HHS Public Access

Author manuscript

J Psychopharmacol. Author manuscript; available in PMC 2015 December 04.

Published in final edited form as:

J Psychopharmacol. 2015 February ; 29(2): 178–196. doi:10.1177/0269881114555252.

Developing treatments for cognitive deficits in schizophrenia: The challenge of translation

J.W. Young and **M.A. Geyer**

Department of Psychiatry, University of California San Diego, 9500 Gilman Drive MC 0804, La Jolla, CA 92093-0804

Research Service, VA San Diego Healthcare System, San Diego, CA

Abstract

Schizophrenia is a life-long debilitating mental disorder affecting tens of millions of people worldwide. The serendipitous discovery of antipsychotics focused pharmaceutical research on developing a better antipsychotic. Our understanding of the disorder has advanced however, with the knowledge that cognitive enhancers are required for patients in order to improve their everyday lives. Whilst antipsychotics treat psychosis, they do not enhance cognition and hence are not antischizophrenics. Developing pro-cognitive therapeutics has been extremely difficult however, especially when no approved treatment exists. In lieu of stumbling on an efficacious treatment, developing targeted compounds can be facilitated by understanding the neural mechanisms underlying altered cognitive functioning in patients. Equally importantly, these cognitive domains will need to be measured similarly in animals and humans so that novel targets can be tested prior to conducting expensive clinical trials. To date, the limited similarity of testing across species has resulted in a translational bottleneck. In this review, we emphasize that schizophrenia is a disorder characterized by abnormal cognitive behavior. Quantifying these abnormalities using tasks having cross-species validity would enable the quantification of comparable processes in rodents. This approach would increase the likelihood that the neural substrates underlying relevant behaviors will be conserved across species. Hence, we detail cross-species tasks which can be used to test the effects of manipulations relevant to schizophrenia and putative therapeutics. Such tasks offer the hope of providing a bridge between non-clinical and clinical testing that will eventually lead to treatments developed specifically for patients with deficient cognition.

THE PROBLEM

Schizophrenia is a life-long debilitating disorder affecting tens of millions of people worldwide (approximately 1% of the population). The characteristics of schizophrenia are well known, especially the positive and negative symptoms. Positive symptoms are behavioral characteristics not normally present but *are present* due to the disease process, e.g., auditory and visual hallucinations. Negative symptoms are behaviors normally present but *are diminished* due to the disease process, e.g., alogia or amotivation. With the

*Correspondence: Jared W. Young, Ph.D., Department of Psychiatry, University of California San Diego, 9500 Gilman Drive MC 0804, La Jolla, CA, 92093-0804, Tel: +01 619 543 3582, Fax: +01 619 735 9205, jaredyoung@ucsd.edu.

serendipitous discovery of antipsychotic treatments in the 1950s (beginning with chlorpromazine, a surgical anesthetic) that alleviated positive symptoms, research focused on developing better antipsychotics with fewer deleterious effects. Research focused on `me-too' style drugs, developing treatments with properties similar to approved treatments. Hence, several new antipsychotics were identified, but all were primarily dopamine D_2 receptor antagonists. While a second generation of antipsychotics with a wider receptor profile (e.g., serotonin 5-HT_{2A} antagonism) was developed, these treatments remained primarily dopamine D_2 receptor antagonists (Richelson and Souder, 2000). This `me-too' approach to treatment development limited research investigating the cognitive deficits experienced by people with schizophrenia (Markou et al., 2009), despite this disorder being first described as *dementia praecox* [premature dementia; (Kraepelin, 1896)].

Antipsychotic treatments resulted in little improvement in functional outcome for patients, becoming clear that more was required for patients' rehabilitation. Increasing evidence identified that cognitive deficits are likely core to the disorder (Geyer et al., 2012), correlating most closely with a patient's ability to reintegrate into society (Green, 1996; 2006). It became clear that antipsychotics were primarily efficacious at treating positive symptoms, with limited if any efficacy at treating cognitive deficits (Harvey and Keefe, 2001, Carter, 2005, Keefe et al., 2007, Mintz and Kopelowicz, 2007). Such limited efficacy likely contributed to the lack of Federal Drug Administration (FDA) approval for antipsychotics being indicated as pro-cognitive. Hence, research has begun focusing on developing drugs to improve cognition in schizophrenia patients (Green, 1996, Floresco et al., 2005, Green, 2006), moving from antipsychotic- to antischizophrenia-drug development (Geyer and Gross, 2012).

A major road-block to developing pro-cognitive treatments for schizophrenia has been that no current treatments exist, hence searching for me-too compounds using a positive control is not possible (Floresco et al., 2005). Moreover, pro-cognitive treatments for other disorders, such as acetylcholinesterase inhibitors for Alzheimer's disease, demonstrate limited efficacy for cognitive deficits in schizophrenia (Friedman, 2004, Sharma et al., 2006, Chouinard et al., 2007, Fagerlund et al., 2007). The (false-positive) evidence for beneficial effects of these and antipsychotic treatments has been reviewed elsewhere (Young et al., 2009, Young et al., 2012) and will not be covered here. Despite the increased research on developing procognitive treatments for schizophrenia, no clinically approved treatments have been approved, creating a `translational bottleneck' between animal and human testing (Hyman and Fenton, 2003). This bottleneck could reflect the use of paradigms in animals that measure a cognitive behavior in animals - `fast and dirty' techniques (Sarter, 2004) - that do not equate to the human cognitive construct (Talpos and Steckler, 2013), e.g., working memory (Dudchenko, 2004).

Measurement And Treatment Research to Improve Cognition in Schizophrenia (MATRICS)

The limited predictive validity of pro-cognitive treatments and the questionable relevance of commonly used rodent tasks to cognitive functions in humans highlight the difficulty facing translating pro-cognitive evidence from rodents to humans (Sarter, 2004). In fact, prior to the National Institute for Mental Health (NIMH)-funded MATRICS (Measurement And

Treatment Research to Improve Cognition in Schizophrenia) program (Marder and Fenton, 2004, Marder, 2006), no mechanism existed for the FDA to approve a pro-cognitive treatment for schizophrenia that did not also treat positive psychotic symptoms. With no currently approved treatments, MATRICS took the approach of characterizing cognitive domains that are consistently deficient in schizophrenia patients (attention, working memory, speed of processing, reasoning and problem solving, social cognition, visual learning and memory, and verbal learning and memory). Such an identification of altered processes (Segal and Geyer, 1985, Matthysse, 1986) enabled the definition of a hypothetical construct and subsequent establishment of operational definitions suitable for the experimental testing of the validity of the construct. Thus, theoretically the neural substrates subserving the behavioral construct could be disentangled using animals. MATRICS focused on using paper and pencil tests of these constructs however (Green and Nuechterlein, 2004, Buchanan et al., 2005), limiting cross-species translational validity (Young et al., 2009). Without the quantification of behavioral abnormalities in tests that can be conducted in rodents, developing pro-cognitive treatments based on rodent research would prove difficult (Young et al., 2009). After all, the validation of any model will only ever be as sound as the information available in the relevant clinical literature (Segal and Geyer, 1985), where human and preclinical research should inform one another (Geyer et al., 2012).

Cognitive Neuroscience Treatment to Improve Cognition in Schizophrenia (CNTRICS)

Another NIMH-funded initiative used a more cognitive neuroscience-based approach. The CNTRICS [Cognitive Neuroscience Treatment to Improve Cognition in Schizophrenia; (Carter and Barch, 2007)] initiative identified tasks from clinical and cognitive neuroscience that would fit specific constructs affected in patients with schizophrenia, increasing the opportunity that experiments could be undertaken in both patients and animals (Moore et al., 2013). Hence, the animal models developed from such research would likely, although not certainly, reflect similar neural mechanisms across species, where human research could inform animal research and vice-versa (Geyer et al., 2012). These constructs will be provided in greater detail below.

Modeling cognitive dysfunction for schizophrenia research

Of primary importance is the understanding that schizophrenia is a disorder characterized by abnormalities of behavior. Sufficient quantification of these abnormalities would enable similar behavior to be quantified in rodents, increasing the likelihood that neural substrates underlying these behaviors will be conserved across species. This approach to schizophrenia relevant research will be presented in the present review. Costa recognized back in (1992) that a bridge must be built between neurobiology and mental illness. By utilizing cross-species research with related tasks, we should be able to increase the likelihood that an identified treatment would cross the species translational gap and prove efficacious in patients. Moreover, this cross-species translational research will be put into the context of understanding cognitive functioning from sensory input to motor output, and thus affecting overall behavior (Fig. 1).

Describing animal manipulations relevant to the pathophysiology of schizophrenia is beyond the scope of the current review and is detailed elsewhere in this special issue. Some key definitions regarding validating animal models relevant to schizophrenia research are required however. Some of these validities are described with specific relevance to using rodent species to develop novel molecules as cognition enhancers (Young et al., 2013). Traditionally, when the validity an animal model is discussed, it is important to take note that both the independent variable (i.e., inducing manipulation) and dependent measures (i.e., behavioral outcome) require validation (Geyer and Markou, 1995, Ellenbroek and Cools, 2000, Young et al., 2010). The manipulation is best taken from information regarding the disease process of schizophrenia and will be covered elsewhere **this issue** as well as manipulations of animals relevant to this disease process **this issue**. For an up-to-date list on animal manipulations relevant to schizophrenia, see http://www.schizophreniaforum.org/res/animal/animal_tables.asp [based on (Carpenter and Koenig, 2008)]. Irrespective of whether the manipulation or the dependent measure is being discussed however, validity criteria are often described similarly and include etiological (manipulation), construct (convergent and discriminant for the dependent measure), reliability, predictive, and face validity. The more types of validity a model satisfies, the greater its likely value, utility, and relevance to the human condition, although some forms of validity are more important than others [i.e., construct and predictive (Pratt et al., 2012)]. These aspects of validity are described in greater detail elsewhere (Geyer and Markou, 1995, Ellenbroek and Cools, 2000, Young et al., 2010) but provided in brief here. *Reliability* refers to the consistency and stability with which the variables of interest are observed (Segal and Geyer, 1985, Geyer and Markou, 1995). *Face validity* refers to the phenomenological similarity between the dependent variable (behavior of the animal) and the specific symptoms of the human condition (Lieberman et al., 1997). Face validity can be useful heuristic starting point and is intuitively appealing, but it is insufficient by itself (Lipska and Weinberger, 1995). *Predictive validity* literally refers to the ability of a model to make correct predictions about the human phenomenon of interest (Geyer and Braff, 1987, Geyer and Markou, 1995). While some use the term to refer to pharmacological isomorphism [drugs having therapeutic value in the model and humans (Matthysse, 1986)], this narrow definition ignores ways in which models can make successful predictions in other forms enhancing ones understanding of a phenomenon (Ellenbroek and Cools, 2000). *Construct validity* refers to the accuracy with which a test measures that which is intended (Geyer et al., 1999). Although vitally important (Lipska et al., 1995, Geyer et al., 1999), its establishment is rare. Of importance to the current review, a test can also have convergent (or concurrent) and discriminant validity, specifically in relation to other tests. *Convergent validity* is the degree to which a test correlates with other tests that attempt to measure the same construct (Taiminen et al., 2000). *Discriminant validity* is the degree to which a test measures aspects of a phenomenon that are different from other aspects of the phenomenon that other tests assess (Taiminen et al., 2000). *Etiological validity* involves evaluating the manipulation and whether it tests an hypothesis about hypotheses about the etiology of the disease (Geyer and Markou, 1995). Etiological validity is vitally important for the development of treatments with no positive control (such as described here for cognition). Unfortunately, the etiologies of psychiatric disorders are not entirely known with so many alterations that etiological validity remains difficult to establish. The pathological alterations

that arise from the disease process are covered in this issue and require further evolution to develop better model organisms.

Hence, numerous aspects of validity exist. To bridge the translational gap that exists between species, it will be vital that the behavioral measures used in rodents be valid for those measuring behaviors in humans. The pertinent aspects for validity of behavioral measures include face, predictive, and construct validities. The behavioral measures described in this review will include descriptions of their respective validity. First however, it is important to understand the cognitive deficits experienced by people with schizophrenia, particularly deficits quantified using laboratory-based measures for similar testing in rodents.

CROSS-SPECIES COGNITIVE ASSESSMENT

Methods for identifying cognitive deficits in patients with schizophrenia

There are a myriad of cognitive processes affected in people with schizophrenia. MATRICS identified 7 affected domains including attention, working memory, speed of processing, reasoning and problem solving, visual learning and memory, verbal learning and memory, and social cognition. Apart from attention/vigilance, for which the continuous performance test (CPT) identical pairs was chosen, the cognitive tests chosen by MATRICS to assess the domains were paper and pencil tests that required language and/or instructions and therefore not readily amenable to translation for rodent testing (Young et al., 2009). For example, the Wechsler III Spatial Span task assesses visual working memory using blocks of various sizes identified in sequence to assess the number of items subjects can remember. While the odor span task (OST) and radial arm maze (RAM) measure the number of items of information rodents can remember (with the latter being visual), rodents are tested only once per day rather than the multiple tests of various span lengths used in human testing (see working memory section below for further details). Furthermore, the tasks identified by MATRICS are impacted by practice effects and deficits in other cognitive domains. More selective tests of specific cognitive constructs are required for cross-species translational testing (Young et al., 2012).

In the subsequent CNTRICS initiative, the focus shifted toward construct-specific aspects of cognition. For example, rather than attention, CNTRICS focused on the cognitive control of attention (focus of attention in response to internal representations), or rather than general learning, they identified reinforcement learning (acquiring behavior as a function of both positive and negative reinforcers). The tasks identified as having putative cross-species translational relevance for these constructs are reviewed extensively by CNTRICS (Bussey et al., 2013, Dudchenko et al., 2013, Gilmour et al., 2013, Lustig et al., 2013, Markou et al., 2013, Millan and Bales, 2013, Moore et al., 2013, Siegel et al., 2013, Young et al., 2013). When psychiatry utilizes consistent behavioral approaches between human and animals in research [e.g., self-administration for smoking cessation studies, (Geyer et al., 2012)], leading to positive results (advent of varenicline), this article reviews tasks available in humans and animals that measure specific cognitive constructs affected in patients with schizophrenia.

Attentional Domain

Deficient attention is one of the hallmark cognitive deficits of people with schizophrenia. In fact, poor attention was thought to be a core cognitive deficit of patients wherein deficient attention deleteriously affected all other domains [see figure 1 for how other domains downstream of attention could be deleteriously affected (Cornblatt and Keilp, 1994, Cornblatt et al., 1997)]. The gold-standard test of attention in the clinic has been a variation of the continuous performance test (CPT). The original CPT developed by Rosvold (1956) required subjects to attend to a visual field, responding to target stimuli (any letter) but inhibiting from responding to non-target stimuli (the letter X). Although variations exist, each task requires both responses to target and the inhibition of responding to non-target stimuli. For example, MATRICS chose the CPT-IP (Nuechterlein et al., 2008), which required subjects to respond to pairs of numbers that were identical, inhibiting from pairs that differed (Cornblatt and Keilp, 1994). These vigilance tasks have been used in clinical testing for over six decades and although adaptations to the task may require other cognitive processes [e.g., AX-CPT was chosen by CNTRICS as a test of working memory maintenance; (Barch et al., 2009)], they are still deemed reliable tests of attention.

Other tests of attention for humans have emerged, using a reverse-translation approach for task development. This approach utilizes the basis of a rodent task, creating a human version for clinical testing. One of the first reverse-translated tests of attention was the 5-choice serial reaction-time task (5CSRTT), which itself was originally based on Leonard's 5CSRTT. The rodent 5CSRTT has been studied extensively and reviewed recently (Robbins, 2002, Lustig et al., 2013). Differences in rat and mouse performance of the 5CSRTT are cause for some concern in relation to the basic strategies used to complete the task. These concerns are detailed elsewhere (Young et al., 2013), but do not detract from the great deal of important research that has been conducted using this paradigm (Robbins, 2002, Lustig et al., 2013). Of considerable interest for the current review is the recent work on human versions of the task. In the human 5CSRTT, patients with schizophrenia exhibit increased variability in reaction times (Barnett et al., 2010), which has been described as impaired attention and/or motor function (Chouinard et al., 2007, Fagerlund et al., 2007). Notably, however, no accuracy, premature responses, or omission deficits have been reported in schizophrenia patients (often the primary measures in the rodent 5CSRTT). A novel human variant of this task has appeared in which subjects are encouraged to respond as quickly as possible throughout the task (Worbe et al., 2014). This 4-choice task also requires the subjects to hold a space bar prior to stimulus presentation. These changes enabled the assessment of premature responses in humans, with serotonin depletion increasing such responses in humans (Worbe et al., 2014), as seen in rats (Harrison et al., 1997, Winstanley et al., 2004). In contrast to the rat findings however, serotonin depletion actually improved the accuracy of humans performing the task (Worbe et al., 2014), while the accuracy of rats remained unchanged (Harrison et al., 1997, Winstanley et al., 2004). More regionally selective serotonin depletion e.g., dorsal- but not median-raphe nucleus serotonin depletion (Harrison et al., 1997) does increase accuracy however. Thus, whilst the utility of this novel 4-choice task for schizophrenia research has yet to be demonstrated it could prove useful in future research.

