

New translational assays for preclinical modelling of cognition in schizophrenia: The touchscreen testing method for mice and rats

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ABSTRACT

We describe a touchscreen method that satisfies a proposed ‘wish-list’ of desirables for a cognitive testing method for assessing rodent models of schizophrenia. A number of tests relevant to schizophrenia research are described which are currently being developed and validated using this method. These tests can be used to study reward learning, memory, perceptual discrimination, object-place associative learning, attention, impulsivity, compulsivity, extinction, simple Pavlovian conditioning, and other constructs. The tests can be deployed using a ‘flexible battery’ approach to establish a cognitive profile for a particular mouse or rat model. We have found these tests to be capable of detecting not just impairments in function, but enhancements as well, which is essential for testing putative cognitive therapies. New tests are being continuously developed, many of which may prove particularly valuable for schizophrenia research.

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1. Introduction: cognitive testing in preclinical schizophrenia research

“Antipsychotic drugs have emptied out our mental institutions, but have delivered their residents to impoverished lives outside. Research has linked elements of this poor psychosocial function to persistent cognitive impairments.” (Geyer and Tamminga, 2004)

It is now widely understood that the profound cognitive changes in schizophrenia, as much as the so-called ‘positive’ and ‘negative’ symptoms (see other articles in this issue), require understanding and treatment. To this end, major initiatives such as Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS), Cognitive Neuroscience Approaches to the Treatment of Impaired Cognition in Schizophrenia (CNTRICS),

and elements of the European Innovative Medicines Initiative (IMI), have been set up to tackle this important facet of the disease.

It is also widely understood that animal models will play an indispensable role in this enterprise; indeed it has been said that it is hard to imagine any substantial progress in the pathophysiology or therapeutics of schizophrenia without good animal models (Nestler and Hyman, 2010). With respect to cognition, the ‘model’ in question is the appropriate combination of a e.g., genetic, pharmacological, lesion or environmental manipulation in an animal (usually a mouse or rat) with appropriate, accurate, reliable cognitive tests. It is a concern, then, that recently a number of articles have appeared with titles like “In search of a better mouse test”, emphasizing the need for improvement in this area (Nestler and Hyman, 2010; Tecott and Nestler, 2004; Wahlsten et al., 2003b). Clearly an important area of development must be the optimization of our cognitive testing methods in animal models.

With this in mind we can allow ourselves to ask what exactly it is we want from our rodent cognitive assays. We would like to suggest the following, probably relatively non-controversial ‘wish-list’ for the ideal cognitive testing method.

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i. It should be automated.

Notwithstanding some unique arguments to the contrary (Crabbe and Morris, 2004), most researchers agree that the same type of automation that has paid such dividends in areas like molecular biology is desirable for cognitive testing as well. Certainly the cognitive testing of clinical populations is becoming increasingly automated (e.g., the Cambridge Neuropsychological Test Automated Battery (CANTAB), CogState, Mindstreams), and so automation may help to achieve another desirable: effective translation (discussed in more detail below). But automation of cognitive testing in animal models confers advantages of its own; perhaps the most obvious to researchers 'on the ground' is a reduction in labour: while one experimenter is testing a single mouse in a maze, an experimenter armed with automated apparatus can test many mice simultaneously. Post-docs working in our lab, for example, routinely test 20 animals at a time, adding up to between 1 and 2 hundred a day. This realization negates the argument that some automated tests take more sessions to generate a result, as such tests would have to be 20 times slower before the equivalent non-automated testing methods start to make any time-economical sense. But it is the scientific arguments for automation that are perhaps the most compelling. With an automated test the computer can present many trials to an animal without having to interfere with the animal during testing. Such interference can have a huge effect, not just by introducing variability into the way the task is run, but also by introducing variability and potential confounds relating to the way the experimenter handles the animals, or even the sight or smell of the experimenter (Wahlsten et al., 2003a). Finally, because automated tasks are controlled by a computer, parameters such as delays and stimulus presentation are identical on every trial, for every animal, and the measures the computer gets back from the animal, for example latencies, can be accurate to the millisecond. All this adds up to a method that is much more likely to be reliable than non-automated methods.

ii. It should be non-aversive and low-stress.

Although some animal models, including those of schizophrenia, utilize stress as a manipulation, unnecessary stress as a feature of a cognitive test is best avoided. Everyone knows that stress can interfere with our experimental manipulations, and can have strong modulatory effects on cognition (Joels and Baram, 2009). Unwanted stress can therefore be a major impediment to the accurate assessment of cognition. Yet some of the most popular methods for cognitive testing involve cold water or electric shock. Such unwanted stressors are best avoided if possible, and so we would suggest that the ideal cognitive testing method should if possible be appetitive (reward-based) rather than aversive. Of course the use of appetitive reinforcers is not always problem-free either; some perturbations in experimental animals can affect animals' motivation to perform vigorously to obtain reward. However appetitive reinforcers themselves generally have a less potentially confounding affect on the organism than stressors.

iii. It should assess multiple cognitive domains.

Currently we often assess an animal's memory in, say, a pool of water, its ability to extinguish a learned association using, say, footshock, and its attentional capacities using, say, an operant chamber. Then we try to compare across these tests. Obviously there are difficulties with this approach. Ideally we would be able to investigate all of these aspects of cognition under the same conditions – in the same apparatus, using the same types of

stimuli, and the same rewards and responses. We can then employ a 'battery' of tests to establish a cognitive profile of an animal, in conditions under which the tests can be compared in a less confounded manner.

iv. It should be translational.

The goal of all of this is of course translation, from mouse to clinic. Currently the tests we use in animals are usually nothing like the tests we use in clinical populations; some of the tests mentioned above provide good examples of this disconnect. In order to translate effectively our findings from animals to humans, the tasks ideally would be as similar as possible. Such 'face validity' does not guarantee construct or predictive validity – further experimentation is needed to do that – but it makes these types of validity, and effective translation, much more likely than when the tests appear on the face of them to have little in common. With respect to schizophrenia, predictive validity presents a particular challenge as there are, as of yet, no approved treatments for the cognitive deficits in schizophrenia.

