The NEWMEDS rodent touchscreen test battery for cognition relevant to schizophrenia

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ABSTRACT

Rationale

The NEWMEDS initiative (Novel Methods leading to New Medications in Depression and Schizophrenia, http://www.newmeds-europe.com) is a large industrial-academic collaborative project aimed at developing new methods for drug discovery for schizophrenia. As part of this project, Work package 2 (WP02) has developed and validated a comprehensive battery of novel touchscreen tasks for rats and mice for assessing cognitive domains relevant to schizophrenia.

Objectives

This article provides a review of the touchscreen battery of tasks for rats and mice for assessing cognitive domains relevant to schizophrenia and highlights validation data presented in several primary articles in this issue and elsewhere.

Methods

The battery consists of the 5-choice serial reaction time task and a novel rodent continuous performance task for measuring attention, a 3-stimulus visual reversal and the serial visual reversal task for measuring cognitive flexibility, novel nonmatching-to-sample based tasks for measuring spatial working memory and paired-associates learning for measuring long term memory.

Results

The rodent (i.e. both rats and mice) touchscreen operant chamber and battery has high translational value across species due to its emphasis on construct as well as face validity. In addition, it offers cognitive profiling of models of diseases with

cognitive symptoms (not limited to schizophrenia) through a battery approach, whereby multiple cognitive constructs can be measured using the same apparatus, enabling comparisons of performance across tasks.

Conclusion

This battery of tests constitutes an extensive tool package for both model characterisation and preclinical drug discovery.

KEY WORDS

Drug discovery, neuropsychiatric disease, attention, working memory, long-term memory, executive function, cognitive flexibility, response inhibition, rat, mouse

INTRODUCTION

The need for treatment of cognitive dysfunction in schizophrenia

Schizophrenia is a chronic brain disorder caused by a complex and largely unknown polygenetic and environmental interplay producing dysfunctions in brain circuitry within and between prefrontal cortical and subcortical structures (Harrison, 1999). These dysfunctions are behaviourally expressed by disturbances of perception, emotion and thinking; often referred to as positive, negative and cognitive symptoms, respectively.

While available neuroleptics can show good efficacy against the positive symptoms as well as moderate efficacy against the negative symptoms, they have frequently been found to have no effects or even detrimental effects on cognition (Weiss et al, 2002). Yet, the degree of cognitive decline correlates better with recovery prognoses than positive or negative symptoms, and deficits in executive function, working memory and verbal memory are stable and detectable in the prodromal period (O'Carroll, 2000; Barnett et al, 2005; Simon et al, 2007). The inability of available neuroleptics to ameliorate these deficits severely limits treatment progression, and is believed to be the cause of the often poor long-term health outcome associated with diagnosis despite existing medication (Green, 1996, 2006; Holthausen et al, 2007; Keefe et al, 2007). However, attempts at tackling this unmet patient need has not resulted in any major advancement – indeed, chlorpromazine (approved in 1954), haloperidol (approved in 1962) and clozapine (approved in 1972) remain the standard treatments.

Drug discovery: limitations of prevalent approaches

Although preclinical science and increased research and development expenditure has provided a wealth of possible drug targets for cognitive improvement in

schizophrenia, this increase in knowledge has so far brought no relief to the patient. A number of challenges have been outlined for realising treatment options from basic preclinical research. Some have emphasised the urgent need for reliable, dose-sensitive preclinical behavioural assays with high construct validity (Moore et al, 2013) and replication of behavioural findings following genetic (Crabbe et al, 1999) or pharmacological manipulations in experimental animals through private-public pre-competitive knowledge exchange (Insel et al, 2013). Prevalent preclinical assays are often non-automated, hand-run tasks with limited application for high-throughput drug discovery. The current rate of translation of preclinical findings into knowledge of the aetiology of schizophrenia and novel therapeutics also suggests lack of validity. While the solution to increasing the success rate within mental health drug discovery is unlikely to be unitary, improving the translational value of preclinical assays is a necessary milestone for making informed decisions about target selection and compound efficacy.