Another reverse-translated attentional task in which deficient performance of schizophrenia patients has been observed is the 5-choice continuous performance test (5C-CPT). The 5C-CPT task was designed for rodents and based on the 5CSRTT, but included non-target stimuli to provide greater consistency with human CPTs (Young et al., 2009). Consistent with human CPTs, signal detection theory (SDT) is used to measure the strength of attentional functioning when the subject is required to respond to target stimuli but inhibit responding to non-target stimuli. Numerous studies exist in the rodent version of this task (Barnes et al., 2012, Harms et al., 2012), demonstrating for example that nicotine can improve performance in normal mice (Young et al., 2013) consistent with healthy humans performing a CPT (Levin et al., 1998). Certain manipulations can impair 5C-CPT performance such as subchronic phencyclidine (Barnes et al., 2012), acute scopolamine (Young et al., 2013), or deficient developmental vitamin D (Turner et al., 2013). None of these deficits recreate the deficient 5C-CPT pattern seen in patients with schizophrenia however, whose vigilance deficit as measured by d' is consistent with other CPT studies (Nuechterlein, 1983, Nuechterlein, 1991). The 5C-CPT deficit of these patients was driven by lower target responses, modestly elevated non-target responses, more variable reaction-times, and an exaggerated vigilance decrement over time, although normal accuracy was observed (Young et al., 2013). The exaggerated vigilance decrement was also seen in patients performing a novel `Raindrops' attentional task which - consistent with the 5C-CPT - used a wide visual array (Hahn et al., 2012). To date, an exaggerated vigilance decrement has only been observed in DBA/2J mice when compared with C57BL/6J mice (Young et al., 2009), which may warrant further study, especially since the mice also exhibited comparable accuracy. The availability of functional magnetic resonance imaging (Mckenna et al., 2013) and electroencephalography versions of the human 5C-CPT provides further opportunity for cognitive neuroscience-based translational research. Hence, the 5C-CPT could be useful for future translational schizophrenia research in assessing attention, but the consistency of deficits in patients should be further investigated in larger numbers and across difference stages of the illness. In terms of translational validity, 36-hour sleep deprivation impairs human and mouse 5C-CPT performance in consistent domains [misses to targets; van (Van Enkhuizen et al., 2013)]. Additionally, the parietal cortex is activated during both target and non-target trials in human fMRI studies (Mckenna et al., 2013), and lesion of the parietal cortex impairs target and non-target responding in mice, impairing attentional performance (Young et al, 2014). Hence, the 5C-CPT offers a great deal of promise but more work is required demonstrating its construct and predictive validity across species, as well as consistency of deficits in patients with schizophrenia.

Another reverse-translated task to assess attentional function is the distracted sustained attention task (dSAT). The sustained attention task was originally developed by Bushnell et al, (1994) with developmental modifications provided by McGaughy and Sarter (1995). During the SAT, during a trial a light is flashed or not, and the rat is required to press the left or right lever depending upon their detecting the lights. This task has been used extensively to investigate the effects of nicotinic acetylcholine receptor agonists (Mcgaughy et al., 1999, Rezvani et al., 2002) as well as their interactions with antipsychotic medications (Rezvani and Levin, 2004, Rezvani et al., 2006). Such studies are important for future pro-cognitive treatment development since most cognition-enhancing compounds will be co-administered

to patients being treated with antipsychotics (Floresco et al., 2005). The dSAT offers a variation from the original task, whereby a distracting flashing light is introduced a third of the way through the trials, assessing the animal's ability to maintain attention during distraction (Howe et al., 2010). A human version of the task was developed utilizing similar properties (Demeter et al., 2011). When tested, patients with schizophrenia exhibited impaired performance throughout the task (detecting the presence of a stimulus) and were affected by distraction equally to healthy comparison subjects (Demeter et al., 2013). Hence, patients were not more sensitive to the distracting stimulus, belying the premise that such distraction is required to assess their attentional functioning. It was noted that patients did not exhibit an exaggerated vigilance decrement in the dSAT, but healthy subjects did not exhibit a vigilance decrement (Demeter et al., 2013). Nor was a vigilance decrement noted in rats performing the dSAT, although a drop in percentage of hits was described (Howe et al., 2010). Importantly for translational research however, this dSAT provides another opportunity to measure attentional functioning in patients and compare results across species. As described above for the 5C-CPT, the consistency of deficits in patients should be further investigated in larger numbers and across difference stages of the illness. To date, few methodological manipulations have been conducted in both the rodent and human dSAT so the cross-species validity requires support beyond face validity. Thus, the construct and predictive validity of the dSAT should be further investigated.

Working Memory

The classical description of human working memory is the requirement to hold information `online' while manipulating such information before its recall (Baddeley, 1992). Hence, tasks used to assess working memory in humans traditionally assess the capacity (number of items that can be held online, e.g., digit span) of working memory, with additional complexity requiring the manipulation of those items (e.g., n-back task). The components of working memory have been conceptualized as visual and phonological stores, with the central executive coordinating these capacities for online manipulation (Baddeley, 1986). The poor working memory in patients with schizophrenia and their possible neurobiological underpinnings have been reviewed recently (Lett et al., 2014) and so this review will focus on understanding the measurement of working memory so that it can be assessed non-clinically. To assess working memory in patients, MATRICS chose the University of Maryland Letter-Number Span Task (UMLNST) and Wechsler Memory Scale-III Spatial Span Task (WMS-III SST), measuring non-spatial and spatial span capacity. Classically however, rodent working memory is described in terms of delay-dependent memory, contrasting with human measurement of working memory (Dudchenko, 2004). In fact, Neuchterlein et al (2005) warned of the difficulty in assessing working memory in rodent paradigms due to the contrasts of span capacity (human) vs. delay dependence (animal). CNTRICS expanded the constructs of interest for working memory, highlighting interference control (online manipulation of information) and including goal maintenance (delay-dependent memory for a single item). To assess these cognitive constructs in humans, CNTRICS chose the Operation/Symmetry Span tasks for interference control and the AX-CPT or dot pattern expectancy (DPX) task to measure goal maintenance (Barch et al., 2009). The Operation/Symmetry Span tasks are essentially span capacity tasks that also include the need to make judgment calls on another aspect of the task, thus requiring the manipulation

of information while it is held online (Unsworth and Engle, 2007). The AX-CPT and DPX are similar paradigms requiring the subject to retain an item of information (the letter A or B, or a series of dot patterns) before other stimuli are presented to them after a delay period - after which they identify if the stimuli pairs were targets or non-targets. The dot patterns benefit from patterns that are not readily recognizable and the delay periods thus challenge working memory representation (Servan-Schreiber et al., 1996). Latterly, the CNTRICS animal sessions included span capacity as an important construct to measure (Dudchenko et al., 2013), given the evidence that patients with schizophrenia may not exhibit delay-dependent, but selective span-capacity, deficits (Gold et al., 2010). The availability of cross-species valid tests for each construct will be covered below, although other details are reviewed more extensively for CNTRICS (Dudchenko et al., 2013) or MATRICS (Young et al., 2009) elsewhere.

Span Capacity—Given that MATRICS highlighted span capacity and the interference-control construct identified by CNTRICS contained a strong span-capacity component, here we will first cover span capacity. Some tasks exist in rodents that likely measure span capacity. For example, the rodent span capacity includes spatial and non-spatial (odor) versions (Dudchenko et al., 2000, Young et al., 2007). Items are presented with increasing number (starting at 1) so that with every novel item (n+1), the rodent must remember the encountered and only ever choose the novel item (either spatially located or a specific odor), up to 24 items. Originally developed to assess memory-load manipulations of hippocampectomized monkeys (Murray and Mishkin, 1998), the task has had increased use lately. Another spatial span task includes the radial arm maze (RAM; (Olton and Werz, 1978, Olton, 1987)], wherein rodents are presented with multiple arms each of which lead to a reward. Spatial cues are provided so that the rodent can `remember' each location visited and thus not re-enter locations already depleted of its reward. Essentially, both sets of tasks require the animal to remember certain items in order to select only novel items (whether odors or locations).

When spatial locations are used, hippocampal lesions deleteriously affect rodent performance on these tasks (Dudchenko et al., 2000); RAM HIPP). Hippocampal lesions do not affect odor span capacity however (Dudchenko et al., 2000). A human version of the odor span task exists in which subjects with hippocampal lesions exhibit a minor drop in performance (Levy et al, 2003), which could have resulted from the use of semantic memory in humans. For the odor span task, nicotine enhances the performance of mice with deficient performance due to over-expression of caspase 3 (Young et al., 2007), or ameliorates normal and subchronic ketamine-induced deficits in rats (Rushforth et al., 2010, Rushforth et al., 2011). Moreover, mice with null mutation of the alpha-7 subunit of the nicotinic acetylcholine receptor (nAChR) exhibit poor performance in the odor span task (Young et al., 2007), while an alpha-7 nAChR agonist improved rat performance in the task (Rushforth et al., 2010). Nicotine can exert beneficial effects on reaction-time in working memory span in never smokers, although it made accuracy worse (Foulds et al., 1996), and there have been few replications. Moreover, nicotine worsened working memory in healthy humans, and did not reverse their deficits when treated with ketamine (D'souza et al., 2012). Furthermore, there are few studies investigating the effects of nicotinic agonists on working

memory in schizophrenia patients that never smoked. Hence, the pharmacological predictive validity of the odor span task remains to be verified, as does the construct validity of the task for measuring span capacity.

In terms of measuring memory capacity, a great deal of research has been accomplished using the radial arm maze (RAM), although many variants of the task exist (Olton, 1987, Hodges, 1996, Young et al., 2009). Here, we will provide a brief review of the paradigm examining the ability of rodents to remember items (arms) within a session using all available items. A human version of this task - often tested in children - is available, providing evidence of comparable performance levels between rat and human testing (O'connor and Glassman, 1993, Glassman et al., 1994). Fetal alcohol syndrome impaired both human (Uecker and Nadel, 1996) and rat (Reyes et al., 1989) performance of a RAM. A virtual RAM exists (Astur et al., 2004, Lee et al., 2014), that activates both hippocampal and frontal cortices (Astur et al., 2005). More importantly, people with hippocampal damage are impaired in the virtual RAM (Goodrich-Hunsaker and Hopkins, 2010) as occurs in rodents. Moreover, patients with schizophrenia exhibit impaired virtual RAM performance (Spieker et al., 2012). Of course, pharmacological validation has yet to be determined between the human and rodent RAMs. Improvements in performance can be seen however in healthy rats using nicotine and nicotinic agonists (Levin et al., 1990, Levin, 2002, Levin et al., 2009), as well as dopamine D_2 family agonists (Tarantino et al., 2011). Although there is limited evidence for nicotine improving traditional measures of working memory in humans, the same D_2 family agonist improved human spatial working memory span capacity in subjects with poor span capacity (Mehta et al., 2001, Gibbs and D'esposito, 2006). Hence, work with the RAM may provide an opportunity for cross-species translational research toward developing treatments to improve cognitive functioning in patients with schizophrenia. A great deal more work is required however, validating the cross-species relevance of the task for schizophrenia research.

A touchscreen version of the RAM is available for the Cambridge Neuropsychological Test Automated Battery (CANTAB) wherein subjects must search a number of boxes to identify a hidden marker. Working memory span is assessed by measuring the number of errors subjects made during the task, with a varying number of boxes per challenge (Owen et al., 1991). Patients with schizophrenia exhibit poor working memory span capacity but only at spans of 4 boxes and above, primarily once a span of 6 and 8 boxes are presented (Pantelis et al., 1997, Potvin et al., 2008), including in first episode patients (Cocchi et al, 2009). Interestingly, modafinil improved spatial working memory measured in this task in healthy subjects only when higher spans were used however, such as 10 and 12 boxes (Muller et al., 2013). This effect of modafinil has not yet been recreated in rodents performing the RAM. Providing such evidence, and whether a dopamine D_2 family agonist would improve human working memory in the CANTAB task, would demonstrate translational evidence for spatial working memory span capacity across paradigms and species.

Goal Maintenance—The symbol complexity and its trial uniqueness makes the dot pattern expectancy (DXP) task an ideal method to measure the maintenance of a single item of information for a certain period of time. Such a task matches with the likes of the trial unique delayed response task (DRT) for primates pioneered by Goldman-Rakic and

colleagues (Arnsten et al., 1994, Goldman-Rakic et al., 2004). Using this DRT, they were able to demonstrate that increased dorsolateral PFC firing occurs to cue the location of the to-be remembered cue and degradation of the firing matches with inaccuracy during choices (Funahashi et al., 1989). Of course, the DRT uses delays up to several minutes, while the DXP uses delays of only several seconds, relying on stimulus complexity to challenge performance. The reliance of such differences to challenge performance in each species may result in altered neural substrates being recruited for performance in each task and requires investigation. For rodents, there are limited trial-unique delay-dependent memory tasks available. Talpos et al (2010) developed a trial-unique, delayed non-matching-to-location (TUNL) task to measure delay-dependent memory using unique stimuli. This task utilizes a row of 3 rows of 9 squares whereby rats perform a delayed-match to sample task using different locations for each trial. The task differs from the complexity of the DXP or AX-CPT but may be useful to measure goal maintenance (Dudchenko et al., 2013). The degree of difficulty of this task is exemplified whereby performance at small separations is at chance, while hippocampal-lesioned rats are at chance levels with only a 6-second delay. Furthermore, mPFC lesions also impaired TUNL performance at 6-second delays (Mcallister et al., 2013). This task is now available for use in mice (Oomen et al., 2013) but requires a great deal of validation for assessment of performance consistent with that of the human tests of goal maintenance of working memory.

Interference Control—In a summary of tasks reported to measure aspects of interference control, it was determined that no rodent task yet exists to measure such a construct (Dudchenko et al., 2013) and so will not be discussed further here.

Perception

The first aspect of cognition is how a subject perceives their environment. Although not highlighted by MATRICS, perception was identified as an important aspect to be measured and improved upon across species by the CNTRICS initiative. Gain control and sensory integration of visual stimuli were identified as two important constructs of perception to be measured. Gain control refers to the ability of sensory systems to adapt and optimize response levels to their immediate context (not long-term adaptations) to make best use of a limited dynamic signaling range (Butler et al., 2012). For humans, the contrast-contrast effect (CCE) task was recommended to measure gain control. CCE arises from a well-known visual illusion where contrast sensitivity is strongly modulated by the visual properties of adjacent or surrounding stimuli (Green et al., 2009). Alternatively, steady-state visual-evoked potentials and contrast sensitivity to M- and P-biased stimuli was also recommended, again requiring visual contrasting of cues (Green et al., 2009). Each of these tasks has some non-human primate analogues but no comparable tasks currently exist in rodents. Other tasks were suggested to measure gain control, such as prepulse inhibition, event-related potentials, and mismatch negativity (Siegel et al., 2013). Each of these tasks also has a human version but their limited correlation with each other (Light and Swerdlow, 2014) dampens enthusiasm that they measure the same cognitive construct. A detailed discussion of their relevance to gain control is provided by Siegel et al, (2013). Hence, much more translational research is required if translating perception from rodent to human studies is to be conducted in novel paradigms.

Long-Term Memory

Both MATRICS and CNTRICS initiatives identified long-term memory as an important cognitive domain negatively impacted by schizophrenia, although MATRICS focused on visual and verbal learning and memory. The constructs identified by CNTRICS were relational encoding and retrieval and item encoding and retrieval. Both constructs required the memory for specific items but that items in the former were in relation to context, stimuli, or events, while the latter held no relational value (Ragland et al., 2009). Within these aspects of long-term memory, CNTRICS also identified reinforcement learning as a key construct impacted by schizophrenia. Reinforcement learning was defined as acquiring behavior as a function of both positive and negative reinforcers (Ragland et al., 2009). Hence, consistent with MATRICS, CNTRICS identified that measuring learning and its outcome would be critically important in treating the cognitive disruption of people with schizophrenia.

Relational Encoding and Retrieval

To assess the encoding and retrieval of relational long-term memories, the CNTRICS initiative recommended the associative inference paradigm (AIP) and relational and item encoding and retrieval (RIER) task. AIP pairs stimuli types, e.g., faces and houses (A + B), then the same stimuli without other types, e.g., the same houses with other faces (B + C), after which the subject can be tested on inferential relationship between A and C stimuli (Eichenbaum, 2000). The memory of healthy subjects for inferential stimuli are greater than non-inferential stimuli, whereas no differences in performance for these pairs are seen in patients with schizophrenia (Armstrong et al., 2012). Although the performance of patients was barely above chance, limiting comparison to healthy subject performance (Armstrong et al., 2012), follow-up tests with an easier task demonstrated similar effects (Armstrong et al., 2012). The simplicity of the AIP task enables it to be conducted reliably in rodents with conserved construct validity across species (Bunsey and Eichenbaum, 1996).

Using the more hierarchical transitive inference paradigm (TIP) where 5, not 2, stimulus pairs are used, evidence was provided that the deficient associative memory performance of patients with schizophrenia in the task was not confounded by reinforcement ambiguity or novelty (Coleman et al., 2010). Such associative learning appears to be mediated by a prefrontal-hippocampal network (Devito et al., 2010, Devito et al., 2010). Little schizophrenia-related research has been conducted with AIP or TIP. Mice lacking the vasopressin 1b receptor exhibited normal transitive inference (Devito et al., 2009), while DBA/2 mice exhibit poorer TIP performance compared to C57BL/6 mice (Andre et al., 2012). Serine racemase knockout mice, which have reduced NMDA receptor function, also exhibit normal TIP performance (Devito et al., 2011). Despite limited findings so far, the development of an automated touchscreen version of the TIP (Silverman et al., 2013) increases the putative utility of the TIP for developing procognitive treatments for relational long-term memory deficits in patients with schizophrenia. This automated task takes several days however, unlike the original task. Such multiple vs. single days of testing introduces new factors such as consolidation that could influence results, as has been seen in tests of attentional set-shifting (Young et al., 2009). In fact, within- vs. between-session testing can produce different results in animal models of schizophrenia. For example, isolation-reared

rats exhibited probabilistic learning deficits over several days, but not when tested within a single session (Amitai et al., 2013). Hence, care should be taken when examining the construct validity of this automated TIP, although the task itself shows promise.