There are probably many as-yet unimagined methodologies that could satisfy this wish-list. In this review we would like to describe one method, which we have been working on for about 20 years now, which we think satisfies this list of desirables and could prove to be very valuable in the cognitive testing of rodent models of schizophrenia. We describe that method generally next, before describing some of the tests that are currently implemented and their relevance to schizophrenia research. We then describe the 'flexible battery' approach and the different ways in which such a battery might be deployed in practise.

2. The touchscreen testing method

With the wish-list in mind, we have developed an automated apparatus and method that uses a computer monitor to present stimuli, and an infra-red 'touch-screen' assembly with which an animal can register its response (Fig. 1). Rewards can be food pellets or liquid reinforcers such as strawberry milkshake (which we have found to be particularly motivating, ameliorating some of the problems that can be associated with decreased motivation described above). We have developed a number of tests that can be run in this apparatus. These tests can be used to study reward learning, memory, perceptual discrimination, object-place associative learning, attention, impulsivity, compulsivity, extinction, simple Pavlovian conditioning, and other constructs. Next we describe some of these tests and their potential for use in schizophrenia research.

2.1. Visual discrimination and reversal: perceptual discrimination, association and inhibition

Visual discrimination and reversal learning is an intuitively straightforward touchscreen task (or rather, two tasks) which, nonetheless, permits the dissociation of multiple cognitive processes. The rodent is presented with two visual stimuli and learns that a response to one stimulus is rewarded (the S+) while a response to the other (the S-) is not (see Fig. 1). The spatial location of the S+ and S- is irrelevant to task solution. Once the task has been acquired, the stimulus-reward contingencies can be reversed. A response to the S- is now rewarded, while the previously correct S+ goes unrewarded. Successful performance on this task thus involves a number of components. The subject must solve the perceptual discrimination and learn the initial stimulus-reward association, then, after the reversal, they must inhibit the prepotent response to the previously rewarded stimulus while learning the

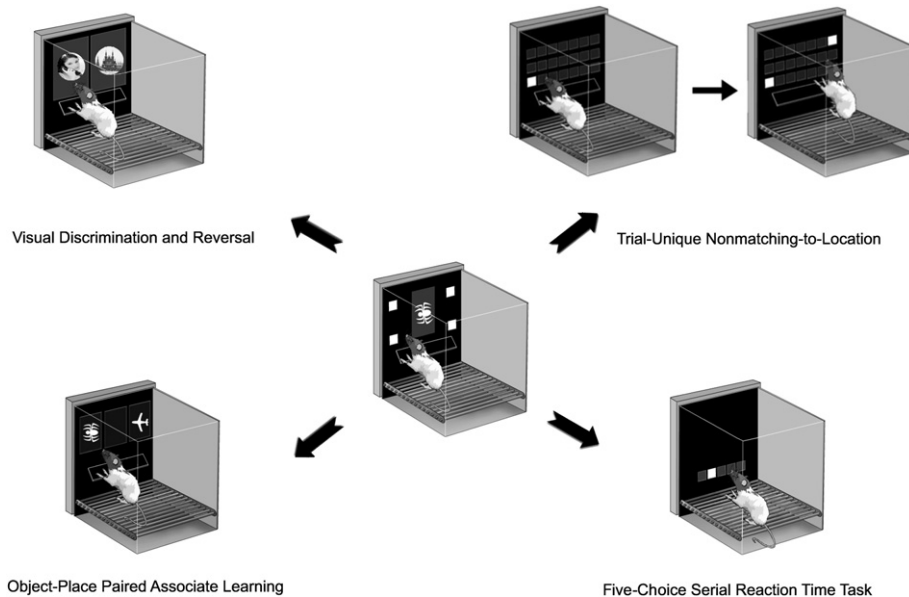


Fig. 1. *Centre:* A rat using a touchscreen. Shapes and locations (delineated by white squares) can serve as stimuli; a nosepoke toward the screen serves as the response. The rat is shown using a 'shelf' directly under the stimulus display upon which it can rear and scan the stimuli before stretching across the shelf to make a response. The shelf serves to slow impulsive rats down, facilitating attention to the stimuli and minimizing impulsive responding, thus improving the rate of learning. Mice behave less impulsively when using the touchscreen, and so a shelf for mice is not required. *Periphery:* The basic method can be used to build a variety of tasks measuring learning, memory, attention, and other cognitive domains. Four examples are shown; the details of these tasks are provided in the text. Components of this figure are courtesy of John Talpos.

new stimulus-reward contingencies. These tasks are learned relatively quickly; Bussey et al. (2008) report that rats can achieve above 80% correct within several 60-trial sessions. The reversal takes longer, probably in the order of about ten or so such sessions. Although considerable progress has been made optimizing some parameters of the touchscreen method (e.g., Bussey et al., 2008), further improvements are being added all the time, and acquisition rates for these tasks are continuing to improve.

Reversal learning has been of particular interest with respect to schizophrenia. Reversal learning is known to depend upon the orbitofrontal region of prefrontal cortex (OFC) and interconnected subcortical areas, most notably the striatum (Bissonette et al., 2008; Chudasama and Robbins, 2003; McAlonan and Brown, 2003; Ragozzino, 2007). Dysfunction within this prefrontal-striatal circuitry is a key feature of schizophrenia (Robbins, 1990) and many studies have described impaired reversal learning in schizophrenia patients (Leeson et al., 2009a; Murray et al., 2008a; Pantelis et al., 1999; Waltz and Gold, 2007; but see also Joyce et al., 2002). Increasingly, such studies use computerised test batteries such as CANTAB (Robbins et al., 1994), in which the test for reversal learning is highly analogous to the rodent touchscreen version.

When rodents are tested on the touchscreen visual discrimination and reversal task, dissociations in performance may be observed between early post-reversal trials, in which the animal must inhibit responding to the previously correct stimulus in order to avoid perseverative errors, and later post-reversal trials, which reflect learning of the new association. Rats with lesions of the OFC, for example, displayed increased perseveration in earlier post-reversal trials, but did not differ from sham controls in the subsequent "new learning" phase (Chudasama and Robbins, 2003). Rats with lesions within the medial prefrontal cortex, by contrast, made significantly more errors than sham animals in the later post-reversal trials, but did not show increased perseveration (Bussey et al., 1997b; Chudasama and Robbins, 2003). A similar dissociation was seen in NR2A knockout mice, which showed impaired acquisition both of the initial discrimination and the new

association post-reversal, but did not show altered perseveration (Brigman et al., 2008). Both types of error are likely to be relevant to schizophrenia. Perseveration is a common feature of the disorder, perhaps reflecting a reduced sensitivity to negative feedback (Leeson et al., 2009a). Striatal dysfunction has been implicated in the cognitive impairments in schizophrenia (Simpson et al., 2010) and dorsomedial striatal inactivation impairs the ability of animals to maintain a new response strategy during reversal learning (Ragozzino, 2007).