The NEWMEDS approach

To address these challenges, the NEWMEDS consortium represents a pre-competitive industry-academia collaboration consisting of 9 major biopharmaceutical and academic partners with the aim of improving of treatment options for cognitive deficits in schizophrenia and depression. Within this consortium, Work Package 2 is focused on animal models of cognitive dysfunction that relate to clinical endpoints. An objective of this work package has been to develop a novel battery of validated neuropsychological tests of cognition that provide preclinical measures in rodents that parallel those affected in patients with schizophrenia (see Fig. 1 for an overview of the structure of the consortium). This battery consists of the 5-choice serial reaction time task and a novel rodent continuous performance task to measure attention, a 2 or 3-

stimulus visual reversal task and the serial visual reversal task to measure cognitive flexibility, novel nonmatching-to-sample-based tasks to measure spatial working memory and paired-associates learning to measure long term memory.

Validation of the current battery was aimed at establishing neurocognitive (construct) validity, whereby task performance in the rodent depends on the expected psychological processes and their associated neural systems or mechanisms. This can be demonstrated by varying parametrically those task parameters that load on the specific construct of interest, e.g. 'working memory' and showing comparable effects in experimental animals and humans. Additional validation is provided by demonstrations that task performance depends on homologous neural or neurochemical structures or systems (e.g. 'fronto-striatal' or hippocampal or dopaminergic), as has been shown in humans. Finally, validation would be also achieved by demonstrating back-translational effects e.g. of drug treatments from the clinic to analogous actions in animal models using comparable tasks.

Construct validity in this sense was established, for example, through excitotoxic lesioning or microinfusions of pharmacological agents at specific neuroanatomical regions critical for performance on human task equivalents. Furthermore, the test battery has been used to evaluate experimental rodent models (for example, by manipulation of genetic, neurodevelopmental or pharmacological factors) of schizophrenia-like phenotypes, and to assess the effect of novel compounds provided by biopharmaceutical partners. It is important to note that, regardless of which perturbation is used to generate the neuropathology and pathophysiology of the disorder (‘the ‘disease model’), the utility and predictive validity of animal models of neuropsychiatric disorders will depend critically on the behavioural test measures used. However, a lack of cognitive profile in an animal model relevant to the human condition cannot necessarily be interpreted as a failing of the cognitive

test, as the disease process may not be adequately captured in that particular model. Indeed, uncertainty with regard to the validity of current ‘disease; models of schizophrenia is pervasive. In light of the circular difficulty of using tasks to evaluate models of disease/disorders, whilst using models of disease/disorders to evaluate tasks, establishing predicted sensitivity to manipulations of specific neural circuit mechanisms becomes increasingly critical. Ultimately, the replication of findings from clinical trials using patients with schizophrenia in pre-clinical work provides the most robust validation (Keeler and Robbins, 2011). Whilst this type of back-translation is not currently established for all of the novel tasks presented, it would be an important direction for future work.

Cognitive domains requiring alleviation in schizophrenia and robust analogous pre-clinical measures have previously been identified by two initiatives for clinical and preclinical work, namely the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) and Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS; see Table 1). Of these, CNTRICS has adopted a focus on the translational value of the tasks selected when possible, but several tasks still lack a clear rodent analogue. These consortiums have formed a solid basis for construct identification and task selection that has informed the work presented in this review.

The CNTRICS and MATRICS domains are necessarily broad constructs, and are made up of a number of cognitive processes that can be defined independently. These “sub”-constructs interact and overlap, as is true for the identified constructs themselves (for example, perception contributes to all sub-domains to some extent; attention contributes to memory paradigms etc). The touchscreen battery of task in the present review can therefore be applied to a number of cognitive domains, as highlighted in Table 2. However, specific tasks are emphasised for their ability to

manipulate variables particularly relevant to certain constructs. For example, whilst reversal learning is listed as involving visual learning, this is complete after the initial acquisition of a visual discrimination, and is not required for performance in the reversal phase, where cognitive flexibility is central. Therefore, the task is emphasised here in the context of its ability to assess cognitive flexibility, and is in terms of perception not designed to offer more than a basic measure of visual ability.

The touchscreen operant chamber battery of tasks for assessing cognition in rats and mice

The current review presents a series of touchscreen cognitive tasks that have been selected as a suggested battery for schizophrenia-oriented preclinical work in the rodent. For several cognitive constructs, a number of tasks have been developed that vary in task design and potential neurocognitive and neuropharmacological sensitivity. As with all validation work, the understanding of how to best utilise these newly developed tasks will further develop with use.