For relational encoding and retrieval as well as item encoding and retrieval, CNTRICS recommended the RIER task. The RIER task is a complex test using pre-task knowledge of relational information (e.g., weight comparisons of a mouse and an elephant) in association with being shown single items and being asked to rate their `pleasantness'. Such knowledge and ratings are used to manipulate the encoding strategies of the test subjects. Manipulating such encoding strategies in rodents would prove particularly difficult although temporal or action-related encoding may be possible in the future.

Probabilistic reinforcement learning

Long-term memory acquisition is important for everyday functioning in patients with schizophrenia. Equally important of course, is the acquisition of these long-term memories. Memories and skills are commonly learned through reinforcement, either positive or negative reinforcement. CNTRICS highlighted the need to study reinforcement learning in patients with schizophrenia. Such reinforcement learning is impaired in patients, driven by poorer reward-associate learning (Waltz et al., 2007). Numerous tasks exist to measure different aspects of reinforcement learning and are primarily probabilistic in nature. Probabilistic learning refers to learning about stimuli that are reinforced or `punished' on different ratios. Because subjects cannot infer advantageous outcomes based on a single trial, probabilistic learning performance enables an objective assessment of participants' propensity to modulate behavior as a function of reward (Ragland et al., 2012). Probabilistic learning and reversal learning can be assessed using a variety of techniques. These techniques include having subjects make a judgment call about the length of a line whereby an asymmetric reinforcement schedule will induce a bias in responding to one line that is imperceptibly longer than another (Pizzagalli et al., 2008, Huys et al., 2013). In this probabilistic reward task, subjects with normal implicit responses to reinforcement should begin selecting that line more often, without being consciously aware of their selection. To date, patients with schizophrenia do not exhibit implicit reward-associative learning in this task (Ahnallen et al., 2012).

Other probabilistic learning tasks exist however, which measure explicit probabilistic reward associative learning. Traditionally, two stimuli are presented with differing reward/punishment probabilities - e.g., 80/20 refers to a stimulus (target) being reinforced 80% and punished 20% of the time it is chosen, while the probabilities are reversed for the other stimulus. Once the subject learns to respond appropriately to the target stimulus, e.g., as exemplified by 8 consecutive target responses, the contingencies are reversed (Lawrence et al., 1999, Swainson et al., 2000). Thus, this task measures not only probabilistic learning, but reversal learning as well. Both probabilistic learning and reversal learning deficits are seen in patients with schizophrenia (Waltz et al., 2007, Strauss et al., 2011, Dowd and Barch, 2012). Importantly, learning and reversal learning studies have a long history of testing in rodents, although most studies to date utilize deterministic (100/0 probabilities) learning. Even with this difference, there is considerable overlap in the construct validities

between rodent deterministic and human probabilistic learning/reversal learning (Ragland et al., 2009, Markou et al., 2013). Deterministic learning also does not provide researchers with an objective assessment of participants' propensity to modulate behavior as a function of reward however, since the non-target (lower reward probability) stimulus is never rewarded. Fortunately, probabilistic learning studies are increasingly being conducted in rodent studies. Rearing rodents in isolation post-weaning has been a commonly used model to the social isolation experienced by patients with schizophrenia (Powell et al., 2009). Isolation rearing induces behavioral abnormalities consistent with schizophrenia such as reduced PPI (Geyer et al., 1993). Isolation-reared rats exhibit deficits in day-to-day probabilistic learning, but normal within-session probabilistic learning (Amitai et al., 2013), the latter more commonly used in human studies. Inactivation of the Nucleus Accumbens shell impaired both initial probabilistic learning and learning when reward contingencies were reversed, while inactivation of the Nucleus Accumbens core did not affect performance (Dalton et al., 2014). Mice that lack the alpha-7 nAChR subunit exhibit impaired learning for rewards while their aversively motivated learning remains intact (Young et al., 2011). The alpha-7 nAChR remains a target for enhancing cognition in schizophrenia (Bencherif et al., 2012) and studies should perhaps focus on its effects on enhancing reward associative learning (Acheson et al., 2013, Young and Geyer, 2013). Such differentiation between aversive and reward associative learning further supports the premise that differing mechanisms contribute to these aspects of learning, e.g., amygdala involvement for aversively motivated learning (Mchugh et al., 2014). Hence, specific structures may relate to learning in response to specific cues. Humans with OFC damage exhibit impaired probabilistic reversal learning as a result of being more likely to shift from both negative and rewarding feedback, specifically shifting after a loss even on the target option (Tsuchida et al., 2010). Blockade of the serotonin transporter impaired probabilistic learning in mice and rats by decreasing negative feedback sensitivity (Ineichen et al., 2012), providing some cross-species relevant findings. Matching human and animal lesion/inactivation/pharmacological studies will prove useful for translational studies.

Executive Functioning

The cognitive domain of executive functioning is a highly varied domain containing numerous aspects of cognition from problem solving, planning, organization, and initiation of tasks, cognitive flexibility, and the inhibition of inappropriate responses (Jurado and Rosselli, 2007, Ardila, 2008). While MATRICS focused on measuring reasoning and problem solving - to distinguish this domain from executive control in working memory - CNTRICS identified the constructs of rule generation and selection, plus dynamic adjustment of control (Carter et al., 2012). Since the mazes task identified by MATRICS was not readily reproducible in animals, the rodent-supported paradigm was the attentional set-shifting task [ASST; (Young et al., 2009)]. Originally developed by Birrell and Brown, (2000), the ASST was designed as a rodent analogue of the intradimensional/ extradimensional (ID/ED) set-shifting task. The ID/ED task was chosen to measure the construct of rule generation and selection in humans, thus providing a great deal of overlap for the translation of test compounds from preclinical to clinical efficacy.

The ASST and ID/ED tasks share a great deal of overlap in their design, procedures, and cognitive domains subserving performance. While the ID/ED task utilizes lines and shapes, the ASST utilizes odors, digging media, or platform textures. Essentially however, there are 7 stages to both tasks (Tait et al., 2013). In stage one (simple discrimination) subjects are required to select between two stimuli of a particular dimension (e.g., odor), one of which is correct 100% of the time (e.g., paprika) while the other is never (0%) correct (e.g., thyme). In stage 2 (compound discrimination) another dimension is introduced (e.g., platform textures such as metal and wood) but the subject must continue to select the original stimulus, ignoring the new dimension. In stage 3 (compound reversal) the stimulus properties are switched such that selecting the previous non-target stimulus (e.g., thyme) is now rewarded, while the other (e.g., paprika) is not. In stage 4 (intradimensional shift) new stimuli pairs are introduced (e.g., garlic and parsley, plus brush and tile) but the original dimension (e.g., odor) remains relevant (e.g., garlic is the target). In stage 5 (intradimensional reversal), the relevance of the two odor stimuli are switched (e.g., parsley is now the target). In stage 6 (extradimensional reversal), another set of novel stimuli are introduced but importantly the first relevant dimension (e.g., odor) is now irrelevant and the previously relevant dimension (e.g., platform texture) becomes relevant. Evidence that an attentional set is formed arises from more trials to acquire stage 6 than stage 4 (hence ID/ED shift). Finally in stage 7 (extradimensional reversal), the relevant stimuli are switched within the dimension. Both rat (Birrell and Brown, 2000, Barense et al., 2002) and mouse (Bissonette et al., 2008, Young et al., 2011) versions of the task are available with considerable evidence of cross-species translational validity, e.g., prefrontal mediation of set-shifting, orbitofrontal mediation of reversal learning, aging effects (Birrell and Brown, 2000, Barense et al., 2002, Mcalonan and Brown, 2003, Bissonette et al., 2008, Young et al., 2010, Young et al., 2012). The primary outcome measures of the two tasks differ however. The primary outcome of the human ID/ED task was the percentage of each group passing each stage. Patients with schizophrenia exhibit a lower percentage passing even the compound discrimination, with large drops of those passing in those passing the extradimensional stage (Tyson et al., 2004, Ceaser et al., 2008). More recent data present error rates (Hilti et al., 2010, Yun et al., 2011). Evidence suggests however, that patients with schizophrenia, including medication-free first episode patients, may have a generalized learning deficit that is not specific to extradimensional shifting (Hilti et al., 2010, Yun et al., 2011). The primary outcome presented for the rodent ASST is that of trials to criterion for each stage, with more trials required at the extradimensional vs. intradimensional stage. While this difference may not be crucial, presentation of consistent outcome measures are more likely to reveal neuroarchitecture that is consistent across species (Tait et al., 2013, Young et al., 2013).

There are other limitations to the interpretation of findings in the ASST however, such as when an ED shift is not observed in control subjects since one could therefore not interpret that an attentional set had been formed (Young et al., 2009, Tait et al., 2013). Pro-cognitive development studies should also be cognizant of the limitations of ASST for pharmaceutical research, including the time of drug administration prior to testing and manual scoring (Gilmour et al., 2013), or the false-positive findings of pro-cognitive effects of antipsychotic treatments (Mclean et al., 2008, Goetghebeur and Dias, 2009). The development of an

automated ASST - albeit requiring specialized equipment (Scheggia et al., 2014) - offers an opportunity for improved testing of ASST-like behaviors for drug discovery. This automated ASST may be limited however, because the trials to criterion of the rodents differed by dimension, an effect also seen when using olfactory or texture cues in observer-rated tasks (Birrell and Brown, 2000, Young et al., 2013). As long as any starting dimension effect on learning did not interact with the experimental factors however, study findings are still likely valid, highlighting the utility of the ASST. Hence, the ID/ED and ASST provide an opportunity to measure rule generation, reversal learning, and set-shifting across humans and rodents (Gilmour et al., 2013, Tait et al., 2013), aiding the search for cognition-enhancing treatments for schizophrenia (Young et al., 2013).

Dynamic Adjustments of Control—CNTRICS highlighted one aspect of executive functioning that should be measured in patients with schizophrenia, namely the dynamic adjustments of control (Carter et al., 2012). This cognitive construct was operationalized as "processes involved in detecting the occurrence of conflict or errors in ongoing processing, identifying the type of control adjustments needed, and recruiting additional control processes". For dynamic adjustments of control, the CNTRICS group suggested development of the inhibitory control task referred to as the stop-signal reaction-time task [SSRT; (Barch et al., 2009)]. The SSRT measures a subject's speed and ability to inhibit an ongoing action (Logan et al., 1984). Originally designed for humans, a rodent analog is available. In the task, rodents are trained to press two levers in quick succession (go-trial, 80% of trials), but must inhibit responding on the second lever if a tone is presented (stop-signal, 20% of trials). The temporal distance between the stop signal from the second response can be varied to alter difficulty level. Thus, the stop reaction-time (latency) is measured as the longest temporal distance between pressing the go lever, a stop-signal being emitted, and the rat successfully inhibiting from responding on the second lever. Go-latencies are also collected to examine non-specific effects on reaction-times.

In humans, the structures subserving SSRT have been examined in detail (Aron and Poldrack, 2006), while numerous lesion studies in rats have examined structures subserving rat SSRT (Eagle and Baunez, 2010). For example, both orbitofrontal lesions and dorsomedial striatum lesions slow the SSRT, but only the former does so in the absence of non-specific slowed go-reaction-times (Eagle and Robbins, 2003, Eagle et al., 2008). Lesions of the subthalamic nucleus, on the other hand, completely impair the rats' ability to inhibit responding (Eagle et al., 2008). Such findings are largely consistent with human studies highlighting the importance of the subthalamic nucleus for stopping reaction-times (Aron and Poldrack, 2005). Hence, there is construct validity for the rodent to human SSRT.

Another important aspect of validity is predictive validity. Certainly, there is conceptual validity for the task since stopping is easier for rodents and humans as the temporal distance between the go and stop signal is increased. Pharmacological predictive validity is also important however, for drug development. Modafinil is a wake-promoting agent that improves SSRT performance in healthy volunteers and ADHD patients, but not patients with schizophrenia (Turner et al., 2003, Turner et al., 2004, Turner et al., 2004). In rats however, modafinil only improved SSRT in poor performers without affecting go-reaction-time (Eagle et al., 2007). Modafinil has sped up reaction-times in other studies however (Young

and Geyer, 2010). The ADHD treatment atomoxetine also sped SSRT without affecting go-reaction-time (Robinson et al., 2008). Given that atomoxetine also reduced false alarm responding and premature responding (Robinson et al., 2008), this mechanism (norepinephrine transporter inhibition) likely affects non-specific inhibitory processes. More recently, the SSRT has also been developed for use in mice, with atomoxetine also enhancing SSRT (Humby et al., 2013). The availability of the task in mice enables targeted genetic assessments, which are likely to be an important aspect in future schizophrenia research.

The specificity for SSRT to measure the construct of dynamic adjustment of control remains to be validated. An important aspect of dynamic adjustment of control is post-error slowing (PES). PES occurs when a subject slows their response after making an error response and can be measured in standard reaction-time tasks (Rabbitt and Rodgers, 1977, Schroder and Moser, 2014). PES is likely mediated by prefrontal control of subthalamic nuclei (Cavanagh et al., 2014), consistent with findings in the SSRT (Aron and Poldrack, 2006). In contrast to human PES studies however, rats performing the SSRT exhibit post-error speeding instead of slowing (Bari and Robbins, 2013). The opposite findings compared to humans could be due to time-out punishments being used in rodents, but this conjecture has yet to be clarified. PES measurement in other tasks, unpunished SSRT, or in fact punished human tasks, should be investigated. Irrespective of its validity to measuring the construct of dynamic adjustment of control, it is clear that the SSRT will be useful for cross-species assessments of manipulations relevant to schizophrenia, leading to the development of pro-cognitive therapeutics. Given that SSRT performance may relate to the inhibitory control over speech (Xue et al., 2008), improving SSRT may provide schizophrenia patients with greater control over all inappropriate responses.

Risk-Based Decision Making

Impairments in decision-making for gains and losses are evident in schizophrenia as well as other psychiatric disorders (Christodoulou et al., 2006, Fond et al., 2012, Mantyla et al., 2012). Such deleterious decision-making can significantly impact quality of life, increasing attempted suicides (Jollant et al., 2007). There are several paradigms that measure such decision making for rewards vs. punishment across species. These paradigms include delayed discounting, risky decision-making, probabilistic learning, and Iowa Gambling Tasks (IGT). There are numerous variables in these tasks, e.g., delay vs. footshocks used as punishment, trial number used to vary probabilities vs. discrete choices of probabilities. Thus, depending on the task setup, various effects of the same manipulation can be seen.

Iowa Gambling Tasks—The IGT utilizes high-yield/high-risk versus low-yield/low-risk options to measure decision making with real-world translational validity (Bechara et al., 1994). Subjects select one at a time from four options. Each option consistently provides either high-yield rewards but at high risk of punishment, or low-yield rewards associated with low risk of punishment. Ultimately, the low-risk options provide greater rewards overall and subjects shift to these options within a single session as trials progress. Schizophrenia patients exhibit disrupted learning in this task, exhibiting a slower learning curve to select the advantageous choices compared to healthy subjects (Brambilla et al.,

2012) (Kim et al, 2009). Interestingly, early learning in patients may be impacted by polymorphisms in the serotonin transporter or the serotonin 5-HT_{1A} receptor (Gu et al., 2013). Although depressed patients are also impaired in the task, it appears their poor performance is a result of greater sensitivity to punishing stimuli (Adida et al., 2011, Must et al., 2013), while the deficient performance of manic patients results from their hypersensitivity to high rewards (Cassidy et al., 1998). These contrasting profiles of deficits in different patient populations may offer the best opportunity to target treatment development to enhance decision-making in patients with schizophrenia.

Based on the human IGT, animal analogues have been created (De Visser et al., 2011). Consistent with the human IGT, in the rodent IGT animals are presented with four options with different reward/punishment probabilities and magnitudes. Consistent with the human IGT, two options offer small rewards and little punishment (safe/advantageous choices), while the other two options offer larger rewards and more punishment (risky/disadvantageous choices). While multiple-session rodent IGT tasks exist (Zeeb et al., 2009, Baarendse et al., 2013, Van Enkhuizen et al., 2013, Zeeb et al., 2013), these studies examine risk-preference on *already learned* decision-making processes. In contrast to these tasks however, the human IGT examines dynamic decision-making *during learning* in a single session, possibly limiting the translational validity of multiple-sessions rodent IGT studies (De Visser et al., 2011). IGT tasks in which rodents learn within a single session exist however (Rivalan et al., 2009, Rivalan et al., 2011), which may provide greater relevance to studies in human IGT tasks.

Conceptual validation of the cross-species relevance of the IGT arises from observations of inter-individual differences in risk preference among healthy humans (Bechara and Damasio, 2002, Weller et al., 2010), rats (Rivalan et al., 2009), and mice (van Enkhuizen et al, 2014), performing the IGT. Construct validity of the rodent IGT is supported by findings that orbitofrontal cortical lesions exaggerated disadvantageous choices of rats (Rivalan et al., 2011), and decreased orbitofrontal activation is associated with more disadvantageous choices in humans (Jollant et al., 2010, Gorlyn et al., 2013). Importantly, some pharmacological predictive validity is evidenced by the finding that elevating dopamine levels in humans results in increased high-risk preference choices (Linnet et al., 2011), consistent in the between- and within-session tasks in mice (Van Enkhuizen et al., 2013, Van Enkhuizen et al., Accepted). Cocaine treatment in either humans (Verdejo-Garcia et al., 2007) or the between-session task in mice (Pena-Oliver et al., 2014) increased risk-preference behavior in the IGT. Hence, even with the between-session task there is sufficient plasticity in the animal's choice for comparable effects to be seen across species. To date, no studies have been detailed examining the IGT performance of models related to schizophrenia. Future studies could however utilize the rodent IGT to assess decision-making for gains and losses across species, enabling the assessment of putative procognitive treatments to enhance decision making for patients.