The touchscreen visual discrimination and reversal task is, in addition, amenable to pharmacological manipulation. For example, a D1-like receptor agonist produced an impairment in early reversal trials, without affecting acquisition of the initial visual discrimination (Izquierdo et al., 2006). While sub-chronic administration of the NMDA receptor antagonist phencyclidine (PCP) did not impair either acquisition or reversal in C57BL/6 mice (Brigman et al., 2009), increased perseveration can certainly be detected using this task (Chudasama and Robbins, 2003), and so ongoing research will attempt to identify a PCP protocol capable of reproducing this effect.

Acquisition of the discrimination is in itself a useful tool for studying visual processing in schizophrenia. Neurotransmitter systems such as the glutamatergic and cholinergic systems have been implicated in the disorder (Coyle, 2006; Raedler et al., 2007). Daily perirhinal cortex infusion of the GABA-A receptor agonist, muscimol, impaired acquisition of touchscreen visual discrimination in rats, as did perirhinal infusion of scopolamine or AP5 (Winters et al., 2010). Impaired acquisition was also seen in GLAST (EAAT-1, excitatory amino-acid transporter 1) knockout mice, further implicating the glutamatergic system (Karlsson et al., 2009). These studies featured the standard shape and photographic stimuli routinely used in touchscreen tasks. Discrimination and reversal can of course be carried out in standard 'Skinner boxes' using, e.g., lights as stimuli, and levers as responses. However in addition to the increased learning observed when stimulus-response contiguity is maximized, the touchscreen offers much richer possibilities for stimulus manipulation. In a recent study, for

example, after rats acquired a shape discrimination we then ‘morphed’, or blended, the stimuli together to increase the perceptual similarity of the stimuli, bringing down baseline performance from ceiling in order better to detect improvements in performance following the administration of putative cognitive enhancers (McCarthy et al., 2011). Furthermore as with all touchscreen tasks the flexibility of stimuli allows for the presentation of stimuli identical to those presented to humans. For example a schizophrenia-relevant task we are currently building on top of the basic pair-wise discrimination template is the attentional set-shifting task, which we are presenting to rats and mice using the same types of shape and line stimuli used in the CANTAB version of this task (Brigman et al., 2005). The visual discrimination and reversal components would be folded into the sequence of testing as they are in the CANTAB version. We are also developing a 3-stimulus version of the reversal task, which will allow us better to distinguish between perseveration and learned irrelevance (Arnsten et al., 1997; Jentsch et al., 2002; Garavan et al., 2000).

Impairments in visual processing are increasingly acknowledged in schizophrenia (Butler and Javitt, 2005) and have recently been highlighted by CNTRICS as a key area for task development (Green et al., 2009). This is in part because deficits in perceptual processing contribute to higher-level cognitive and social dysfunction, and thus to poorer functional outcome (Klosterkötter et al., 2001; Rassovsky et al., 2010). Visual processing deficits in schizophrenia are particularly prominent in the lower resolution magnocellular system (Butler and Javitt, 2005), although deficits in the faster, higher resolution, parvocellular system have also been reported (Slaghuis, 1998). Additional impairments are seen in gain control – the process by which neurons adapt their responses to optimise sensitivity to detect stimuli in a given environmental context (Dakin et al., 2005; Kim et al., 2006), and integration – the ability to extract a “global whole” from isolated local elements (Kurylo et al., 2007; Silverstein et al., 2006). The touchscreen method, with its rich possibilities for stimulus manipulation, may thus offer a new means of investigating some of these relatively overlooked, but robust and functionally relevant deficits. Although we have not yet attempted it, it is also of course possible to present moving stimuli to rodents, perhaps allowing the study of motion discrimination.

2.2. The TUNL task: working memory and pattern separation

Working memory dysfunction is a key aspect of cognitive impairment in schizophrenia. Identified by both the MATRICS (Nuechterlein et al., 2008a) and CNTRICS (Barch et al., 2009) initiatives as one of several dimensions of interest, working memory impairments have been reliably documented in schizophrenic patients, as well as back-translated to studies of primate and rodent models of schizophrenia. The work of Patricia Goldman-Rakic was instrumental in demonstrating that dopaminergic systems could underlie schizophrenia-like working memory impairments in rhesus monkeys, with similar results found in rodents (Castner et al., 2000; Floresco and Phillips, 2001; Phillips et al., 2004; Sawaguchi and Goldman-Rakic, 1991). Indeed, visuo-spatial working memory (SWM) has been identified as a putative cognitive endophenotype of schizophrenia (Park and Holzman, 1992; Park et al., 1995; Saperstein et al., 2006).

These findings regarding working memory have linked mainly to the role of prefrontal cortex in working memory (Courtney et al., 1998) and the hypofrontality observed in schizophrenia (Carter et al., 1998). However the hippocampus has also been implicated in schizophrenia (Harrison, 2004): volume is decreased in schizophrenic patients (Bogerts et al., 1990; Lawrie and Abukmeil, 1998; Nelson et al., 1998; Velakoulis et al., 1999), and hippocampal

volume in patients can correlate with cognitive performance (Goldberg et al., 1994; Heckers et al., 1998). As the hippocampus is important for working memory in rodents (e.g., Kesner et al., 1993; McHugh et al., 2008; Wan et al., 1994), spatial working memory in particular has been seen as a fruitful approach to studying working memory in animals. The major automated working memory test in rodents has been the Delayed Non-Matching to Position (DNMTP) task, during a trial of which the animal is presented with one of two levers, and after a variable delay, must choose which of the two levers was *not* presented prior to the delay (i.e., the animal must ‘non-match’). DNMTP impairments result from manipulations to schizophrenia-relevant structures such as the hippocampus or prefrontal cortex (Aggleton et al., 1992; Dunnett et al., 1990), and more recently, impairments on DNMTP have been observed in mice with mutation of schizophrenia-associated genes such as *DISC1* (Li et al., 2007). The prefrontal cortex has been of particular interest, as lesions cause DNMTP impairment specific to working memory function (Granon et al., 1994). However, serious questions regarding the utility of DNMTP emerged when ‘mediating behaviours’ were observed in rats performing the task (Chudasama and Muir, 1997). These behaviours are possible because it is determined during the sample phase which location will be correct during the choice phase. Thus the rodent can use orientation toward the lever, or other responses, to bridge the delay and thus reduce or eliminate the need for memory per se. The need for a method of assessing working memory that minimises mediating behaviours led to the development of the Trial-Unique Delayed Non-Matching to Location (TUNL) task (Talpos et al., 2010).

