitive flexibility
Mean Incorrect Latency	MIL	Processing speed

Table 3

Validation of preclinical rodent tasks for the Attention/Vigilance Domain.

Validation	Human CPT	5CSR task	SAT	LRT
Medial prefrontal cortex involvement	(Ringholz, 1989; Rueckert & Grafman, 1996; Salqado-Pineda et al, 2003)	Barbelivien et al, 2001; Muir et al, 1996; Passetti et al, 2001	Miner et al, 1997	Dowd & Dunnett, 2004; 2005
Thalamus Important	(Hager et al, 1998)	Baunez & Robbins, 1999	Kozak et al, 2005	NSF
Parietal Cortex Needed	(Salqado- Pineda et al, 2003)	NOT Muir et al, 1996	Broussard et al (2006)	NOT Rosner & Mittleman, 1996
Hippocampus Not Needed	(Salqado-Pineda et al, 2003)	Kirkby & Higgins, 1995; but see Le Pen 2003	NSF	NSF
Age-related reduction in Performance	(Mani et al 2005)	Jones et al, 1995; Muir et al, 1999; Grottick & Higgins, 2002	McGaughy & Sarter, 1995; Burk et al, 2002	NSF
Sleep-Deprivation mediated deficit	(Jewett *et al*., 1999; Caldwell et al, 2000)	Godoi et al, 2005; Cordova et al, 2006	NSF	NSF
Improved by amphetamine, caffeine and nicotine	(Koelega, 1993) (Levin et al, 1998)	Grottick & Higgins, 2002, but see Bizarro & Stolerman, 2003, 2001; Young et al, 2004; but see Blondel, 1999	Rezvani, 2002; NOT McGaughy & Sarter, 1995; Turchi et al, 1995	NSF
Task Manipulation affecting performance (Event rate shift, SD reduction, Increasing session length)	Increasing sess. duration, ITI, red. SD- impairs (Parasuraman, 1998)	Grottick & Higgins, 2002; Stolerman et al, 2001	McGaughy & Sarter, 1995	NSF

CPT: continuous performance test; **5CSR** 5-choice serial reaction; **SAT**: sustained attention task; **LRT**: lateralized reaction-time task; **NSF**: No studies found

Table 4

Validation of preclinical rodent tasks for the Reasoning and Problem Solving domain.

Validation	Human task	ASST	CMRST	Operant Reversal Task
Dorsolateral prefrontal cortex mediation of ED shift only	Milner, 1963; Stuss & Alexander, 2000	Birrell & Brown, 2000 – did not impair ID or Reversals	Ragozzino et al, 1999, Floresco et al, 2008	ED shift not applicable
Orbitofrontal cortex mediation of reversals	Pantelis et al, 1999; 2004	McAlonan & Brown, 2002	Ghods-Sharifi et al, 2008	Boulouqouris et al, 2007
Age-related reduction in Performance	Owen et al, 1991	Barense et al, 2002	NSF	NSF
Sleep-Deprivation mediated deficit	Jones et al, 2001	McCoy et al, 2007	NSF	NSF
Stimulant effects	Modafinil improved ED in schizophrenia patients (Turner et al, 2001)	Modafinil improved ED in animal model of schizophrenia Goetghebeur & Dias, 2008)	NSF	NSF
Drug perturbation	Cannabis-induced impaired performance (Lane et al, 2007)	Cannabis-induced impaired performance (Egerton et al, 2005)	NSF	NSF

ASST: Attentional set shifting task; **CMRST**: Cross maze rule shifting task; **ED**: Extra-dimensional; **NSF**: No studies found

Table 5

Validation of preclinical rodent tasks for the Visual Learning and Memory Domain.