Delay Discounting—In delay discounting, high vs. low rewards are offered. Choosing the high reward results in a delay period prior to the reward being made available. Choosing the low reward results in an immediate reward, although the same delay occurs before the next trial can begin. Hence, the task measures a subject's preference for immediate low vs.

tolerance to a delay for a high reward. Patients with schizophrenia exhibit delay discounting deficits, preferring the immediate low reward as opposed to waiting for higher reward values (Heerey et al., 2007, Ahn et al., 2011), although no differences have also been reported when smoking status was taken into account (Mackillop and Tidey, 2011). Certainly, when the individual's consistency of responding (not simply aberrant responses) was assessed, no differences in delay discounting between patients and healthy subjects were reported (Weller et al., 2014). Delay discounting can be measured similarly in rodents whereby behavioral pharmacological effects can readily be tested. For example, nicotine increased choices for the large risky reward in probabilistic discounting while not affecting delay discounting, while scopolamine treatment increased choice of the small immediate reward while not affecting probabilistic discounting (Mitchell et al., 2012). It is interesting to note that ventral medial PFC inactivation did not increase preference for immediate low rewards in rats (Feja and Koch, 2014), despite this region being important for delay-discounting performance especially when encoding small immediate rewards (Sripada et al., 2011). Since ventral medial PFC inactivation in rats increased premature responses in the 5CSRTT (Feja and Koch, 2014), more work may be required to evaluate the validity of this task across species.

Definitive work is also required detailing whether deficits in delay discounting exist in patients with schizophrenia, or whether the deficits stem from delayed learning of the delay/reward contingencies as links to working memory deficits may suggest (Heerey et al., 2007). Finally, any decision-making studies assessing the subject's tolerance for delays should also assess interval-timing capabilities since patients with schizophrenia have poor timing ability that is related to the degree of their illness (Papageorgiou et al., 2013).

Probabilistic choice and risk-decision making—Numerous tasks exist that measure decision making in subjects after stimuli are presented in a probabilistic fashion. For example, when presented with a limited set of stimuli having different probabilistic values, patients with schizophrenia have greater difficulty identifying the more rewarding stimuli, likely as a result of reduced activation of the ventral striatum and ventral tegmental area (Rausch et al., 2014). Some tasks use hypothetical reward values and gambling within the task, demonstrating that deficient performance in patients stems from cognitive deficits (Brown et al., 2013). Several variations of rodent tasks also exist. For example, punishing stimuli (e.g., footshock) can be used instead of the simple absence of a reward. For example, in the risky decision task, rats are presented with a choice of a large or small food reward, where choosing the large reward may result in a mild footshock (Simon et al., 2009). In the probabilistic discounting task however, rats are provided the choice of a large or small food reward, where choosing the large reward may result in no reward (Cardinal et al., 2000, St Onge et al., 2011). In this sense, the probabilistic learning tasks described above could also be used to measure decision making (Bari et al., 2009, Amitai et al., 2013). In human studies, most paradigms will use some form of punishment - e.g., loss of points, but few studies in schizophrenia will use physical punishments. Although a full comparison of every task and result is beyond the scope of this review, it should be noted that care must be taken when interpreting results from rodent studies evaluating 'decision making under risk' to human studies as the task parameters and hence neural mechanisms underlying performance

could be very different. After all, not all decision making will be made equally, with numerous cognitive domains supporting such decisions (Fig. 1).

POINTS TO REMEMBER

When developing pro-cognitive treatments for schizophrenia, several points should also be considered in addition to the research described above. For example, there are many lessons that should be learned for clinical trial studies undertaken so far, e.g., studies may be underpowered, doses were too low, and differing phases of illness examined (Keefe et al., 2013). Hence, the design of clinical trials to test developed treatments are also vital.

In addition, the clinical studies conducted to date were unlikely to have been driven based on the modern research paradigms presented here. Hence, the non-clinical cognitive tasks used to generate evidence of efficacy may not have had relevance to the cognitive domain/construct tested in the clinical study. Another point worthy of note is that a previously neglected domain has been the motivation of subjects - whether patients or rodents - to perform the task. In fact, CNTRICS felt this area worth raising as their meetings progressed, being described from their non-clinical reports (Markou et al., 2013) even though they never appeared in clinical reports. Changes in motivation can alter task performance including during decision-making tasks (Kim et al., 2012). In some rodent studies, measures of motivation are included, e.g., latency to collect reward (Robbins, 2002). In addition, response rate can also be measured as responsivity bias in the 5C-CPT (Young et al., 2009). Hence, secondary measures are included in rodent studies that are not always available in human studies. Such motivational assessments are therefore important to be included.

An important topic not covered in this review has been tasks relevant to investigating social cognition. A critical review of such tasks relevant to the CNTRICS constructs and the issues surrounding their translational value have been described elsewhere however (Millan and Bales, 2013). Given the disparity between tasks used in clinical vs. non-clinical testing, as well as the differences in preferred modality of socializing between species, such studies may continue to prove difficult to bridge between human and animal research (Young et al., 2009). Another cognitive domain that could be targeted is paired associative learning to measure long-term memory (Bussey et al., 2013, Young et al., 2013). The type of memory (e.g., episodic) measured using the paired associate learning task has been linked to the functional outcome of first-episode patients with schizophrenia (Barnett et al, 2005). Such paradigms may also prove useful in future cross-species research.

Simply providing a treatment and expecting enhanced cognition may not be the ideal strategy for patients with schizophrenia whom have had decades living with altered neurochemistry (Swerdlow, 2011). Another strategy for developing cognition enhancers would be to discover methods to enhance cognitive remediation via enhancing, e.g., plasticity (Barak and Weiner, 2011), reward-associative learning (Acheson et al., 2013), or identifying mechanisms linked to positive cognitive remediation effects (Swerdlow, 2011; 2012). A successful example from such an approach includes co-treatments, e.g., cyclodextrine, for cognitive behavioral therapy for anxiety disorders (Hofmann et al., 2013).

Pharmacologically augmenting cognitive training in patients could be an ideal strategy for future drug research (Swerdlow, 2012, Acheson et al., 2013, Gilleen et al., 2014)

A vital aspect of future research - as identified by CNTRICS and others (Carter et al., 2011, Barch et al., 2012, Light et al., 2012, Luck et al., 2012) - will be the use of biomarkers of effects in future studies. Utilizing such biomarkers whereby improvements in performance in a model is linked to altered neural physiology that can be measured in the clinic should become a standard in research. An excellent example of this work stems from observations that modafinil reversed phencyclidine-induced extradimensional shifting deficits of rats in the ASST (Dawson et al., 2012, Pratt et al., 2012; Goetghebeur and Dias, 2009). Such findings are important because modafinil improved attentional set-shifting in patients with chronic schizophrenia (Turner et al., 2004), summarized by Insel [(2013); Figure 2]. Beyond this consistency of behavioral pharmacology however, these authors also demonstrated that phencyclidine also induced hypometabolism in the PFC, which was restored with modafinil treatment (Dawson et al., 2012). Given that the PFC of rats underlies the extradimensional shifting of rats (Birrell and Brown, 2000), and modafinil improves set-shifting in patients with schizophrenia [(Turner et al., 2004); although not in first-episode patients (Scoriels et al., 2013)] these data tie together important neural constructs, with cross-species tasks. Full translation would see set-shifting of patients with schizophrenia being improved in a fMRI setting whereby modafinil enhanced PFC function during task performance. Hence, these studies are possible to conduct and are an example for future researchers.

This review has focused on using rodents as non-clinical subjects to determine the efficacy of pro-cognitive treatments for patients with schizophrenia. While not discussed, it is important to remember that non-human primates (Young et al., 2013) and more often now zebra fish (Stewart et al., 2014) can and are also used for such studies. The relevance of the tasks used in these species for human research warrant future discussions.

Irrespective of the species used, the task selected, or the biomarker data, it is vital to recognize that a pro-cognitive treatment for schizophrenia will likely be co-administered with an antipsychotic (dopamine D_2 receptor antagonist) to patients. Hence, understanding the effects of such treatments on performance of these tasks should be investigated in normal animals in combination with putative therapeutics (Barak and Weiner, 2011). A good example of this work has been conducted by Levin, Rezvani, and colleagues for the SAT (see Attentional Domain). This work will have to be extended to all non-clinical studies. While this work would increase the cost and time of such studies, this cost is little compared to the vast expense of Phase III studies (Keeler and Robbins, 2011, Keefe et al., 2013). Hence, early investment in animal studies may prove beneficial in the long-term in terms of costs, the continuous enrollment of patients in studies, and the benefit of not raising patients' hopes needlessly.

SUMMARY

It is worth reiterating that of primary importance is the understanding that schizophrenia is a disorder characterized by abnormalities of behavior. Quantifying these abnormalities using cross-species relevant tasks would enable the quantification of such behavior in rodents.

This approach would increase the likelihood that the neural substrates underlying these behaviors will be conserved across species. As described by Moore and colleagues (2013), if the cognitive processes of interest are defined, their neural mechanism mapped out, and particularly if they map on to a task quantified in patients, much progress will be made. Cross-species translational research has come to the fore in cognitive neuroscience and the research represented here suggests that while the bridge between non-clinical and clinical research requires finishing, the framework has largely been laid. Finally, the cross-species behavioral framework presented here - while discussed in relation to schizophrenia - will also be relevant for other disorders or in fact in the NIMH Research Domain Criteria (RDoC) initiative, a new way of classifying psychopathology based on dimensions of functioning (Cuthbert and Insel, 2010, Insel et al., 2010, Morris and Cuthbert, 2012, Insel, 2014).

Acknowledgements

We thank Drs. Marder, Green, Barch, and Carter for their support during MIRECC and CNTRICS meetings. The authors have been supported by NIH grants R01-MH071916, R01-MH104344, and R01-MH042228, as well as by the Veteran's Administration VISN 22 Mental Illness Research, Education, and Clinical Center.

REFERENCES

Acheson DT, Twamley EW, Young JW. Reward Learning as a Potential Target for Pharmacological Augmentation of Cognitive Remediation for Schizophrenia: A Roadmap for Preclinical Development. Front Neurosci. 2013; 7:103. [PubMed: 23785309]

Adida M, Jollant F, Clark L, Besnier N, Guillaume S, Kaladjian A, Mazzola-Pomietto P, Jeanningros R, Goodwin GM, Azorin JM, Courtet P. Trait-Related Decision-Making Impairment in the Three Phases of Bipolar Disorder. Biol Psychiatry. 2011; 70:357–365. [PubMed: 21429477]

Ahn WY, Rass O, Fridberg DJ, Bishara a J, Forsyth JK, Breier A, Busemeyer JR, Hetrick WP, Bolbecker a R, O'donnell BF. Temporal Discounting of Rewards in Patients with Bipolar Disorder and Schizophrenia. J Abnorm Psychol. 2011; 120:911–921. [PubMed: 21875166]

Ahnallen CG, Liverant GI, Gregor KL, Kamholz BW, Levitt JJ, Gulliver SB, Pizzagalli DA, Koneru VK, Kaplan GB. The Relationship between Reward-Based Learning and Nicotine Dependence in Smokers with Schizophrenia. Psychiatry Res. 2012; 196:9–14. [PubMed: 22342123]

Amitai N, Young JW, Higa K, Sharp RF, Geyer MA, Powell SB. Isolation Rearing Effects on Probabilistic Learning and Cognitive Flexibility in Rats. Cogn Affect Behav Neurosci. 2013

Andre JM, Cordero KA, Gould TJ. Comparison of the Performance of Dba/2 and C57bl/6 Mice in Transitive Inference and Foreground and Background Contextual Fear Conditioning. Behav Neurosci. 2012; 126:249–257. [PubMed: 22309443]

Ardila A. On the Evolutionary Origins of Executive Functions. Brain Cogn. 2008; 68:92–99. [PubMed: 18397818]

Armstrong K, Kose S, Williams L, Woolard A, Heckers S. Impaired Associative Inference in Patients with Schizophrenia. Schizophr Bull. 2012; 38:622–629. [PubMed: 21134974]

Armstrong K, Williams LE, Heckers S. Revised Associative Inference Paradigm Confirms Relational Memory Impairment in Schizophrenia. Neuropsychology. 2012; 26:451–458. [PubMed: 22612578]

Arnsten, a F.; Cai, JX.; Murphy, BL.; Goldman-Rakic, PS. Dopamine D1 Receptor Mechanisms in the Cognitive Performance of Young Adult and Aged Monkeys. Psychopharmacology (Berl). 1994; 116:143–151. [PubMed: 7862943]

Aron, a R.; Poldrack, RA. The Cognitive Neuroscience of Response Inhibition: Relevance for Genetic Research in Attention-Deficit/Hyperactivity Disorder. Biol Psychiatry. 2005; 57:1285–1292. [PubMed: 15950000]

Aron, a R.; Poldrack, RA. Cortical and Subcortical Contributions to Stop Signal Response Inhibition: Role of the Subthalamic Nucleus. J Neurosci. 2006; 26:2424–2433. [PubMed: 16510720]

Astur RS, St Germain SA, Baker EK, Calhoun V, Pearlson GD, Constable RT. Fmri Hippocampal Activity During a Virtual Radial Arm Maze. Appl Psychophysiol Biofeedback. 2005; 30:307–317. [PubMed: 16167193]

Astur RS, Tropp J, Sava S, Constable RT, Markus EJ. Sex Differences and Correlations in a Virtual Morris Water Task, a Virtual Radial Arm Maze, and Mental Rotation. Behav Brain Res. 2004; 151:103–115. [PubMed: 15084426]

Baarendse PJ, Winstanley CA, Vanderschuren LJ. Simultaneous Blockade of Dopamine and Noradrenaline Reuptake Promotes Disadvantageous Decision Making in a Rat Gambling Task. Psychopharmacology (Berl). 2013; 225:719–731. [PubMed: 22968659]

Baddeley A. Working Memory: The Interface between Memory and Cognition. J Cogn Neurosci. 1992; 4:281–288. [PubMed: 23964884]

Baddeley, a D. Working Memory. Oxford University Press; Oxford: 1986.

Barak S, Weiner I. Putative Cognitive Enhancers in Preclinical Models Related to Schizophrenia: The Search for an Elusive Target. Pharmacol Biochem Behav. 2011; 99:164–189. [PubMed: 21420999]

Barch DM, Berman MG, Engle R, Jones JH, Jonides J, Macdonald a 3rd, Nee DE, Redick TS, Sponheim SR. Cntrics Final Task Selection: Working Memory. Schizophr Bull. 2009; 35:136–152. [PubMed: 18990711]

Barch DM, Braver TS, Carter CS, Poldrack RA, Robbins TW. Cntrics Final Task Selection: Executive Control. Schizophr Bull. 2009; 35:115–135. [PubMed: 19011235]

Barch DM, Carter CS, Arnsten A, Buchanan RW, Cohen JD, Geyer M, Green MF, Krystal JH, Nuechterlein K, Robbins T, Silverstein S, Smith EE, Strauss M, Wykes T, Heinssen R. Selecting Paradigms from Cognitive Neuroscience for Translation into Use in Clinical Trials: Proceedings of the Third Cntrics Meeting. Schizophr Bull. 2009; 35:109–114. [PubMed: 19023126]

Barch DM, Moore H, Nee DE, Manoach DS, Luck SJ. Cntrics Imaging Biomarkers Selection: Working Memory. Schizophr Bull. 2012; 38:43–52. [PubMed: 22080498]

Barense MD, Fox MT, Baxter MG. Aged Rats Are Impaired on an Attentional Set-Shifting Task Sensitive to Medial Frontal Cortex Damage in Young Rats. Learn Mem. 2002; 9:191–201. [PubMed: 12177232]

Bari A, Eagle DM, Mar a C, Robinson ES, Robbins TW. Dissociable Effects of Noradrenaline, Dopamine, and Serotonin Uptake Blockade on Stop Task Performance in Rats. Psychopharmacology (Berl). 2009; 205:273–283. [PubMed: 19404616]

Bari A, Robbins TW. Noradrenergic Versus Dopaminergic Modulation of Impulsivity, Attention and Monitoring Behaviour in Rats Performing the Stop-Signal Task: Possible Relevance to Adhd. Psychopharmacology (Berl). 2013; 230:89–111. [PubMed: 23681165]

Barnes SA, Young JW, Neill JC. D(1) Receptor Activation Improves Vigilance in Rats as Measured by the 5-Choice Continuous Performance Test. Psychopharmacology (Berl). 2012; 220:129–141. [PubMed: 21901319]

Barnes SA, Young JW, Neill JC. Rats Tested after a Washout Period from Sub-Chronic Pcp Administration Exhibited Impaired Performance in the 5-Choice Continuous Performance Test (5c-Cpt) When the Attentional Load Was Increased. Neuropharmacology. 2012; 62:1432–1441. [PubMed: 21569782]

Barnett JH, Robbins TW, Leeson VC, Sahakian BJ, Joyce EM, Blackwell a D. Assessing Cognitive Function in Clinical Trials of Schizophrenia. Neurosci Biobehav Rev. 2010; 34:1161–1177. [PubMed: 20105440]

Bechara A, Damasio a R, Damasio H, Anderson SW. Insensitivity to Future Consequences Following Damage to Human Prefrontal Cortex. Cognition. 1994; 50:7–15. [PubMed: 8039375]

Bechara A, Damasio H. Decision-Making and Addiction (Part I): Impaired Activation of Somatic States in Substance Dependent Individuals When Pondering Decisions with Negative Future Consequences. Neuropsychologia. 2002; 40:1675–1689. [PubMed: 11992656]

Bencherif M, Stachowiak MK, Kucinski a J, Lippiello PM. Alpha7 Nicotinic Cholinergic Neuromodulation May Reconcile Multiple Neurotransmitter Hypotheses of Schizophrenia. Med Hypotheses. 2012; 78:594–600. [PubMed: 22336089]

Birrell JM, Brown VJ. Medial Frontal Cortex Mediates Perceptual Attentional Set Shifting in the Rat. J Neurosci. 2000; 20:4320–4324. [PubMed: 10818167]

Bissonette GB, Martins GJ, Franz TM, Harper ES, Schoenbaum G, Powell EM. Double Dissociation of the Effects of Medial and Orbital Prefrontal Cortical Lesions on Attentional and Affective Shifts in Mice. J Neurosci. 2008; 28:11124–11130. [PubMed: 18971455]

Brambilla P, Perlini C, Bellani M, Tomelleri L, Ferro A, Cerruti S, Marinelli V, Rambaldelli G, Christodoulou T, Jogia J, Dima D, Tansella M, Balestrieri M, Frangou S. Increased Salience of Gains Versus Decreased Associative Learning Differentiate Bipolar Disorder from Schizophrenia During Incentive Decision Making. Psychological Medicine. 2012:1–10.