An advantage of the touchscreen method for spatial tasks is that stimulus options are not limited to two locations determined by two levers as in DNMTP (Talpos et al., 2008). Thus although the TUNL task is similar to DNMTP in that two locations are used during a given trial, any of a number of alternative locations can serve as the correct stimulus on choice (Talpos et al., 2010; see Fig. 1). Thus, unlike in DNMTP the animal cannot know, during the delay, which location will be correct on choice – and therefore cannot orient toward it. Indeed, systematic video analysis of potential mediating behaviours in TUNL showed little evidence for performance-enhancing mediating behaviours (Talpos et al., 2010).

The use of multiple locations confers an additional advantage; namely pairs of locations can be chosen which are either close together, far apart, or somewhere in between. This allows assessment of ‘pattern separation’ alongside the assessment of memory across a variable delay. ‘Pattern separation’ is the ability to form distinct representations from similar inputs that are closely presented in space (and/or time), and is thought to be important for keeping similar episodes distinct in memory. (This function of the hippocampus and its possible relevance to schizophrenia is discussed further in the next section.) Kesner and colleagues have shown that hippocampal lesions impair performance at small, but not large separations, indicating a deficit in pattern separation ability (Kesner et al., 2004). Talpos et al. (2010) examined the effects of excitotoxic lesions of the hippocampus on performance of TUNL under conditions of different separations and delays. Hippocampal lesions were shown to significantly impair performance when the delay period was increased, or the separation decreased. Intriguingly, recent preliminary results indicate that prefrontal cortex lesions in the rat impair memory across a delay in TUNL, but *not* pattern separation (K.A.L. McAllister et al., unpublished results). If this result holds up, TUNL would represent a task for which the hippocampus and PFC are dissociable, but at the same time interact in the service of working memory. This is particularly relevant to schizophrenia, as it has been widely acknowledged that structural and functional changes in both the hippocampus and prefrontal cortex play an important role in the pathophysiology of

schizophrenia (see above). Furthermore, schizophrenic brains show altered connectivity between hippocampus and prefrontal cortex (Meyer-Lindenberg et al., 2005), and impaired hippocampal-prefrontal synchrony during performance on a working memory task has been observed in a mouse with a microdeletion on human chromosome 22 (22q11.2), a genetic risk factor for schizophrenia (Sigurdsson et al., 2010). This mirrors human data where abnormal coupling is seen between the prefrontal cortex and hippocampus in patients with schizophrenia and healthy carriers of *rs1344706* risk genotypes (Esslinger et al., 2009).

A disadvantage of TUNL is that it takes several weeks to train; however we are currently working on more rapidly-acquired versions, as well as a version for the mouse.

2.3. The location discrimination (LD) task: focus on dentate gyrus and neurogenesis-dependent pattern separation

As described above, schizophrenic brains can exhibit gross changes in hippocampal morphology. However more detailed analyses have led many researchers to emphasise more subtle changes within the subregions of the hippocampus, and in particular in the dentate gyrus (DG), including changes in adult neurogenesis in this region (DeCarolis and Eisch, 2010; Eisch et al., 2008; Reif et al., 2006, 2007; Toro and Deakin, 2007). The finding of aberrant neurogenesis is consistent with the idea that the aetiology of schizophrenia may, at least in part, involve abnormal neurodevelopment. Notably, altered neurogenesis is also observed in mouse models of schizophrenia susceptibility genes, such as mice that have a mutant form of *DISC1* (Duan et al., 2007) or constitutively lack the bHLH transcription factor *NPAS3* (Pieper et al., 2005). Furthermore, pharmacological models of schizophrenia, such as treatment with the NMDA receptor antagonists PCP and ketamine have been shown to decrease hippocampal cell proliferation and survival (Keilhoff et al., 2004; Liu et al., 2006; Maeda et al., 2007). Disturbances in components of the Wnt signalling pathway, which mediates neurogenesis, have additionally been reported in schizophrenia (Beasley et al., 2001; Cotter et al., 1998; Kozlovsky et al., 2005). Additionally, within the DG, a reduction in the number of mossy fibers synapses onto CA3 neurons has been documented in patients (Kolomeets et al., 2005, 2007) in addition to decreased levels of NR1 mRNA, the obligate subunit of the NMDA receptor, which has been shown to be selectively reduced in the DG (Gao et al., 2000; Law and Deakin, 2001).

As described in the previous section, the DG in particular has been implicated in pattern separation. This idea is based on a number of sources of evidence, including the architecture of the DG and the nature of its projections to the CA3 (reviewed by Aimone et al., 2010; Deng et al., 2010), computational modelling (O'Reilly and McClelland, 1994; Rolls and Kesner, 2006), lesion studies in rodents (Gilbert et al., 2001; Hunsaker and Kesner, 2008), electrophysiological data (Leutgeb et al., 2007) and reports that NMDA receptors within the DG, specifically the NR1 subunit, are important for pattern separation (McHugh et al., 2007). Additionally, human fMRI studies also indicate that activity in the DG/CA3 regions is correlated with pattern separation demands (Bakker et al., 2008). Using a spatial pattern separation task that has been developed in the touchscreen (McTighe et al., 2009), a functional role for hippocampal neurogenesis in pattern separation has recently been described (Clelland et al., 2009). Although the TUNL task described above has the advantage that it measures memory across a delay in addition to pattern separation, the LD task was designed to be a more rapidly-acquired task that focuses selectively on pattern separation. In the LD task, animals are trained to discriminate the correct one of two spatial locations delineated by illuminated squares. By varying the distance between the choice

locations, the requirement for pattern separation can be manipulated. Training on this task takes only a few weeks. Mice with neurogenesis ablation perform similarly to control mice when discriminating two stimuli that were located spatially distant to one another, but were impaired when the stimuli were located closer in proximity, suggesting that neurogenesis is required for spatial pattern separation (Clelland et al., 2009). In line with these findings, a subsequent study revealed that mice with increased neurogenesis induced by wheel-running displayed *enhanced* pattern separation ability compared to non-exercising mice (Creer et al., 2010).