Validation	Visual Learning & Memory*	BVMT-R	NORT	Water Maze
Frontal cortex mediation	(Klingberg & Roland, 1998; Rossi et al., 2006) For review# see (Buckner & Wheeler, 2001; Ranganath et al., 2008; Simons & Spiers, 2003; Ungerleider, 1995)	NSF	No effect of mPFC lesion (Yee, 2000) but see (Kamei et al., 2006; Nagai et al., 2007) for effects of pharmacological manipulations of PFC.	mPFC lesions impair behavioral flexibility in the task (de Bruin et al., 1994; McDonald et al., 2008) and memory under partial-cue conditions (Jo et al., 2007)
Perirhinal cortex mediation	Danckert et al. 2007 Activated with contextually novel objects (Pihlajamaki et al. 2004)	NSF	Important for object novelty detection not for spatial novelty (Winters & Bussey 2005; Winters et al. 2004)	Delay-dependent effect on recall (Liu & Bilkey 1998a, 1998b); But see (Moses et al. 2005; Machin et al. 2002; Futter et al. 2006)
Role of Hippocampus	Activated with spatially novel objects (Pihlajamaki et al., 2004); Also see (Danckert et al., 2007; Pascalis et al., 2004) Reviewed in (Buckner & Wheeler, 2001; Ranganath et al., 2008; Simons & Spiers, 2003; Ungerleider, 1995)	In PD patients, correlation with left hippocampal volume (Bouchard et al., 2008)	Lesions impair (Ainge et al., 2006; Clark et al., 2000); No Effect (Forwood et al., 2005; Mumby et al., 2002; Winters et al., 2004); Discrepancies based on delay, size of lesion, sample phase, degree of spatial cues	(Ferbinteanu et al., 1999; Morris et al., 1982; Sutherland et al., 1983)
Age-related reduction in Performance	(Driscoll et al., 2003; Fahle & Daum, 1997; Gale et al., 2007; Grady et al., 1995)	(Gale et al., 2007)	(Scali et al., 1997; Vannucchi et al., 1997)	(Carrasco et al., 2006; Connor et al., 1992; Richter-Levin & Segal, 1996)
Sleep- Deprivation mediated deficit	(Walker & Stickgold, 2004); but see (Harrison & Horne, 2000)	NSF	Mice (Palchykova et al., 2006b); Djungarian hamsters (Palchykova et al., 2006a)	(Guan et al., 2004; Tartar et al., 2006)
Improved by amphetamine, caffeine and nicotine	Modafinil (Randall et al., 2005); (D. Turner et al., 2003), trend for improvement in schizophrenia (D. C. Turner et al., 2004); No effect of caffeine + taurine (Warburton et al., 2001)	Slight (non-significant) improvement with amphetamine (Benedict et al., 2008)	Nicotine (Puma et al., 1999) and caffeine (Costa et al., 2008a; Costa et al., 2008b) improve; Amphetamine improves and disrupts (Ventura et al., 2004)	Amphetamine improves (Brown et al., 2000); but high doses of amphetamine and caffeine impair learning (Kant, 1993)

PD: Parkinson's disears; **NORT**: Novel object recognition task; **BVMT-R:** Brief Visuospatial Memory Task – Revised; **NSF**: No studies found; **KO**: Knockout; **WT**: Wildtype; **MWM**: Morris water maze; **mPFC**: medial prefrontal cortex; **CANTAB**: Cambridge neuropsychological test automated battery

*General domain - based on a variety of neuropsychological tests (e.g., visuospatial recognition task; pattern recognition memory [in CANTAB]; non-verbal paired associates task, etc.) many of which are computer-based for use in neuroimaging studies.

#See reviews for discussion of imaging vs. lesion data, influence of verbal rehearsal in the tasks, etc.

Table 6

Validation of preclinical rodent tasks for the Working Memory Domain.

Validation	Spatial and non-spatial span tasks	RAM
Medial prefrontal cortex involvement	See Curtis 2006	Taylor et al, 2003
Parietal Cortex Needed	See Curtis 2006	Ammassari-Teule et al, 1998; possible learning confound
Hippocampus Not Needed	Cave & Squire, 1992	Taylor et al, 2003; when delays not in place
Sleep deprivation impairing performance	Kim et al, 2001	NOT Smith et al, 1998; but a possible ceiling effect confound
Age-related reduction in Performance	Hester et al, 2004	Ingram et al, 1981
Stimulant effects	Modafinil improved non-spatial (Randall et al, 2005; Turner et al, 2003)	NSF

NSF: no studies found; **RAM**: radial arm maze