Brown EC, Wiersema JR, Pourtois G, Brune M. Modulation of Motor Cortex Activity When Observing Rewarding and Punishing Actions. Neuropsychologia. 2013; 51:52–58. [PubMed: 23159701]

Buchanan RW, Davis M, Goff D, Green MF, Keefe RS, Leon a C, Nuechterlein KH, Laughren T, Levin R, Stover E, Fenton W, Marder SR. A Summary of the Fda-Nimh-Matrics Workshop on Clinical Trial Design for Neurocognitive Drugs for Schizophrenia. Schizophr Bull. 2005; 31:5–19. [PubMed: 15888422]

Bunsey M, Eichenbaum H. Conservation of Hippocampal Memory Function in Rats and Humans. Nature. 1996; 379:255–257. [PubMed: 8538790]

Bushnell PJ, Kelly KL, Crofton KM. Effects of Toluene Inhalation on Detection of Auditory Signals in Rats. Neurotoxicol Teratol. 1994; 16:149–160. [PubMed: 8052189]

Bussey TJ, Barch DM, Baxter MG. Testing Long-Term Memory in Animal Models of Schizophrenia: Suggestions from Cntrics. Neurosci Biobehav Rev. 2013; 37:2141–2148. [PubMed: 23792049]

Butler PD, Chen Y, Ford JM, Geyer MA, Silverstein SM, Green MF. Perceptual Measurement in Schizophrenia: Promising Electrophysiology and Neuroimaging Paradigms from Cntrics. Schizophr Bull. 2012; 38:81–91. [PubMed: 21890745]

Cardinal RN, Robbins TW, Everitt BJ. The Effects of D-Amphetamine, Chlordiazepoxide, Alpha-Flupenthixol and Behavioural Manipulations on Choice of Signalled and Unsignalled Delayed Reinforcement in Rats. Psychopharmacology (Berl). 2000; 152:362–375. [PubMed: 11140328]

Carpenter WT, Koenig JI. The Evolution of Drug Development in Schizophrenia: Past Issues and Future Opportunities. Neuropsychopharmacology. 2008; 33:2061–2079. [PubMed: 18046305]

Carter CS. Applying New Approaches from Cognitive Neuroscience to Enhance Drug Development for the Treatment of Impaired Cognition in Schizophrenia. Schizophr Bull. 2005; 31:810–815. [PubMed: 16107584]

Carter CS, Barch DM. Cognitive Neuroscience-Based Approaches to Measuring and Improving Treatment Effects on Cognition in Schizophrenia: The Cntrics Initiative. Schizophr Bull. 2007; 33:1131–1137. [PubMed: 17630405]

Carter CS, Barch DM, Bullmore E, Breiling J, Buchanan RW, Butler P, Cohen JD, Geyer M, Gollub R, Green MF, Jaeger J, Krystal JH, Moore H, Nuechterlein K, Robbins T, Silverstein S, Smith EE, Strauss M, Wykes T. Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia Ii: Developing Imaging Biomarkers to Enhance Treatment Development for Schizophrenia and Related Disorders. Biol Psychiatry. 2011; 70:7–12. [PubMed: 21529781]

Carter CS, Minzenberg M, West R, Macdonald a 3rd. Cntrics Imaging Biomarker Selections: Executive Control Paradigms. Schizophr Bull. 2012; 38:34–42. [PubMed: 22114099]

Cassidy F, Forest K, Murry E, Carroll BJ. A Factor Analysis of the Signs and Symptoms of Mania. Arch Gen Psychiatry. 1998; 55:27–32. [PubMed: 9435757]

Cavanagh JF, Sanguinetti JL, Allen JJ, Sherman SJ, Frank MJ. The Subthalamic Nucleus Contributes to Post-Error Slowing. J Cogn Neurosci. 2014

Ceaser, a E.; Goldberg, TE.; Egan, MF.; Mcmahon, RP.; Weinberger, DR.; Gold, JM. Set-Shifting Ability and Schizophrenia: A Marker of Clinical Illness or an Intermediate Phenotype? Biol Psychiatry. 2008; 64:782–788. [PubMed: 18597738]

Chouinard S, Stip E, Poulin J, Melun JP, Godbout R, Guillem F, Cohen H. Rivastigmine Treatment as an Add-on to Antipsychotics in Patients with Schizophrenia and Cognitive Deficits. Curr Med Res Opin. 2007; 23:575–583. [PubMed: 17355738]

Christodoulou T, Lewis M, Ploubidis GB, Frangou S. The Relationship of Impulsivity to Response Inhibition and Decision-Making in Remitted Patients with Bipolar Disorder. Eur Psychiatry. 2006; 21:270–273. [PubMed: 16762532]

Coleman MJ, Titone D, Krastoshevsky O, Krause V, Huang Z, Mendell NR, Eichenbaum H, Levy DL. Reinforcement Ambiguity and Novelty Do Not Account for Transitive Inference Deficits in Schizophrenia. Schizophr Bull. 2010; 36:1187–1200. [PubMed: 19460878]

Cornblatt B, Obuchowski M, Schnur DB, O'brien JD. Attention and Clinical Symptoms in Schizophrenia. Psychiatr Q. 1997; 68:343–359. [PubMed: 9355134]

Cornblatt BA, Keilp JG. Impaired Attention, Genetics, and the Pathophysiology of Schizophrenia. Schizophr Bull. 1994; 20:31–46. [PubMed: 8197420]

Costa E. Building a Bridge between Neurobiology and Mental Illness. J Psychiatr Res. 1992; 26:449–460. [PubMed: 1337107]

Cuthbert BN, Insel TR. Toward New Approaches to Psychotic Disorders: The Nimh Research Domain Criteria Project. Schizophr Bull. 2010; 36:1061–1062. [PubMed: 20929969]

D'souza DC, Ahn K, Bhakta S, Elander J, Singh N, Nadim H, Jatlow P, Suckow RF, Pittman B, Ranganathan M. Nicotine Fails to Attenuate Ketamine-Induced Cognitive Deficits and Negative and Positive Symptoms in Humans: Implications for Schizophrenia. Biol Psychiatry. 2012; 72:785–794. [PubMed: 22717030]

Dalton GL, Phillips a G, Floresco SB. Preferential Involvement by Nucleus Accumbens Shell in Mediating Probabilistic Learning and Reversal Shifts. J Neurosci. 2014; 34:4618–4626. [PubMed: 24672007]

Dawson N, Thompson RJ, Mcvie A, Thomson DM, Morris BJ, Pratt JA. Modafinil Reverses Phencyclidine-Induced Deficits in Cognitive Flexibility, Cerebral Metabolism, and Functional Brain Connectivity. Schizophr Bull. 2012; 38:457–474. [PubMed: 20810469]

De Visser L, Homberg JR, Mitsogiannis M, Zeeb FD, Rivalan M, Fitoussi A, Galhardo V, Van Den Bos R, Winstanley CA, Dellu-Hagedorn F. Rodent Versions of the Iowa Gambling Task: Opportunities and Challenges for the Understanding of Decision-Making. Front Neurosci. 2011; 5:109. [PubMed: 22013406]

Demeter E, Guthrie SK, Taylor SF, Sarter M, Lustig C. Increased Distractor Vulnerability but Preserved Vigilance in Patients with Schizophrenia: Evidence from a Translational Sustained Attention Task. Schizophr Res. 2013; 144:136–141. [PubMed: 23374860]

Demeter E, Hernandez-Garcia L, Sarter M, Lustig C. Challenges to Attention: A Continuous Arterial Spin Labeling (Asl) Study of the Effects of Distraction on Sustained Attention. Neuroimage. 2011; 54:1518–1529. [PubMed: 20851189]

Devito LM, Balu DT, Kanter BR, Lykken C, Basu a C, Coyle JT, Eichenbaum H. Serine Racemase Deletion Disrupts Memory for Order and Alters Cortical Dendritic Morphology. Genes Brain Behav. 2011; 10:210–222. [PubMed: 21029376]

Devito LM, Kanter BR, Eichenbaum H. The Hippocampus Contributes to Memory Expression During Transitive Inference in Mice. Hippocampus. 2010; 20:208–217. [PubMed: 19405137]

Devito LM, Konigsberg R, Lykken C, Sauvage M, Young WS 3rd, Eichenbaum H. Vasopressin 1b Receptor Knock-out Impairs Memory for Temporal Order. J Neurosci. 2009; 29:2676–2683. [PubMed: 19261862]

Devito LM, Lykken C, Kanter BR, Eichenbaum H. Prefrontal Cortex: Role in Acquisition of Overlapping Associations and Transitive Inference. Learn Mem. 2010; 17:161–167. [PubMed: 20189961]

Dowd EC, Barch DM. Pavlovian Reward Prediction and Receipt in Schizophrenia: Relationship to Anhedonia. PLoS One. 2012; 7:e35622. [PubMed: 22574121]

Dudchenko PA. An Overview of the Tasks Used to Test Working Memory in Rodents. Neurosci Biobehav Rev. 2004; 28:699–709. [PubMed: 15555679]

Dudchenko PA, Talpos J, Young J, Baxter MG. Animal Models of Working Memory: A Review of Tasks That Might Be Used in Screening Drug Treatments for the Memory Impairments Found in Schizophrenia. Neurosci Biobehav Rev. 2013; 37:2111–2124. [PubMed: 22464948]

Dudchenko PA, Wood ER, Eichenbaum H. Neurotoxic Hippocampal Lesions Have No Effect on Odor Span and Little Effect on Odor Recognition Memory but Produce Significant Impairments on

Spatial Span, Recognition, and Alternation. J Neurosci. 2000; 20:2964–2977. [PubMed: 10751449]

Eagle DM, Baunez C. Is There an Inhibitory-Response-Control System in the Rat? Evidence from Anatomical and Pharmacological Studies of Behavioral Inhibition. Neurosci Biobehav Rev. 2010; 34:50–72. [PubMed: 19615404]

Eagle DM, Baunez C, Hutcheson DM, Lehmann O, Shah a P, Robbins TW. Stop-Signal Reaction-Time Task Performance: Role of Prefrontal Cortex and Subthalamic Nucleus. Cereb Cortex. 2008; 18:178–188. [PubMed: 17517682]

Eagle DM, Robbins TW. Lesions of the Medial Prefrontal Cortex or Nucleus Accumbens Core Do Not Impair Inhibitory Control in Rats Performing a Stop-Signal Reaction Time Task. Behav Brain Res. 2003; 146:131–144. [PubMed: 14643466]

Eagle DM, Tufft MR, Goodchild HL, Robbins TW. Differential Effects of Modafinil and Methylphenidate on Stop-Signal Reaction Time Task Performance in the Rat, and Interactions with the Dopamine Receptor Antagonist Cis-Flupenthixol. Psychopharmacology (Berl). 2007; 192:193–206. [PubMed: 17277934]

Eichenbaum H. Hippocampus: Mapping or Memory? Curr Biol. 2000; 10:R785–787. [PubMed: 11084350]

Ellenbroek BA, Cools a R. Animal Models for the Negative Symptoms of Schizophrenia. Behav Pharmacol. 2000; 11:223–233. [PubMed: 11103877]

Fagerlund B, Soholm B, Fink-Jensen A, Lublin H, Glenthoj BY. Effects of Donepezil Adjunctive Treatment to Ziprasidone on Cognitive Deficits in Schizophrenia: A Double-Blind, Placebo-Controlled Study. Clin Neuropharmacol. 2007; 30:3–12. [PubMed: 17272964]

Feja M, Koch M. Ventral Medial Prefrontal Cortex Inactivation Impairs Impulse Control but Does Not Affect Delay-Discounting in Rats. Behav Brain Res. 2014; 264:230–239. [PubMed: 24556205]

Floresco SB, Geyer MA, Gold LH, Grace a A. Developing Predictive Animal Models and Establishing a Preclinical Trials Network for Assessing Treatment Effects on Cognition in Schizophrenia. Schizophr Bull. 2005; 31:888–894. [PubMed: 16079387]

Fond G, Bayard S, Capdevielle D, Del-Monte J, Mimoun N, Macgregor A, Boulenger JP, Gely-Nargeot MC, Raffard S. A Further Evaluation of Decision-Making under Risk and under Ambiguity in Schizophrenia. European Archives of Psychiatry & Clinical Neuroscience. 2012

Foulds J, Stapleton J, Swettenham J, Bell N, Mcsorley K, Russell MA. Cognitive Performance Effects of Subcutaneous Nicotine in Smokers and Never-Smokers. Psychopharmacology (Berl). 1996; 127:31–38. [PubMed: 8880941]

Friedman JI. Cholinergic Targets for Cognitive Enhancement in Schizophrenia: Focus on Cholinesterase Inhibitors and Muscarinic Agonists. Psychopharmacology (Berl). 2004; 174:45–53. [PubMed: 15205878]

Funahashi S, Bruce CJ, Goldman-Rakic PS. Mnemonic Coding of Visual Space in the Monkey's Dorsolateral Prefrontal Cortex. J Neurophysiol. 1989; 61:331–349. [PubMed: 2918358]

Geyer, MA.; Braff, D.; Swerdlow, NR. Startle-Response Measures of Information Processing in Animals. In: Haug, M.; Whalen, Re, editors. Animal Models of Human Emotion & Cognition. APA Books; Washington D.C.: 1999.

Geyer MA, Braff DL. Startle Habituation and Sensorimotor Gating in Schizophrenia and Related Animal Models. Schizophr Bull. 1987; 13:643–668. [PubMed: 3438708]

Geyer, MA.; Gross, G. Novel Antischizophrenia Treatments. Vol. 213 . Springer-Verlag Berlin; Heidelberg: 2012.

Geyer, MA.; Markou, A. Animal Models of Psychiatric Disorders. In: Bloom, Fe; Kupfer, D., editors. Psychopharmacology: The Fourth Generation of Progress. Raven Press; New York: 1995.