Thus the LD task is highly sensitive to hippocampal dysfunction, and in particular DG neurogenesis impairment. As the DG and neurogenesis have been implicated in schizophrenia, this task may be a rapid and useful assay of this aspect of dysfunction in schizophrenia. Of course the foregoing discussion raises the question of whether there is a link between schizophrenia and pattern separation in humans, which could of course contribute to the working memory impairments seen in schizophrenia (outlined above). Although no study has yet explicitly examined pattern separation in schizophrenic patients, growing evidence suggests this may be a relevant cognitive function of interest for future studies (Tammimga et al., 2010).

2.4. Object-place paired-associate learning

Schizophrenic patients are impaired on certain forms of associative learning i.e. the correct recall of contextual information regarding certain events, which can lead to errors in source monitoring (Brebion et al., 1997; Diaz-Asper et al., 2008; Johnson et al., 1993; Keefe et al., 1999; Vinogradov et al., 1997; Waters et al., 2004). Impairments in object-place associative memory in schizophrenic patients have been evaluated using the object-place paired-associate-learning (PAL) test from CANTAB. Studies using the CANTAB-PAL have revealed an impairment in patients with established schizophrenia (Aubin et al., 2009; Chouinard et al., 2007; Donohoe et al., 2008; Wood et al., 2002). Furthermore, PAL was found to be impaired in the prodromal phase of the disease and in individuals with an increased risk of developing schizophrenia (Barnett et al., 2005; Bartok et al., 2005), although this finding is not supported by all studies (Wood et al., 2002). Notably, PAL performance was found to be correlated with symptom severity and normal daily functioning (Aubin et al., 2009; Barnett et al., 2005; Prouteau et al., 2004, 2005; Ritsner and Blumenkrantz, 2007) and test results allow differentiation between schizophrenia and schizoaffective disorder (Stip et al., 2005).

Encoding and retrieval of paired associates in humans is thought to rely on concurrent prefrontal and hippocampal activation (Eichenbaum, 1999, 2000; Milner et al., 1997; Owen et al., 1995; Simons and Spiers, 2003). Similarly in rodents both the hippocampus and prefrontal cortex are thought to comprise a circuit underlying object-place learning (unpublished findings reported in Warburton and Brown, 2010), and as discussed above, schizophrenia has been associated with deficient prefrontal-hippocampal interaction. Thus object-place paired associate learning seems to rely on structures implicated in schizophrenia, perhaps explaining why paired-associate learning, and associative learning in general, can be compromised in schizophrenia.

With this background in mind, we sought to develop a task for the touchscreen in which rodents learned associations between objects (shapes) and locations on the computer screen (Talpos et al., 2009). In this task, animals learn to associate three different visual patterns (A, B and C) with three unique spatial locations (1, 2 and 3) on a screen. Pattern A is only correct if it appears in location 1; B is correct in location 2 and C is correct in 3. On each trial animals are

presented with two choices e.g. A1 and B3 and are subsequently required to touch the screen in the correct location (A1) in order to receive a food reward. Thus the touchscreen paired-associate learning task involves the association of a certain object (visual pattern) with a location on the screen. Post-acquisition performance of this task has been shown to require an intact dorsal hippocampus, and more specifically activation of NMDA and AMPA receptors in the hippocampus (Talpos et al., 2009). Experiments in mice indicate dependence on the cholinergic system (Bartko et al., 2010). Mice carrying deletions of the schizophrenia-associated gene *Dlg2* (Consortium, 2008; Walsh et al., 2008) show severe impairments in this task (Nithianantharajah et al., 2009). Ongoing research projects include investigating the role of other receptor systems and structures such as the prefrontal cortex in this task, and developing more rapidly acquired versions of the task (currently rats require a mean of approximately 20–30 90-trial sessions to reach a criterion of 80% correct).

2.5. The 5-choice task: attention, impulsivity and compulsivity

Attentional changes in schizophrenia are well known (Fioravanti et al., 2005; Luck and Gold, 2008; Nuechterlein et al., 2006; Young et al., 2009) and are often assessed using the continuous performance test (CPT). The CPT is a paradigm comprising several procedural variants, many of which have proven reliable indicators for the presence of, and susceptibility to, schizophrenia. In its basic form, the CPT involves rapid, externally-paced (i.e., not under subject control) presentation of a large number of consecutive stimuli, to which subjects are instructed to respond only upon detection of a designated target stimulus or sequence. The CPT is generally considered primarily as a measure of vigilance or sustained attention, with performance variables (e.g., accuracy or response latency) typically worsening as the session proceeds. However, performance is dependent on task parameters and the task may be modified to be more or less sensitive to elements of sustained attention, selective attention, impulsivity or executive control. Versions of the CPT have recently been selected by both the MATRICS and CNTRICS groups for inclusion in their batteries for assessing cognitive dysfunction in schizophrenia patients (Barch et al., 2009; Nuechterlein et al., 2008b).

Although the CPT appears to be sensitive to certain attentional and cognitive processes disturbed in schizophrenia, uncovering their neural and neurochemical basis, as well as the mechanisms of pharmacotherapeutic agents would greatly benefit from a translational preclinical model of cognitive function. The five-choice serial reaction time task (5-CSRTT) for the rodent has been developed and proposed as an analogue of the CPT in humans (see Chudasama and Robbins, 2004, 2006; Robbins, 2002 for recent extensive reviews). Similar to the CPT, the 5-CSRTT involves presentation of a large number of discrete consecutive trials. On each trial, subjects are required to scan a horizontal array of five locations (i.e., divided attention) for the presence of a brief light stimulus during a short (e.g., 5 s) inter-trial interval (ITI) (see Fig. 1). Behavioural measures include accuracy, omissions (when the animal does not nose poke any of the front panel locations within the 'limited hold' period following stimulus offset), premature responses (responses during the ITI, prior to the presentation of the visual stimulus, an index of impulsivity), perseverative responses (repeated responses, a measure of compulsivity), as well as response and reward collection latencies.

Dysfunction in regions of the prefrontal cortex is one of the most studied and consistent findings in schizophrenia research (see above) and has been associated with disruptions in performance on versions of the CPT (Fallgatter, 2001; Yoon et al., 2008). Moreover, dysregulation of various neurotransmitters in these prefrontal

regions, in particular dopamine and glutamate, have been extensively documented in schizophrenia and have been linked to performance changes in cognitive tasks such as the CPT (Braver et al., 1999; Coyle, 2006; Paz et al., 2008; Purdon et al., 2008; Stone et al., 2007; Tammimga, 1999). Similar neural systems underpin performance on the 5-CSRTT. In the rat, large excitotoxic lesions of the mPFC cause substantial but fairly selective reductions in response accuracy and increases in response latency compared with sham-lesioned controls (Muir et al., 1996; Passetti et al., 2003). More discrete excitotoxic lesions show that the effect on discrimination accuracy, particularly following variable ITI and noise burst challenges, may be restricted to damage of the anterodorsal mPFC (Chudasama et al., 2003; Passetti et al., 2003). Similar decrements in response accuracy and increases in response latencies are observed following lesions of the dorsomedial striatum (Rogers et al., 2001). This functional circuitry is further supported by the observation that asymmetrical, disconnection preparations (in which a lesion to the mPFC in one hemisphere is combined with a lesion to the medial striatum in the other hemisphere), produce effects similar to that of the bilateral lesions (Christakou et al., 2001). In-vivo microdialysis studies have revealed that cortical, and particularly prefrontal, DA is highly engaged during 5-CSRTT performance (Dalley et al., 2002b). Site-specific infusion of dopamine D1 receptor agonists directly into the mPFC enhances accuracy in animals having low baseline performance, while, conversely, dopamine D1 receptor antagonists impair accuracy in animals with relatively high baseline performance (Granon et al., 2000). In contrast, mPFC infusion of the D2 receptor antagonist, sulpiride, showed no significant effects in normal animals, although intra-accumbens infusion of sulpiride could remediate the impairments in attentional accuracy produced by mPFC lesions (Pezze et al., 2009). In addition, site-specific bilateral injection of competitive NMDA antagonist, CPP, into the mPFC of the rat produced reductions in choice accuracy, as well as increases in omissions and correct response latency (Baviera et al., 2008; Murphy et al., 2005).

Putative animal models of schizophrenia affect performance on the 5-CSRTT. Rats given repeated treatment with amphetamine showed impairments in choice accuracy and increased trial omissions under reduced stimulus duration conditions (Fletcher et al., 2007). These effects were reversed by infusion of the D1 receptor agonist, SKF38393, directly into the mPFC. Several studies have demonstrated that acute systemic administration of NMDA receptor antagonists MK-801 or PCP can cause reductions in choice accuracy and response latencies in rats and mice on the 5-CSRTT (see Amitai and Markou, 2010 for review; Amitai et al., 2007; Paine and Carlezon, 2009; Paine et al., 2007). Moreover, repeated dosing of PCP in rats produces significant reductions in discrimination accuracy, as well as increases in correct response latency and premature responses (Amitai and Markou, 2009; Amitai et al., 2007). Sub-chronic or chronic intermittent treatment PCP may result in somewhat milder effects, with moderate slowing of responding (Thomson et al., 2011) and subtle impairments in accuracy observed only after the ITI is reduced (preliminary unpublished results described in Neill et al., 2010). Neonatal ventral hippocampal lesions (nVHL) were observed to produce mild impairments in choice accuracy and more pronounced increases in correct response latencies, which could be exacerbated by introducing distracting white noise prior to stimulus presentation, but not by varying the stimulus duration or ITI (Le Pen et al., 2003). In addition, nVHL rats showed increased sensitivity to the performance disruptive effects of acute PCP, but not acute amphetamine, treatment (Le Pen et al., 2003). In genetic mouse models, heterozygous reeler mice did not exhibit any behavioural deficits in acquisition or performance on a modified 3-choice procedure

(Krueger et al., 2006). However, a recent study using an imprinting centre deletion mouse model for PWS showed these mice to have decreased choice accuracy, increased omissions, and longer correct reaction times compared to controls, which were exacerbated under reduced stimulus duration conditions (Relkovic et al., 2010).

The 5-CSRTT also appears sensitive to the remediating effects of first and second generation antipsychotic medications. Under baseline 5-CSRTT conditions using 'normal' rats, the typical antipsychotics, haloperidol or sulpiride, and the atypical antipsychotics clozapine, risperidone, quetiapine, or olanzapine, do not affect performance except for the behavioural disruptions of decreased correct responses (all except haloperidol), and increased omissions (sulpiride, clozapine, risperidone and olanzapine) at higher doses (Amitai et al., 2007; Harrison et al., 1997; Paine and Carlezon, 2009). However, in mPFC-lesioned animals, systemic administration of sulpiride can ameliorate the impairment in attentional accuracy (Passetti et al., 2003), an improvement that is also observed after site-specific infusions of sulpiride into the nucleus accumbens (Pezze et al., 2009). Acute administration of low doses of clozapine, but not haloperidol, can remediate the accuracy deficits and increased omissions induced by acute MK-801 administration (Paine and Carlezon, 2009). Clozapine, but not haloperidol, can improve the accuracy deficits induced by mPFC infusion of CPP (both clozapine and haloperidol reduced the mPFC CPP-induced elevations in premature responses, but neither were effective in altering the increased omissions and correct response latencies) (Baviera et al., 2008). In another pair of studies, low doses of sertindole and clozapine prevented mPFC infusion of CPP-induced accuracy deficits, anticipatory over-responding and the rise in glutamate release induced by CPP (Carli et al., 2010a), and oral aripiprazole and olanzapine, but not haloperidol, abolished a CPP-induced accuracy deficit and were associated with a decrease in glutamate release (Carli et al., 2010b). Further, chronic treatment with clozapine (Amitai et al., 2007), but not quetiapine (Amitai and Markou, 2009) can attenuate the reductions in accuracy and increases in premature responding following repeated PCP exposure.