Geyer MA, Olivier B, Joels M, Kahn RS. From Antipsychotic to Anti-Schizophrenia Drugs: Role of Animal Models. Trends Pharmacol Sci. 2012; 33:515–521. [PubMed: 22810174]

Geyer MA, Wilkinson LS, Humby T, Robbins TW. Isolation Rearing of Rats Produces a Deficit in Prepulse Inhibition of Acoustic Startle Similar to That in Schizophrenia. Biol Psychiatry. 1993; 34:361–372. [PubMed: 8218603]

Gibbs SE, D'esposito M. A Functional Magnetic Resonance Imaging Study of the Effects of Pergolide, a Dopamine Receptor Agonist, on Component Processes of Working Memory. Neuroscience. 2006; 139:359–371. [PubMed: 16458442]

Gilleen J, Michalopoulou PG, Reichenberg A, Drake R, Wykes T, Lewis SW, Kapur S. Modafinil Combined with Cognitive Training Is Associated with Improved Learning in Healthy Volunteers--a Randomised Controlled Trial. Eur Neuropsychopharmacol. 2014; 24:529–539. [PubMed: 24485800]

Gilmour G, Arguello A, Bari A, Brown VJ, Carter C, Floresco SB, Jentsch DJ, Tait DS, Young JW, Robbins TW. Measuring the Construct of Executive Control in Schizophrenia: Defining and Validating Translational Animal Paradigms for Discovery Research. Neurosci Biobehav Rev. 2013; 37:2125–2140. [PubMed: 22548905]

Glassman RB, Garvey KJ, Elkins KM, Kasal KL, Couillard NL. Spatial Working Memory Score of Humans in a Large Radial Maze, Similar to Published Score of Rats, Implies Capacity Close to the Magical Number 7 +/− 22. Brain Res Bull. 1994; 34:151–159. [PubMed: 8044689]

Goetghebeur P, Dias R. Comparison of Haloperidol, Risperidone, Sertindole, and Modafinil to Reverse an Attentional Set-Shifting Impairment Following Subchronic Pcp Administration in the Rat--a Back Translational Study. Psychopharmacology (Berl). 2009; 202:287–293. [PubMed: 18392753]

Goetghebeur P, Dias R. Comparison of Haloperidol, Risperidone, Sertindole, and Modafinil to Reverse an Attentional Set-Shifting Impairment Following Subchronic Pcp Administration in the Rat-a Back Translational Study. Psychopharmacology (Berl). 2009; 202:287–293. [PubMed: 18392753]

Gold JM, Hahn B, Zhang WW, Robinson BM, Kappenman ES, Beck VM, Luck SJ. Reduced Capacity but Spared Precision and Maintenance of Working Memory Representations in Schizophrenia. Arch Gen Psychiatry. 2010; 67:570–577. [PubMed: 20530006]

Goldman-Rakic PS, Castner SA, Svensson TH, Siever LJ, Williams GV. Targeting the Dopamine D1 Receptor in Schizophrenia: Insights for Cognitive Dysfunction. Psychopharmacology (Berl). 2004; 174:3–16. [PubMed: 15118803]

Goodrich-Hunsaker NJ, Hopkins RO. Spatial Memory Deficits in a Virtual Radial Arm Maze in Amnesic Participants with Hippocampal Damage. Behav Neurosci. 2010; 124:405–413. [PubMed: 20528085]

Gorlyn M, Keilp JG, Oquendo MA, Burke a K, John Mann J. Iowa Gambling Task Performance in Currently Depressed Suicide Attempters. Psychiatry Res. 2013; 207:150–157. [PubMed: 23489594]

Green MF. What Are the Functional Consequences of Neurocognitive Deficits in Schizophrenia? Am J Psychiatry. 1996; 153:321–330. [PubMed: 8610818]

Green MF. Cognitive Impairment and Functional Outcome in Schizophrenia and Bipolar Disorder. J Clin Psychiatry. 2006; 67(Suppl 9):3–8. discussion 36–42. [PubMed: 16965182]

Green MF, Butler PD, Chen Y, Geyer MA, Silverstein S, Wynn JK, Yoon JH, Zemon V. Perception Measurement in Clinical Trials of Schizophrenia: Promising Paradigms from Cntrics. Schizophr Bull. 2009; 35:163–181. [PubMed: 19023123]

Green MF, Nuechterlein KH. The Matrics Initiative: Developing a Consensus Cognitive Battery for Clinical Trials. Schizophr Res. 2004; 72:1–3. [PubMed: 15531401]

Gu H, Liu C, Chen M, Zhang Q, Zhai J, Wang K, Ji F, Xu Z, Shen Q, Bao X, Chen X, Li J, Dong Q, Chen C. The Combined Effects of the 5- Httlpr and Htr1a Rs6295 Polymorphisms Modulate Decision Making in Schizophrenia Patients. Genes Brain Behav. 2013; 12:133–139. [PubMed: 23036158]

Hahn B, Robinson BM, Harvey a N, Kaiser ST, Leonard CJ, Luck SJ, Gold JM. Visuospatial Attention in Schizophrenia: Deficits in Broad Monitoring. J Abnorm Psychol. 2012; 121:119–128. [PubMed: 21604825]

Harms LR, Turner KM, Eyles DW, Young JW, Mcgrath JJ, Burne TH. Attentional Processing in C57bl/6j Mice Exposed to Developmental Vitamin D Deficiency. PLoS One. 2012; 7:e35896. [PubMed: 22563415]

Harrison, a A.; Everitt, BJ.; Robbins, TW. Doubly Dissociable Effects of Median- and Dorsal-Raphe Lesions on the Performance of the Five-Choice Serial Reaction Time Test of Attention in Rats. Behav Brain Res. 1997; 89:135–149. [PubMed: 9475622]

Harvey PD, Keefe RS. Studies of Cognitive Change in Patients with Schizophrenia Following Novel Antipsychotic Treatment. Am J Psychiatry. 2001; 158:176–184. [PubMed: 11156796]

Heerey EA, Robinson BM, Mcmahon RP, Gold JM. Delay Discounting in Schizophrenia. Cogn Neuropsychiatry. 2007; 12:213–221. [PubMed: 17453902]

Hilti CC, Delko T, Orosz a T, Thomann K, Ludewig S, Geyer MA, Vollenweider FX, Feldon J, Cattapan-Ludewig K. Sustained Attention and Planning Deficits but Intact Attentional Set-Shifting in Neuroleptic-Naive First-Episode Schizophrenia Patients. Neuropsychobiology. 2010; 61:79–86. [PubMed: 20016226]

Hodges H. Maze Procedures: The Radial-Arm and Water Maze Compared. Brain Res Cogn Brain Res. 1996; 3:167–181. [PubMed: 8806020]

Hofmann SG, Asmundson GJ, Beck a T. The Science of Cognitive Therapy. Behav Ther. 2013; 44:199–212. [PubMed: 23611069]

Howe WM, Ji J, Parikh V, Williams S, Mocaer E, Trocme-Thibierge C, Sarter M. Enhancement of Attentional Performance by Selective Stimulation of Alpha4beta2(*) Nachrs: Underlying Cholinergic Mechanisms. Neuropsychopharmacology. 2010; 35:1391–1401. [PubMed: 20147893]

Humby T, Eddy JB, Good MA, Reichelt a C, Wilkinson LS. A Novel Translational Assay of Response Inhibition and Impulsivity: Effects of Prefrontal Cortex Lesions, Drugs Used in Adhd, and Serotonin 2c Receptor Antagonism. Neuropsychopharmacology. 2013; 38:2150–2159. [PubMed: 23657439]

Huys QJ, Pizzagalli DA, Bogdan R, Dayan P. Mapping Anhedonia onto Reinforcement Learning: A Behavioural Meta-Analysis. Biol Mood Anxiety Disord. 2013; 3:12. [PubMed: 23782813]

Hyman SE, Fenton WS. Medicine. What Are the Right Targets for Psychopharmacology? Science. 2003; 299:350–351. [PubMed: 12532001]

Ineichen C, Sigrist H, Spinelli S, Lesch KP, Sautter E, Seifritz E, Pryce CR. Establishing a Probabilistic Reversal Learning Test in Mice: Evidence for the Processes Mediating Reward-Stay and Punishment-Shift Behaviour and for Their Modulation by Serotonin. Neuropharmacology. 2012; 63:1012–1021. [PubMed: 22824190]

Insel T, Cuthbert B, Garvey M, Heinssen R, Pine DS, Quinn K, Sanislow C, Wang P. Research Domain Criteria (Rdoc): Toward a New Classification Framework for Research on Mental Disorders. Am J Psychiatry. 2010; 167:748–751. [PubMed: 20595427]

Insel T, Krystal J, Ehlers M. New Drug Development for Cognitive Enhancement in Mental Health: Challenges and Opportunities. Neuropharmacology. 2013; 64:2–7. [PubMed: 23145450]

Insel TR. The Nimh Research Domain Criteria (Rdoc) Project: Precision Medicine for Psychiatry. Am J Psychiatry. 2014; 171:395–397. [PubMed: 24687194]

Jollant F, Guillaume S, Jaussent I, Bellivier F, Leboyer M, Castelnau D, Malafosse A, Courtet P. Psychiatric Diagnoses and Personality Traits Associated with Disadvantageous Decision-Making. Eur Psychiatry. 2007; 22:455–461. [PubMed: 17764910]

Jollant F, Lawrence NS, Olie E, O'daly O, Malafosse A, Courtet P, Phillips ML. Decreased Activation of Lateral Orbitofrontal Cortex During Risky Choices under Uncertainty Is Associated with Disadvantageous Decision-Making and Suicidal Behavior. Neuroimage. 2010; 51:1275–1281. [PubMed: 20302946]

Jurado MB, Rosselli M. The Elusive Nature of Executive Functions: A Review of Our Current Understanding. Neuropsychol Rev. 2007; 17:213–233. [PubMed: 17786559]

Keefe RS, Bilder RM, Davis SM, Harvey PD, Palmer BW, Gold JM, Meltzer HY, Green MF, Capuano G, Stroup TS, Mcevoy JP, Swartz MS, Rosenheck RA, Perkins DO, Davis CE, Hsiao JK, Lieberman JA. Neurocognitive Effects of Antipsychotic Medications in Patients with Chronic Schizophrenia in the Catie Trial. Arch Gen Psychiatry. 2007; 64:633–647. [PubMed: 17548746]

Keefe RS, Buchanan RW, Marder SR, Schooler NR, Dugar A, Zivkov M, Stewart M. Clinical Trials of Potential Cognitive-Enhancing Drugs in Schizophrenia: What Have We Learned So Far? Schizophr Bull. 2013; 39:417–435. [PubMed: 22114098]

Keeler JF, Robbins TW. Translating Cognition from Animals to Humans. Biochem Pharmacol. 2011; 81:1356–1366. [PubMed: 21219876]

Kim YT, Sohn H, Kim S, Oh J, Peterson BS, Jeong J. Disturbances of Motivational Balance in Chronic Schizophrenia During Decision-Making Tasks. Psychiatry Clin Neurosci. 2012; 66:573–581. [PubMed: 23252923]

Kraepelin, E. Dementia Praecox. 1896.

Lawrence, a D.; Sahakian, BJ.; Rogers, RD.; Hodge, JR.; Robbins, TW. Discrimination, Reversal, and Shift Learning in Huntington's Disease: Mechanisms of Impaired Response Selection. Neuropsychologia. 1999; 37:1359–1374. [PubMed: 10606011]

Lee JY, Kho S, Yoo HB, Park S, Choi JS, Kwon JS, Cha KR, Jung HY. Spatial Memory Impairments in Amnestic Mild Cognitive Impairment in a Virtual Radial Arm Maze. Neuropsychiatr Dis Treat. 2014; 10:653–660. [PubMed: 24790448]

Lett TA, Voineskos a N, Kennedy JL, Levine B, Daskalakis ZJ. Treating Working Memory Deficits in Schizophrenia: A Review of the Neurobiology. Biol Psychiatry. 2014; 75:361–370. [PubMed: 24011822]

Levin ED. Nicotinic Receptor Subtypes and Cognitive Function. J Neurobiol. 2002; 53:633–640. [PubMed: 12436426]

Levin ED, Conners CK, Silva D, Hinton SC, Meck WH, March J, Rose JE. Transdermal Nicotine Effects on Attention. Psychopharmacology (Berl). 1998; 140:135–141. [PubMed: 9860103]

Levin ED, Lee C, Rose JE, Reyes A, Ellison G, Jarvik M, Gritz E. Chronic Nicotine and Withdrawal Effects on Radial-Arm Maze Performance in Rats. Behav Neural Biol. 1990; 53:269–276. [PubMed: 2331235]

Levin ED, Petro A, Rezvani a H, Pollard N, Christopher NC, Strauss M, Avery J, Nicholson J, Rose JE. Nicotinic Alpha7- or Beta2-Containing Receptor Knockout: Effects on Radial-Arm Maze Learning and Long-Term Nicotine Consumption in Mice. Behav Brain Res. 2009; 196:207–213. [PubMed: 18831991]

Lieberman JA, Sheitman BB, Kinon BJ. Neurochemical Sensitization in the Pathophysiology of Schizophrenia: Deficits and Dysfunction in Neuronal Regulation and Plasticity. Neuropsychopharmacology. 1997; 17:205–229. [PubMed: 9326746]

Light GA, Swerdlow NR. Neurophysiological Biomarkers Informing the Clinical Neuroscience of Schizophrenia: Mismatch Negativity and Prepulse Inhibition of Startle. Curr Top Behav Neurosci. 2014

Light GA, Swerdlow NR, Rissling a J, Radant A, Sugar CA, Sprock J, Pela M, Geyer MA, Braff DL. Characterization of Neurophysiologic and Neurocognitive Biomarkers for Use in Genomic and Clinical Outcome Studies of Schizophrenia. PLoS One. 2012; 7:e39434. [PubMed: 22802938]

Linnet J, Moller A, Peterson E, Gjedde A, Doudet D. Dopamine Release in Ventral Striatum During Iowa Gambling Task Performance Is Associated with Increased Excitement Levels in Pathological Gambling. Addiction. 2011; 106:383–390. [PubMed: 20883460]

Lipska BK, Swerdlow NR, Geyer MA, Jaskiw GE, Braff DL, Weinberger DR. Neonatal Excitotoxic Hippocampal Damage in Rats Causes Post-Pubertal Changes in Prepulse Inhibition of Startle and Its Disruption by Apomorphine. Psychopharmacology (Berl). 1995; 122:35–43. [PubMed: 8711062]

Lipska BK, Weinberger DR. Genetic Variation in Vulnerability to the Behavioral Effects of Neonatal Hippocampal Damage in Rats. Proc Natl Acad Sci U S A. 1995; 92:8906–8910. [PubMed: 7568041]

Logan GD, Cowan WB, Davis KA. On the Ability to Inhibit Simple and Choice Reaction Time Responses: A Model and a Method. J Exp Psychol Hum Percept Perform. 1984; 10:276–291. [PubMed: 6232345]

Luck SJ, Ford JM, Sarter M, Lustig C. Cntrics Final Biomarker Selection: Control of Attention. Schizophr Bull. 2012; 38:53–61. [PubMed: 21765166]

Lustig C, Kozak R, Sarter M, Young JW, Robbins TW. Cntrics Final Animal Model Task Selection: Control of Attention. Neurosci Biobehav Rev. 2013; 37:2099–2110. [PubMed: 22683929]

Mackillop J, Tidey JW. Cigarette Demand and Delayed Reward Discounting in Nicotine-Dependent Individuals with Schizophrenia and Controls: An Initial Study. Psychopharmacology (Berl). 2011; 216:91–99. [PubMed: 21327760]

Mantyla T, Still J, Gullberg S, Del Missier F. Decision Making in Adults with Adhd. J Atten Disord. 2012; 16:164–173. [PubMed: 20410321]

Marder SR. The Nimh-Matrics Project for Developing Cognition-Enhancing Agents for Schizophrenia. Dialogues Clin Neurosci. 2006; 8:109–113. [PubMed: 16640121]

Marder SR, Fenton W. Measurement and Treatment Research to Improve Cognition in Schizophrenia: Nimh Matrics Initiative to Support the Development of Agents for Improving Cognition in Schizophrenia. Schizophr Res. 2004; 72:5–9. [PubMed: 15531402]

Markou A, Chiamulera C, Geyer MA, Tricklebank M, Steckler T. Removing Obstacles in Neuroscience Drug Discovery: The Future Path for Animal Models. Neuropsychopharmacology. 2009; 34:74–89. [PubMed: 18830240]

Markou A, Salamone JD, Bussey TJ, Mar a C, Brunner D, Gilmour G, Balsam P. Measuring Reinforcement Learning and Motivation Constructs in Experimental Animals: Relevance to the Negative Symptoms of Schizophrenia. Neurosci Biobehav Rev. 2013; 37:2149–2165. [PubMed: 23994273]

Matthysse S. Animal Models in Psychiatric Research. Prog Brain Res. 1986; 65:259–270. [PubMed: 2878468]

Mcallister KA, Saksida LM, Bussey TJ. Dissociation between Memory Retention across a Delay and Pattern Separation Following Medial Prefrontal Cortex Lesions in the Touchscreen Tunl Task. Neurobiol Learn Mem. 2013; 101:120–126. [PubMed: 23396186]

Mcalonan K, Brown VJ. Orbital Prefrontal Cortex Mediates Reversal Learning and Not Attentional Set Shifting in the Rat. Behav Brain Res. 2003; 146:97–103. [PubMed: 14643463]

Mcgaughy J, Decker MW, Sarter M. Enhancement of Sustained Attention Performance by the Nicotinic Acetylcholine Receptor Agonist Abt-418 in Intact but Not Basal Forebrain-Lesioned Rats. Psychopharmacology (Berl). 1999; 144:175–182. [PubMed: 10394999]

Mcgaughy J, Sarter M. Behavioral Vigilance in Rats: Task Validation and Effects of Age, Amphetamine, and Benzodiazepine Receptor Ligands. Psychopharmacology (Berl). 1995; 117:340–357. [PubMed: 7770610]

Mchugh SB, Barkus C, Huber A, Capitao L, Lima J, Lowry JP, Bannerman DM. Aversive Prediction Error Signals in the Amygdala. J Neurosci. 2014; 34:9024–9033. [PubMed: 24990922]

Mckenna BS, Young JW, Dawes SE, Asgaard GL, Eyler LT. Bridging the Bench to Bedside Gap: Validation of a Reverse-Translated Rodent Continuous Performance Test Using Functional Magnetic Resonance Imaging. Psychiatry Res. 2013; 212:183–191. [PubMed: 23570915]

Mclean SL, Beck JP, Woolley ML, Neill JC. A Preliminary Investigation into the Effects of Antipsychotics on Sub-Chronic Phencyclidine-Induced Deficits in Attentional Set-Shifting in Female Rats. Behav Brain Res. 2008; 189:152–158. [PubMed: 18282619]

Mehta MA, Swainson R, Ogilvie a D, Sahakian J, Robbins TW. Improved Short-Term Spatial Memory but Impaired Reversal Learning Following the Dopamine D(2) Agonist Bromocriptine in Human Volunteers. Psychopharmacology (Berl). 2001; 159:10–20. [PubMed: 11797064]

Millan MJ, Bales KL. Towards Improved Animal Models for Evaluating Social Cognition and Its Disruption in Schizophrenia: The Cntrics Initiative. Neurosci Biobehav Rev. 2013; 37:2166–2180. [PubMed: 24090822]

Mintz J, Kopelowicz A. Cutlass Confirms Catie. Arch Gen Psychiatry. 2007; 64:978. author reply 979–980. [PubMed: 17679644]

Mitchell MR, Mendez IA, Vokes CM, Damborsky JC, Winzer-Serhan UH, Setlow B. Effects of Developmental Nicotine Exposure in Rats on Decision-Making in Adulthood. Behav Pharmacol. 2012; 23:34–42. [PubMed: 22123182]

Moore H, Geyer MA, Carter CS, Barch DM. Harnessing Cognitive Neuroscience to Develop New Treatments for Improving Cognition in Schizophrenia: Cntrics Selected Cognitive Paradigms for Animal Models. Neurosci Biobehav Rev. 2013; 37:2087–2091. [PubMed: 24090823]

Morris SE, Cuthbert BN. Research Domain Criteria: Cognitive Systems, Neural Circuits, and Dimensions of Behavior. Dialogues Clin Neurosci. 2012; 14:29–37. [PubMed: 22577302]

Muller U, Rowe JB, Rittman T, Lewis C, Robbins TW, Sahakian BJ. Effects of Modafinil on Non-Verbal Cognition, Task Enjoyment and Creative Thinking in Healthy Volunteers. Neuropharmacology. 2013; 64:490–495. [PubMed: 22820554]

Murray EA, Mishkin M. Object Recognition and Location Memory in Monkeys with Excitotoxic Lesions of the Amygdala and Hippocampus. J Neurosci. 1998; 18:6568–6582. [PubMed: 9698344]

Must A, Horvath S, Nemeth VL, Janka Z. The Iowa Gambling Task in Depression - What Have We Learned About Sub-Optimal Decision-Making Strategies? Front Psychol. 2013; 4:732. [PubMed: 24133474]

Nuechterlein KH. Signal Detection in Vigilance Tasks and Behavioral Attributes among Offspring of Schizophrenic Mothers and among Hyperactive Children. J Abnorm Psychol. 1983; 92:4–28. [PubMed: 6833631]

Nuechterlein, KH. Vigilance in Schizoprhenia and Related Disorders. In: Steinhauer, Sr; Gruzelier, Jh; Zubin, J., editors. Neuropsychology, Pscyhophysiology, and Information Processing. Hanbook of Schizophrenia. Vol. Vol. 5. Elsevier Science; New York: 1991.