The 5-CSRTT thus appears to be a highly promising translational behavioural paradigm that can sensitively assess aspects of attentional/cognitive dysfunction that is observed clinically in schizophrenia. Although the task has typically been carried out in the "nine-hole box" apparatus, the task runs well in touchscreens (Sahgal and Steckler, 1994; Steckler and Sahgal, 1995). Indeed we have found that mice progress from the end of pre-training to a baseline stimulus duration of 2 s within 3 weeks. We have obtained stimulus duration-dependent effects on accuracy in muscarinic knock-out mice and mouse models of Alzheimer's disease and have shown facilitations of attention by the anticholinesterase donepezil in both rats and mice (McTighe et al., unpublished results; Romberg et al., 2011). The reversal of impairments in vigilance in Alzheimer's mice with donepezil parallels strikingly the same effects in patients on an analogous task, indicating predictive validity at least with respect to this task and Alzheimer's disease. With respect to schizophrenia, given that muscarinic agonists have been suggested as a treatment (Sellin et al., 2008), is the finding that mice with deletion of the M1 receptor show increased striatal dopamine release (Gerber et al., 2001), and abnormal responding consistent with striatal dopaminergic manipulations in rats (Bartko et al., submitted). Thus the touchscreen may prove to be a particularly useful way to run the 5-CSRTT in mice and rats, with the advantage of improved comparability with results from other tests of learning, memory etc carried out in the same apparatus. In addition, the flexibility of stimulus material in the touchscreen could allow the marriage of spatial locations as in the 5-CSRTT and non-spatial (e.g., shape)

stimuli to create tests of object-based attentional tasks using, e.g., rapid visual presentation of non-spatial stimuli, or the use of non-spatial stimuli as distractors. Such modifications are currently under development.

2.6. Extinction: inhibition of responding in the face of non-reward

"My first extinction curve showed up by accident. A rat was pressing the lever in an experiment on satiation when the pellet dispenser jammed. I was not there at the time, and when I returned I found a beautiful curve. The rat had gone on pressing although no pellets were received.... I was terribly excited. It was a Friday afternoon and there was no one in the laboratory who I could tell. All that weekend I crossed streets with particular care and avoided all unnecessary risks to protect my discovery from loss through my accidental death" (Skinner, 1979).

Fortunately for posterity, Skinner made it through the weekend and went on to describe his observation of operant extinction in his rats. As Skinner noted, Pavlov had reported extinction of classical conditioned responses some fifty years earlier (Pavlov, 1927). Both forms of extinction can be operationally defined as a form of learning in which a response is reduced after repeated experience of a stimulus that elicits the response, in the absence of the previously paired reinforcer.

Extinction has been surprisingly understudied in schizophrenic patients. However, recent evidence indicates that extinction of fear responses, which has been intensively studied in the context of anxiety disorders (Holmes and Quirk, 2010), is also impaired in schizophrenia. Holt and colleagues (2008) trained subjects to associate a visual stimulus with electric shock in one room and then extinguished the fear (skin conductance) response evoked by repeatedly presenting the stimulus without shock in a different test room. Medicated schizophrenic patients were more likely than normal controls to retain fear responses the following day when presented with the stimulus in the extinction test room, indicating a deficit in extinction recall and/or a failure to link the extinction room with a safety signal. Given the dependence of extinction on prefrontal and hippocampal function (Corcoran and Quirk, 2007; Holmes and Wellman, 2009), the deficits might be related to abnormalities in these regions, which are thought to be dysfunctional in schizophrenic patients (Nelson et al., 1998; Taylor et al., 2007).

We have used a touchscreen extinction task to test mice with mutations in various molecules of the glutamatergic system, a neurotransmitter system which has been repeatedly implicated in schizophrenia (Coyle, 2006). We employed a procedure in which mice are first trained to reliably make a touchscreen response at a simple visible stimulus (white square) for food reward. Extinction is then measured as the rate at which the mouse demonstrates low levels (>20%) of responding over (30-trial) daily sessions. This method has been extensively characterized across different inbred mouse strains (Hefner et al., 2008; Lederle et al., 2011). Mutant mice lacking the NR2A subunit of the NMDA receptor have a significant impairment in pairwise visual discrimination, but extinguish a stimulus-response as well as do littermate controls (Brigman et al., 2008). A similar phenotypic profile of impaired discrimination but intact extinction is found in mutants with deletion of the glutamate transporter (Karlsson et al., 2009), GLAST (EAAT-1, excitatory amino-acid transporter 1), a mutant which exhibits a constellation of antipsychotic-reversible 'schizophrenia-related' phenotypes (Karlsson et al., 2008). By contrast, in another mutant with 'schizophrenia-related' behavioural abnormalities (Fitzgerald et al., 2010; Wiedholz et al., 2008), the AMPA receptor GluA1 subunit knockout mouse, discrimination and reversal are

unimpaired while extinction is severely impaired (Barkus et al., submitted).

A general conclusion is that these tasks provide assays of different forms of ‘cognitive flexibility’ and ‘perseveration’ that are dissociable at the molecular level. This underscores the utility of adopting a battery approach to assessing cognitive function in future studies (see discussion below). Precisely why it is that targeting these different nodes within the glutamate system produces different patterns of impairment on these tasks is currently unclear. Indeed, this will be a key question for future studies aimed at dissecting the role of this and interacting systems in mediating schizophrenia-related cognitive impairment.

2.7. *Autoshaping: Pavlovian approach and the mesolimbic dopamine system*

The role of striatal dopamine in schizophrenia has long been known (Kleinman et al., 1988), and its role in cognition in particular has been forcefully argued (Simpson et al., 2010). Of particular interest is the ventral striatum (Robbins, 1990). One recent idea is that dopaminergic neurons that extend from the midbrain to the ventral striatum code “reward prediction error”, the teaching signal which underlies the acquisition of stimulus-outcome associations (Schultz and Dickinson, 2000). A recent fascinating finding is that patients with psychosis exhibit abnormal physiological responses associated with prediction error in the striatum (as well as other structures) (Murray et al., 2008b).