Nuechterlein KH, Green MF, Kern RS, Baade LE, Barch DM, Cohen JD, Essock S, Fenton WS, Frese FJ 3rd, Gold JM, Goldberg T, Heaton RK, Keefe RS, Kraemer H, Mesholam-Gately R, Seidman LJ, Stover E, Weinberger DR, Young a S, Zalcman S, Marder SR. The Matrics Consensus Cognitive Battery, Part 1: Test Selection, Reliability, and Validity. Am J Psychiatry. 2008; 165:203–213. [PubMed: 18172019]

Nuechterlein KH, Robbins TW, Einat H. Distinguishing Separable Domains of Cognition in Human and Animal Studies: What Separations Are Optimal for Targeting Interventions? A Summary of Recommendations from Breakout Group 2 at the Measurement and Treatment Research to Improve Cognition in Schizophrenia New Approaches Conference. Schizophr Bull. 2005; 31:870–874. [PubMed: 16150960]

O'connor RC, Glassman RB. Human Performance with a Seventeen-Arm Radial Maze Analog. Brain Res Bull. 1993; 30:189–191. [PubMed: 8420630]

Olton DS. The Radial Arm Maze as a Tool in Behavioral Pharmacology. Physiol Behav. 1987; 40:793–797. [PubMed: 3313453]

Olton DS, Werz MA. Hippocampal Function and Behavior: Spatial Discrimination and Response Inhibition. Physiol Behav. 1978; 20:597–605. [PubMed: 684094]

Oomen CA, Hvoslef-Eide M, Heath CJ, Mar a C, Horner a E, Bussey TJ, Saksida LM. The Touchscreen Operant Platform for Testing Working Memory and Pattern Separation in Rats and Mice. Nat Protoc. 2013; 8:2006–2021. [PubMed: 24051961]

Owen, a M.; Roberts, a C.; Polkey, CE.; Sahakian, BJ.; Robbins, TW. Extra-Dimensional Versus Intra-Dimensional Set Shifting Performance Following Frontal Lobe Excisions, Temporal Lobe Excisions or Amygdalo-Hippocampectomy in Man. Neuropsychologia. 1991; 29:993–1006. [PubMed: 1762678]

Pantelis C, Barnes TR, Nelson HE, Tanner S, Weatherley L, Owen a M, Robbins TW. Frontal-Striatal Cognitive Deficits in Patients with Chronic Schizophrenia. Brain. 1997; 120(Pt 10):1823–1843. [PubMed: 9365373]

Papageorgiou C, Karanasiou IS, Kapsali F, Stachtea X, Kyprianou M, Tsianaka EI, Karakatsanis NA, Rabavilas a D, Uzunoglu NK, Papadimitriou GN. Temporal Processing Dysfunction in Schizophrenia as Measured by Time Interval Discrimination and Tempo Reproduction Tasks. Prog Neuropsychopharmacol Biol Psychiatry. 2013; 40:173–179. [PubMed: 23367507]

Pena-Oliver Y, Sanchez-Roige S, Stephens DN, Ripley TL. Alpha-Synuclein Deletion Decreases Motor Impulsivity but Does Not Affect Risky Decision Making in a Mouse Gambling Task. Psychopharmacology (Berl). 2014; 231:2493–2506. [PubMed: 24402137]

Pizzagalli DA, Evins a E, Schetter EC, Frank MJ, Pajtas PE, Santesso DL, Culhane M. Single Dose of a Dopamine Agonist Impairs Reinforcement Learning in Humans: Behavioral Evidence from a Laboratory-Based Measure of Reward Responsiveness. Psychopharmacology (Berl). 2008; 196:221–232. [PubMed: 17909750]

Potvin S, Pampoulova T, Lipp O, Ait Bentaleb L, Lalonde P, Stip E. Working Memory and Depressive Symptoms in Patients with Schizophrenia and Substance Use Disorders. Cogn Neuropsychiatry. 2008; 13:357–366. [PubMed: 18622790]

Powell SB, Zhou X, Geyer MA. Prepulse Inhibition and Genetic Mouse Models of Schizophrenia. Behav Brain Res. 2009; 204:282–294. [PubMed: 19397931]

Pratt J, Winchester C, Dawson N, Morris B. Advancing Schizophrenia Drug Discovery: Optimizing Rodent Models to Bridge the Translational Gap. Nat Rev Drug Discov. 2012; 11:560–579. [PubMed: 22722532]

Rabbitt P, Rodgers B. What Does a Man Do after He Makes an Error? An Analysis of Response Programming. Quarterly Journal of Experimental Psychology. 1977; 29:727–743.

Ragland JD, Cohen NJ, Cools R, Frank MJ, Hannula DE, Ranganath C. Cntrics Imaging Biomarkers Final Task Selection: Long-Term Memory and Reinforcement Learning. Schizophr Bull. 2012; 38:62–72. [PubMed: 22102094]

Ragland JD, Cools R, Frank M, Pizzagalli DA, Preston A, Ranganath C, Wagner a D. Cntrics Final Task Selection: Long-Term Memory. Schizophr Bull. 2009; 35:197–212. [PubMed: 18927344]

Rausch F, Mier D, Eifler S, Esslinger C, Schilling C, Schirmbeck F, Englisch S, Meyer-Lindenberg A, Kirsch P, Zink M. Reduced Activation in Ventral Striatum and Ventral Tegmental Area During Probabilistic Decision-Making in Schizophrenia. Schizophr Res. 2014; 156:143–149. [PubMed: 24831391]

Reyes E, Wolfe J, Savage DD. The Effects of Prenatal Alcohol Exposure on Radial Arm Maze Performance in Adult Rats. Physiol Behav. 1989; 46:45–48. [PubMed: 2813555]

Rezvani, a H.; Bushnell, PJ.; Levin, ED. Effects of Nicotine and Mecamylamine on Choice Accuracy in an Operant Visual Signal Detection Task in Female Rats. Psychopharmacology (Berl). 2002; 164:369–375. [PubMed: 12457266]

Rezvani, a H.; Caldwell, DP.; Levin, ED. Chronic Nicotine Interactions with Clozapine and Risperidone and Attentional Function in Rats. Prog Neuropsychopharmacol Biol Psychiatry. 2006; 30:190–197. [PubMed: 16310917]

Rezvani, a H.; Levin, ED. Nicotine-Antipsychotic Drug Interactions and Attentional Performance in Female Rats. Eur J Pharmacol. 2004; 486:175–182. [PubMed: 14975706]

Richelson E, Souder T. Binding of Antipsychotic Drugs to Human Brain Receptors Focus on Newer Generation Compounds. Life Sci. 2000; 68:29–39. [PubMed: 11132243]

Rivalan M, Ahmed SH, Dellu-Hagedorn F. Risk-Prone Individuals Prefer the Wrong Options on a Rat Version of the Iowa Gambling Task. Biol Psychiatry. 2009; 66:743–749. [PubMed: 19482266]

Rivalan M, Coutureau E, Fitoussi A, Dellu-Hagedorn F. Inter-Individual Decision-Making Differences in the Effects of Cingulate, Orbitofrontal, and Prelimbic Cortex Lesions in a Rat Gambling Task. Front Behav Neurosci. 2011; 5:22. [PubMed: 21559308]

Robbins TW. The 5-Choice Serial Reaction Time Task: Behavioural Pharmacology and Functional Neurochemistry. Psychopharmacology (Berl). 2002; 163:362–380. [PubMed: 12373437]

Robinson ES, Eagle DM, Mar a C, Bari A, Banerjee G, Jiang X, Dalley JW, Robbins TW. Similar Effects of the Selective Noradrenaline Reuptake Inhibitor Atomoxetine on Three Distinct Forms of Impulsivity in the Rat. Neuropsychopharmacology. 2008; 33:1028–1037. [PubMed: 17637611]

Rosvold H, A. M, Sarason I, Bransome a D J, Beck LH. A Continuous Performance Test of Brain Damage. Journal of Consulting Psychology. 1956; 20:343–350. [PubMed: 13367264]

Rushforth SL, Allison C, Wonnacott S, Shoaib M. Subtype-Selective Nicotinic Agonists Enhance Olfactory Working Memory in Normal Rats: A Novel Use of the Odour Span Task. Neurosci Lett. 2010; 471:114–118. [PubMed: 20083163]

Rushforth SL, Steckler T, Shoaib M. Nicotine Improves Working Memory Span Capacity in Rats Following Sub-Chronic Ketamine Exposure. Neuropsychopharmacology. 2011; 36:2774–2781. [PubMed: 21956441]

Sarter M. Animal Cognition: Defining the Issues. Neurosci Biobehav Rev. 2004; 28:645–650. [PubMed: 15555674]

Scheggia D, Bebensee A, Weinberger DR, Papaleo F. The Ultimate Intra-/Extra-Dimensional Attentional Set-Shifting Task for Mice. Biol Psychiatry. 2014; 75:660–670. [PubMed: 23810621]

Schroder HS, Moser JS. Improving the Study of Error Monitoring with Consideration of Behavioral Performance Measures. Front Hum Neurosci. 2014; 8:178. [PubMed: 24723878]

Scoriels L, Jones PB, Sahakian BJ. Modafinil Effects on Cognition and Emotion in Schizophrenia and Its Neurochemical Modulation in the Brain. Neuropharmacology. 2013; 64:168–184. [PubMed: 22820555]

Segal, DS.; Geyer, MA. Animal Models of Psychopathology. In: Judd, Ll; Groves, Pm, editors. Psychobiological Foundations of Clinical Psychiatry. J.B. Lippincott Co.; Philadelphia: 1985.

Servan-Schreiber D, Cohen JD, Steingard S. Schizophrenic Deficits in the Processing of Context. A Test of a Theoretical Model. Arch Gen Psychiatry. 1996; 53:1105–1112. [PubMed: 8956676]

Sharma T, Reed C, Aasen I, Kumari V. Cognitive Effects of Adjunctive 24-Weeks Rivastigmine Treatment to Antipsychotics in Schizophrenia: A Randomized, Placebo-Controlled, Double-Blind Investigation. Schizophr Res. 2006; 85:73–83. [PubMed: 16797163]

Siegel SJ, Talpos JC, Geyer MA. Animal Models and Measures of Perceptual Processing in Schizophrenia. Neurosci Biobehav Rev. 2013; 37:2092–2098. [PubMed: 23867801]

Silverman JL, Gastrell PT, Karras MN, Solomon M, Crawley JN. Cognitive Abilities on Transitive Inference Using a Novel Touchscreen Technology for Mice. Cereb Cortex. 2013

Simon NW, Gilbert RJ, Mayse JD, Bizon JL, Setlow B. Balancing Risk and Reward: A Rat Model of Risky Decision Making. Neuropsychopharmacology. 2009; 34:2208–2217. [PubMed: 19440192]

Spieker EA, Astur RS, West JT, Griego JA, Rowland LM. Spatial Memory Deficits in a Virtual Reality Eight-Arm Radial Maze in Schizophrenia. Schizophr Res. 2012; 135:84–89. [PubMed: 22154760]

Sripada CS, Gonzalez R, Phan KL, Liberzon I. The Neural Correlates of Intertemporal Decision-Making: Contributions of Subjective Value, Stimulus Type, and Trait Impulsivity. Hum Brain Mapp. 2011; 32:1637–1648. [PubMed: 20886577]

St Onge JR, Abhari H, Floresco SB. Dissociable Contributions by Prefrontal D1 and D2 Receptors to Risk-Based Decision Making. J Neurosci. 2011; 31:8625–8633. [PubMed: 21653866]

Stewart, a M.; Braubach, O.; Spitsbergen, J.; Gerlai, R.; Kalueff, a V. Zebrafish Models for Translational Neuroscience Research: From Tank to Bedside. Trends Neurosci. 2014; 37:264–278. [PubMed: 24726051]

Strauss GP, Frank MJ, Waltz JA, Kasanova Z, Herbener ES, Gold JM. Deficits in Positive Reinforcement Learning and Uncertainty-Driven Exploration Are Associated with Distinct Aspects of Negative Symptoms in Schizophrenia. Biol Psychiatry. 2011; 69:424–431. [PubMed: 21168124]

Swainson R, Rogers RD, Sahakian BJ, Summers BA, Polkey CE, Robbins TW. Probabilistic Learning and Reversal Deficits in Patients with Parkinson's Disease or Frontal or Temporal Lobe Lesions: Possible Adverse Effects of Dopaminergic Medication. Neuropsychologia. 2000; 38:596–612. [PubMed: 10689037]

Swerdlow NR. Are We Studying and Treating Schizophrenia Correctly? Schizophr Res. 2011; 130:1–10. [PubMed: 21645998]

Swerdlow NR. Beyond Antipsychotics: Pharmacologically-Augmented Cognitive Therapies (Pacts) for Schizophrenia. Neuropsychopharmacology. 2012; 37:310–311. [PubMed: 22157876]

Taiminen T, Jaaskelainen S, Ilonen T, Meyer H, Karlsson H, Lauerma H, Leinonen KM, Wallenius E, Kaljonen A, Salokangas RK. Habituation of the Blink Reflex in First-Episode Schizophrenia, Psychotic Depression and Non-Psychotic Depression. Schizophr Res. 2000; 44:69–79. [PubMed: 10867313]

Tait DS, Chase EA, Brown VJ. Attentional Set-Shifting in Rodents: A Review of Behavioural Methods and Pharmacological Results. Curr Pharm Des. 2013

Talpos J, Steckler T. Touching on Translation. Cell Tissue Res. 2013; 354:297–308. [PubMed: 23949375]

Talpos JC, Mctighe SM, Dias R, Saksida LM, Bussey TJ. Trial-Unique, Delayed Nonmatchingto-Location (Tunl): A Novel, Highly Hippocampus-Dependent Automated Touchscreen Test of Location Memory and Pattern Separation. Neurobiol Learn Mem. 2010; 94:341–352. [PubMed: 20692356]

Tarantino IS, Sharp RF, Geyer MA, Meves JM, Young JW. Working Memory Span Capacity Improved by a D2 but Not D1 Receptor Family Agonist. Behav Brain Res. 2011; 219:181–188. [PubMed: 21232557]

Tsuchida A, Doll BB, Fellows LK. Beyond Reversal: A Critical Role for Human Orbitofrontal Cortex in Flexible Learning from Probabilistic Feedback. J Neurosci. 2010; 30:16868–16875. [PubMed: 21159958]

Turner DC, Clark L, Dowson J, Robbins TW, Sahakian BJ. Modafinil Improves Cognition and Response Inhibition in Adult Attention-Deficit/Hyperactivity Disorder. Biol Psychiatry. 2004; 55:1031–1040. [PubMed: 15121488]

Turner DC, Clark L, Pomarol-Clotet E, Mckenna P, Robbins TW, Sahakian BJ. Modafinil Improves Cognition and Attentional Set Shifting in Patients with Chronic Schizophrenia. Neuropsychopharmacology. 2004; 29:1363–1373. [PubMed: 15085092]

Turner DC, Robbins TW, Clark L, Aron a R, Dowson J, Sahakian BJ. Cognitive Enhancing Effects of Modafinil in Healthy Volunteers. Psychopharmacology (Berl). 2003; 165:260–269. [PubMed: 12417966]

Turner KM, Young JW, Mcgrath JJ, Eyles DW, Burne TH. Cognitive Performance and Response Inhibition in Developmentally Vitamin D (Dvd)-Deficient Rats. Behav Brain Res. 2013; 242:47–53. [PubMed: 23275047]

Tyson PJ, Laws KR, Roberts KH, Mortimer a M. Stability of Set-Shifting and Planning Abilities in Patients with Schizophrenia. Psychiatry Res. 2004; 129:229–239. [PubMed: 15661316]

Uecker A, Nadel L. Spatial Locations Gone Awry: Object and Spatial Memory Deficits in Children with Fetal Alcohol Syndrome. Neuropsychologia. 1996; 34:209–223. [PubMed: 8868278]

Unsworth N, Engle RW. The Nature of Individual Differences in Working Memory Capacity: Active Maintenance in Primary Memory and Controlled Search from Secondary Memory. Psychol Rev. 2007; 114:104–132. [PubMed: 17227183]

Van Enkhuizen J, Acheson D, Risbrough V, Drummond S, Geyer MA, Young JW. Sleep Deprivation Impairs Performance in the 5-Choice Continuous Performance Test: Similarities between Humans and Mice. Behav Brain Res. 2013; 261C:40–48. [PubMed: 24333377]

Van Enkhuizen J, Geyer MA, Young JW. Differential Effects of Dopamine Transporter Inhibitors in the Rodent Iowa Gambling Task : Relevance to Mania. Psychopharmacology. 2013; 225:661–674. [PubMed: 22945515]

Van Enkhuizen J, Geyer MA, Young JW. Differential Effects of Dopamine Transporter Inhibitors in the Rodent Iowa Gambling Task : Relevance to Mania. Psychopharmacology (Berl). 2013; 225:661–674. [PubMed: 22945515]

Van Enkhuizen J, Henry BL, Minassian A, Perry W, Milienne-Petiot M, Higa K, Geyer MA, Young JW. Reduced Dopamine Transporter Functioning Induces High-Reward Risk-Preference Consistent with Bipolar Disorder. Neuropsychopharmacology. Accepted.

Verdejo-Garcia A, Benbrook A, Funderburk F, David P, Cadet JL, Bolla KI. The Differential Relationship between Cocaine Use and Marijuana Use on Decision-Making Performance over Repeat Testing with the Iowa Gambling Task. Drug Alcohol Depend. 2007; 90:2–11. [PubMed: 17367959]

Waltz JA, Frank MJ, Robinson BM, Gold JM. Selective Reinforcement Learning Deficits in Schizophrenia Support Predictions from Computational Models of Striatal-Cortical Dysfunction. Biol Psychiatry. 2007; 62:756–764. [PubMed: 17300757]

Weller JA, Levin IP, Bechara A. Do Individual Differences in Iowa Gambling Task Performance Predict Adaptive Decision Making for Risky Gains and Losses? Journal of Clinical & Experimental Neuropsychology. 2010; 32:141–150. [PubMed: 19484643]

Weller RE, Avsar KB, Cox JE, Reid MA, White DM, Lahti a C. Delay Discounting and Task Performance Consistency in Patients with Schizophrenia. Psychiatry Res. 2014; 215:286–293. [PubMed: 24388727]

Winstanley CA, Dalley JW, Theobald DE, Robbins TW. Fractionating Impulsivity: Contrasting Effects of Central 5-Ht Depletion on Different Measures of Impulsive Behavior. Neuropsychopharmacology. 2004; 29:1331–1343. [PubMed: 15054475]

Worbe Y, Savulich G, Voon V, Fernandez-Egea E, Robbins TW. Serotonin Depletion Induces 'Waiting Impulsivity' on the Human Four-Choice Serial Reaction Time Task: Cross-Species Translational Significance. Neuropsychopharmacology. 2014; 39:1519–1526. [PubMed: 24385133]

Xue G, Aron a R, Poldrack RA. Common Neural Substrates for Inhibition of Spoken and Manual Responses. Cereb Cortex. 2008; 18:1923–1932. [PubMed: 18245044]

Young J, Kamenski M, Geyer M. Delayed `Eureka' of Alpha 7 Nicotinic Acetylcholine Receptor Knockout Mice in a Probabilistic Reversal Learning Paradigm. Schizophrenia Research. 2012; 136:S361.

Young, JW.; Amitai, N.; Geyer, MA. Behavioral Animal Models to Assess Pro-Cognitive Treatments for Schizophrenia. In: Geyer, Ma; Gross, G., editors. Hanbook of Experimental Pharmacology, Vol. Novel Antischizophrenia Treatments. Springer; Heidelberg: 2012.

Young JW, Crawford N, Kelly JS, Kerr LE, Marston HM, Spratt C, Finlayson K, Sharkey J. Impaired Attention Is Central to the Cognitive Deficits Observed in Alpha 7 Deficient Mice. Eur Neuropsychopharmacol. 2007; 17:145–155. [PubMed: 16650968]

Young JW, Geyer MA. Action of Modafinil-Increased Motivation Via the Dopamine Transporter Inhibition and D1 Receptors? Biol Psychiatry. 2010; 67:784–787. [PubMed: 20132929]

Young JW, Geyer MA. Evaluating the Role of the Alpha-7 Nicotinic Acetylcholine Receptor in the Pathophysiology and Treatment of Schizophrenia. Biochem Pharmacol. 2013; 86:1122–1132. [PubMed: 23856289]

Young JW, Geyer MA, Rissling a J, Sharp RF, Eyler LT, Asgaard GL, Light GA. Reverse Translation of the Rodent 5c-Cpt Reveals That the Impaired Attention of People with Schizophrenia Is Similar to Scopolamine-Induced Deficits in Mice. Transl Psychiatry. 2013; 3:e324. [PubMed: 24217494]

Young JW, Jentsch JD, Bussey TJ, Wallace TL, Hutcheson DM. Consideration of Species Differences in Developing Novel Molecules as Cognition Enhancers. Neurosci Biobehav Rev. 2013; 37:2181–2193. [PubMed: 23064177]

Young JW, Kerr LE, Kelly JS, Marston HM, Spratt C, Finlayson K, Sharkey J. The Odour Span Task: A Novel Paradigm for Assessing Working Memory in Mice. Neuropharmacology. 2007; 52:634–645. [PubMed: 17097694]

Young JW, Light GA, Marston HM, Sharp R, Geyer MA. The 5-Choice Continuous Performance Test: Evidence for a Translational Test of Vigilance for Mice. PLoS ONE. 2009; 4:e4227. [PubMed: 19156216]

Young JW, Meves JM, Geyer MA. Nicotinic Agonist-Induced Improvement of Vigilance in Mice in the 5-Choice Continuous Performance Test. Behav Brain Res. 2013; 240:119–133. [PubMed: 23201359]

Young JW, Meves JM, Tarantino IS, Caldwell S, Geyer MA. Delayed Procedural Learning in Alpha7-Nicotinic Acetylcholine Receptor Knockout Mice. Genes Brain Behav. 2011; 10:720–733. [PubMed: 21679297]

Young JW, Powell SB, Geyer MA. Mouse Pharmacological Models of Cognitive Disruption Relevant to Schizophrenia. Neuropharmacology. 2012; 62:1381–1390. [PubMed: 21726569]

Young JW, Powell SB, Geyer MA, Jeste DV, Risbrough VB. The Mouse Attentional Set-Shifting Task: A Method for Assaying Successful Cognitive Aging? Cognitive, Affective & Behavioral Neuroscience. 2010; 10:243–251.

Young JW, Powell SB, Risbrough V, Marston HM, Geyer MA. Using the Matrics to Guide Development of a Preclinical Cognitive Test Battery for Research in Schizophrenia. Pharmacol Ther. 2009; 122:150–202. [PubMed: 19269307]

Young, JW.; Zhou, X.; Geyer, MA. Animal Models of Schizophrenia. In: Swerdlow, Nr, editor. Behavioral Neurobiology of Schiozphrenia and Its Treatment. Springer; Berlin: 2010.

Yun L, Gu Y, Hou Y. No Association between Schizophrenia and Rs27388 of the Megf10 Gene in Chinese Case-Control Sample. Psychiatry Res. 2011; 186:467–468. [PubMed: 20813413]

Zeeb FD, Robbins TW, Winstanley CA. Serotonergic and Dopaminergic Modulation of Gambling Behavior as Assessed Using a Novel Rat Gambling Task. Neuropsychopharmacology. 2009; 34:2329–2343. [PubMed: 19536111]

Zeeb FD, Wong a C, Winstanley CA. Differential Effects of Environmental Enrichment, Social-Housing, and Isolation-Rearing on a Rat Gambling Task: Dissociations between Impulsive Action and Risky Decision-Making. Psychopharmacology (Berl). 2013; 225:381–395. [PubMed: 22864967]

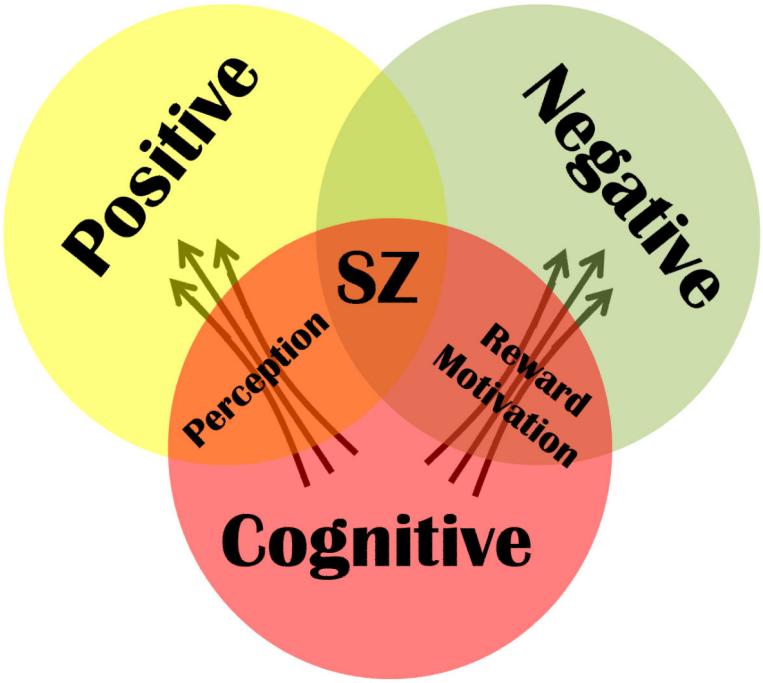

Figure 1. Representation of the symptoms experienced by patients with schizophrenia

Schizophrenia is a life-long neuropsychiatric disorder in which patients suffer from a variety of symptoms grouped into three types: positive; negative; and cognitive. Positive symptoms are behavioral abnormalities that are present due to the disease, such as auditory and/or visual hallucinations, grandiosity, etc. Negative symptoms are behavioral abnormalities that are diminished due to the disease, such as alogia, anhedonia, affective flattening, and amotivation. Finally, cognitive symptoms are wide-ranging (e.g., reward processing, perception, attention, and working memory) and link most closely to a patient's ability to function in society and can impact the other symptoms. Antipsychotic treatments are only efficacious for positive symptoms. Treating cognitive disruption may however, be key to developing the first truly antischizophrenia medication (Geyer and Gross, 2012).

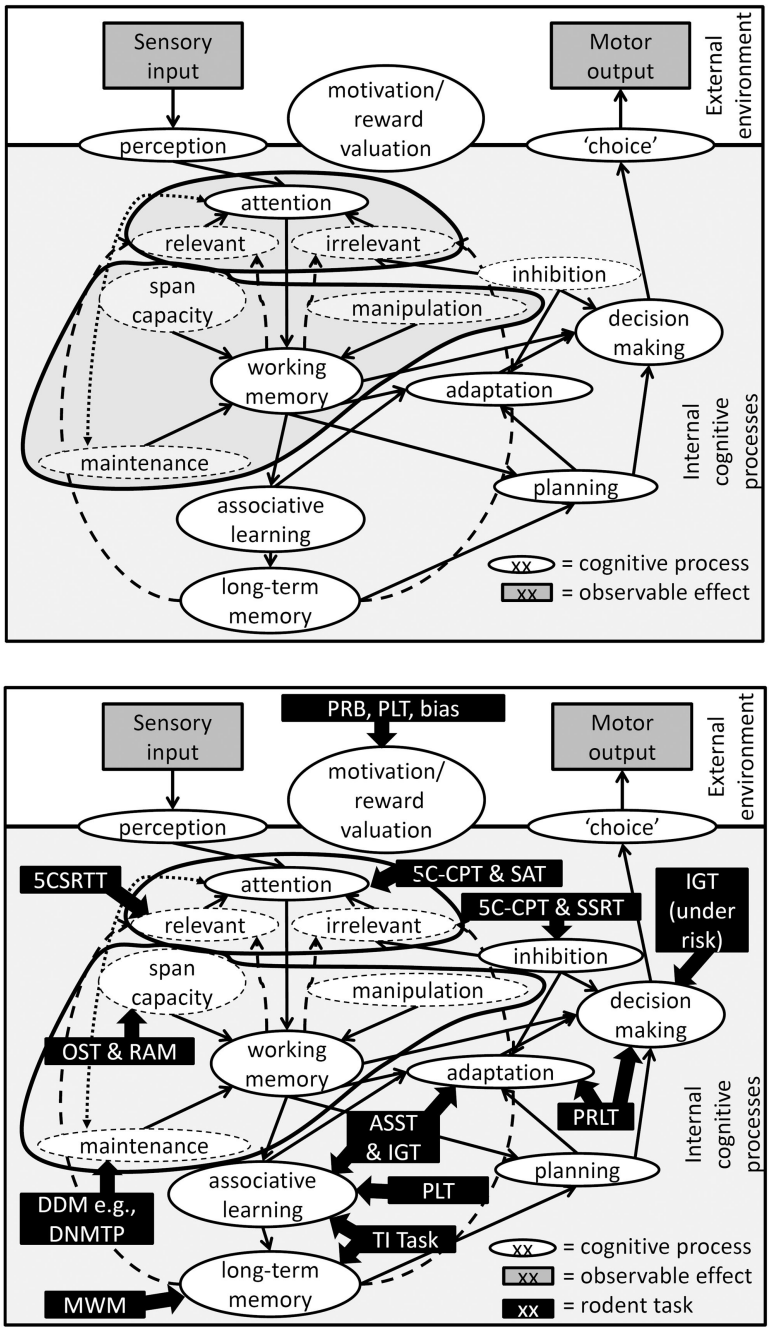

Figure 2. Schematic of how environmental sensory input is processed through schizophrenia-relevant cognitive processes resulting environmental action

The left panel describes how environmental stimuli are perceived and attentional processes brought to bear through cognitive processes until decisions are made and action is taken. This process is detailed in the right panel which also includes paradigms with cross-species relevance to that cognitive domain. As stimuli are perceived, knowledge of relevance/ irrelevance of these stimuli enables attending to currently appropriate stimuli. Knowledge of relevant and irrelevant stimuli may be located in either working or long-term memory (indicated by dashed arrow). Because the 5C-CPT and SAT contain relevant and irrelevant

stimuli, these tasks measure attention consistent with the CPTs used in humans which includes responding to relevant and irrelevant information. The 5CSRTT measures sustained attention to relevant information. Attention to external stimuli enables information to enter working memory. Working memory is another multi-faceted process which has subsystems of span capacity and maintenance of information which are held online for the manipulation of that information. As is clear, while span capacity (OST & RAM) and maintenance of information (DDM) can be measured in animals, the manipulation of information and working memory cannot. Working memory is important however, for associative learning leading to long-term memory, planning, adaptation, and decision making. Associative learning enables information to enter long-term memory and can be measured using the ASST, PLT, and TI tasks. Long-term memory can also be measured using tasks like the MWM and TI task. Adaptation to changing rules in the environment can be measured using the ASST and PRLT. Working memory, long-term memory, and adaptation, all contribute to planning, another behavior that has yet to be measured in rodents due to its internal nature. Inhibitory control is important for non-responses to irrelevant stimuli as well as adaptation to the environment and decision making. Inhibition of responding to irrelevant stimuli can be measured using the 5C-CPT or go-nogo tasks, while inhibitory processes to initiated behaviors can be measured using the SSRT. Decision making is the final process incorporating aspects of working memory, planning, and adaptation. Decision making can be inferred from changing behaviors to reward or punishment during learning, e.g., IGT, PLT, and PRLT. Finally, the motivation or the perceived reward value of the stimuli also contribute to the degree these cognitive processes are engaged. The properties of these behaviors can be measured using PRB studies, PLT, and bias in response to reward probabilities.

Table 1

Breakdown of cognitive domains and constructs taken from MATRICS and CNTRICS initiatives with cross-species relevant tasks for developing pro-cognitive treatments for patients with schizophrenia

Domain	Construct	Humans	Animals	Ref.
Executive functioning	Rule Generation & Selection	Intradimensional/Extradimensional set-shifting task	Reversal Learning & Attentional Set-Shifting Task	Gilmour et al, 2013; Carter et al, 2012; Rivalan et al, 2009
	Dynamic Adjustment of Control	1–2 AX-continuous performance test (CPT)	Stop Signal Reaction-Time Task?	
	Decision-making	Iowa Gambling Task	Iowa Gambling Task	
Working Memory	Goal Maintenance	AX-CPT	Delayed-dependent tasks?	Dudchenko et al, 2013
	Memory Capacity	*None specified*	Odor Span Task & Radial Arm Maze	
	Interference Control	n-back task	Temporal Order	
Attention	Control of Attention	Guided Search, Distracter-Sustained Attention Task, 5-choice CPT, 5-Choice Reaction-Time Task?	Distracter-Sustained Attention Task, 5-choice CPT, 5-Choice Reaction-Time Task?	Lustig et al, 2013; Nuechterlein et al 2009
Long Term Memory	Relational encoding & retrieval	Associative inference paradigm, Relational & item encoding and retrieval (RIER), Transitive inference paradigm	Paired-associative learning, Object location learning, Transitive inference paradigm	Ragland et al, 2009; Bussey et al, 2013; Markou et al, 2013
	Item encoding & rptripval	RIER	*None specified*	
	Reinforcement Learning	Probabilistic learning tasks (including selection & reversal tasks)	Autoshaping task, Probabilistic learning, Response bias learning	
Perceptual Processing	Gain Control	Contrast-contrast effect task	Prepulse inhibition? auditory ERP? Mismatch negativity?	Siegel et al, 2013; Green et al, 2009
	Sensory Integration	Contour Integration and Coherent Motion	*None specified*	

? = further development recommended for relevance to cognitive construct and/or deficiency in patients with schizophrenia