The striatal dopamine system, and midbrain-ventral striatal “prediction error” system in particular, can be targeted using a simple task we call “Autoshaping” (Bussey et al., 1997a). This is a very rapidly administered test of simple classical conditioning that capitalizes on and measures “Pavlovian approach” to stimuli predictive of reward. On a given trial of this task a stimulus (vertical white bar) appears on the left or the right of the screen for several seconds. Either the left or the right stimulus is deemed the CS₊; the other is the CS₋. Immediately on offset of the stimulus CS₊, a food reward is delivered. After the CS₋ no reward is delivered. Over trials, the mouse or rat learns that the CS₊ predicts reward and makes increasingly more approaches and touches to it. Approaches and touches to the CS₋ decrease or stay the same. The difference between the number or proportion of approaches or touches to the CS₊ and CS₋, and well as the difference between the latency to approach or touch, can be taken as an indication of learning. The task is very rapidly acquired; significant discrimination by rats can be observed even within a single session. Lesions of the ventral striatum, dopamine receptor antagonism, and dopamine depletion within this region, impair learning (Dalley et al., 2002a, 2005; Parkinson et al., 2002). This task dissociates striatal dopamine from other systems, for example, the task is not affected by lesions of the prefrontal cortex (Bussey et al., 1997a) or the hippocampus and related structures (Bussey et al., 2000; Ito et al., 2005). The Autoshaping test has already been used in many studies involving lesion and drug manipulations (Cardinal et al., 2003; Di Ciano et al., 2001; Parkinson et al., 2002, 1999, 2000). For the purposes of schizophrenia research, because it is a classical conditioning procedure it could perhaps be modified to administer other schizophrenia-relevant tests, for example latent inhibition (Solomon et al., 1981; Weiner and Feldon, 1987; Weiner et al., 1984).

3. A ‘flexible’ battery approach

“All putative animal models [of neuropsychiatric disorders] should be evaluated with the broadest range possible of behavioral assays”
Nestler and Hyman (2010)

Although each of the above tasks can be used alone, we would advocate the use of a ‘battery’ approach to establish a cognitive profile of an animal. In this way a given task in the battery not only yields useful results in its own right, it can serve as a control for other tasks in the battery. Thus, if an animal fails object-place paired associate learning but performs well on visual discrimination and reversal, it is unlikely that the paired associate learning impairment is due to a difficulty with perceptually discriminating objects. Similarly if an animal is impaired on TUNL but not 5-CSRTT, an attentional explanation for the TUNL impairment would seem unlikely. These comparisons can be made with confidence, because all of the tasks use the same types of stimuli, responses and reward, and of course are all carried out in the same testing apparatus.

Yet to suggest a battery approach is not to suggest slavish adherence to an immutable sequence of tests; for example each of these tasks can be followed by behavioural probes to follow up interesting findings. For example, shape or photographic stimuli can be ‘morphed’ to increase the premium on perceptual discrimination (McCarthy et al., 2011). Parameters in TUNL can be further varied, for example inter-trial intervals might be varied to increase or decrease interference. The 5-CSRTT can be followed by sessions of rapid presentation of stimuli during long sessions in order to examine sustained vigilance. And so on.

How, practically, does one implement the battery? There are different models, depending on one’s needs. The extremes are 1. Run each task in a new cohort of naïve animals, or 2. Run many tasks in each animal (we are currently working out what tasks ‘go together’ best, and are settling on a sequence in which the tasks appear not to interfere with one another). Option 1 might be the better choice for, say, a progressive disease model or a drug study; option 2 has its own advantages, for example fewer animals are used, which is desirable in cases where large numbers of animals are difficult to obtain. Which approach is taken depends on several factors that may differ from experiment to experiment.

Finally of course brand new tasks for the battery are being developed all the time, some of which could prove particularly useful for schizophrenia research; we have already alluded above to attentional set-shifting tests similar to those administered using the CANTAB method (Leeson et al., 2009b); in addition we are having success developing a touchscreen version of the object recognition memory test used so widely to study animal models of schizophrenia (e.g., Duffy et al., 2010; Grayson et al., 2007). Furthermore, some researchers are currently expanding the method to incorporate other techniques such as *in vivo* electrophysiology and dialysis.

Are there any disadvantages to this method? An obvious one is that, being a relatively new method, there does not yet exist the extensive database behind it that some methods – for example, the Morris water maze – enjoy. But the touchscreen database is expanding: at this time we know of roughly 30 labs using touchscreen technology with rodents, and so the validation and development of this method is continuing apace. Another has been alluded to above: although the touchscreen method avoids the aversive stimuli and stressors endemic to some other methods, any method which uses gustatory rewards is vulnerable to the potential effects of some perturbations on motivation to perform for reward. Indeed we have experienced such problems with certain mouse models, and to some extent were able to mitigate them by, for example, using larger volumes of highly palatable reinforcers (e.g., 20ul strawberry milkshake), and requiring fewer trials per session (from the control groups as well, of course). Finally, although all things considered we strongly advocate a battery approach in which all tests are carried out in the same apparatus, such an approach might make within-subjects task designs more vulnerable to negative or positive transfer between tasks. Of course this is

a potential problem when any within-subjects battery is used; however the problem could be exacerbated when contexts are so similar between tasks. When designing within-subjects testing sequences, we try to combine tests which are least likely to interfere with one another – although such interference can only be definitively ruled out by retesting naive animals on the task in question.

There is still much work to be done. Much more validation is required to establish the neural circuits and transmitters involved in the tasks. We are currently piloting the mouse and rat tasks in human subjects, to allow even tighter translation and the ability to test whether the same circuits, neurotransmitters etc, and psychological processes (e.g., habit versus goal-directed performance) are involved in these tasks in rodents and humans. Another issue we will need to address is test-retest reliability, and what are the pharmacological sensitivities of each of the tasks. What is already clear from the foregoing discussion is that the touchscreen method offers much more than a 'glorified Skinner box'. The apparatus can theoretically be used to run any task that can be run in a box with lights and levers, but the myriad of stimuli that are possible, and the multiple locations in which they can be presented, offer virtually unlimited possibilities for task development.

4. Summary

The touchscreen testing method satisfies what we think is a fairly non-controversial 'wish-list' of desirables for a cognitive testing method for assessing rodent models of schizophrenia. A number of tests relevant to schizophrenia research are currently being validated. These tasks can be deployed using a 'flexible battery' approach to establish a cognitive profile for a particular mouse model. We have found these tasks to be capable of detecting not just impairments in function, but enhancements as well, which is essential for testing putative cognitive therapies. New tasks are continuously coming 'on-line', many of which may prove particularly valuable for schizophrenia research.

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