The use of touchscreen operant chambers is in our opinion a valuable step towards achieving high construct validity, as making the testing environment, stimuli and lack of aversive feedback as similar as possible in rodent behavioural testing to patient testing reduces the likelihood of polluting outcome measures with confounding variables. The development of the touchscreen approach for rodents was inspired in part by the established Cambridge Neuropsychological Test Automated Battery (CANTAB; Sahakian and Owen, 1992; Barnett et al, 2010), designed to assess specific mental functions to enable a profile of performance indicative of a particular patient group. CANTAB is based on cross-species neuropsychological work and emphasises the importance of dissecting cognitive function across tasks. For example, deficits in spatial planning may be related to issues in the encoding and maintenance

of relevant information, the successful manipulation of that information, or both (Sahakian and Owen, 1992). Through decades of work with CANTAB, a rich understanding of the neural underpinnings of each task has been established (Barnett et al, 2010), and the battery has repeatedly identified deficits in long and short term memory, attention and executive function in patients with schizophrenia (Levaux et al, 2007; Barnett et al, 2010). Through use of non-verbal stimuli, the CANTAB battery allows for simple back-translation to preclinical work, enabling the development of a parallel touchscreen battery for animals including rodents.

The touchscreen operant chamber offers an ideal opportunity to develop reliable preclinical assays for a wide range of cognitive functions through easily implementable, automated, non-aversive, standardised, flexible and valid behavioural assays (Bussey et al, 2012). A major advantage of touchscreen-based preclinical testing is the translational value in terms of both construct and face validity, as well as the ability to assess multiple cognitive constructs using the same apparatus. This allows for comparisons across cognitive tasks (to decompose cognitive processes), and mirrors the CANTAB battery approach in enabling behavioural phenotyping relevant to specific neuropsychiatric or neurodegenerative disease (for further discussions on the translational validity of this approach, see Bussey et al, 2008, 2012; Horner et al, 2013; Oomen et al, 2013; Mar et al, 2013). The touchscreen testing environment therefore offers a superior setting for high-throughput behavioural phenotyping, pharmacological characterisation, cross-site replication studies and drug-discovery. Many tasks are optimised for use with repeated pharmacological manipulations and all have near-identical clinical analogues for swift back-translation (Bussey et al, 2001, 2008, 2012; Keeler and Robbins, 2011; Mar et al, 2013; Horner et al, 2013; Oomen et al, 2013; Nithianantharajah et al, 2013). We hope that this

approach can help shape the agenda for future studies and advance the field of behavioural neuroscience for targeting patient need.

Continuous Performance Test (rCPT)

Attentional dysfunction is at the core of the neurocognitive deficits of schizophrenia, as it is present throughout periods of both psychosis and remission (Wohlberg and Kornetsky, 1973; Asarnow and MacCrimmon, 1978; Nuechterlein et al, 1992). Attention is not a unitary construct, but is a composite term describing a defined set of interacting processes encompassing components of selection, vigilance and control (Parasuraman, 1992). Selection refers to processing selectively within a limited-capacity system, and is sensitive to distracting stimuli. Vigilance (or sustained attention) refers to the maintenance of goal directed processing over time. Interestingly, task manipulations that reduce accuracy in selection increases vigilance (Bahri and Parasuraman, 1989), whilst increases in accuracy are associated with reduced vigilance (See et al, 1995). Vigilance and selection may therefore be competing and dissociable systems (Parasuraman, 1992). Attentional control refers to a wider concept of coordinating selection, vigilance and other concurrent cognitive processes, and as such shares features of executive function and working memory.

In light of the range of attentional constructs available for selection CNTRICS narrowed their definition to focus on tasks measuring attentional control in preclinical research, as patients with schizophrenia are impaired in this domain as compared to implementation of input selection (Luck and Gold, 2008; Nuechterlein et al, 2009). CNTRICS recommend the 5-choice Serial Reaction Time Task (5CSRTT; reviewed in Robbins, 2002), the 5-choice Continuous Performance Task (5CSRTT-CPT) and the Distractor Condition Sustained Attention Task (dSAT, McGaughy and Sarter, 1995; Lustig et al, 2013). We have focused on two similar tasks for development in the

touchscreen, namely the CPT (Rosvold et al, 1956), and the well established 5CSRTT (Robbins, 2002). These tasks represent measures of sustained visual attention and divided spatial attention respectively, offering a comprehensive range of attentional measures when utilised as part of a battery.

Tests of attentional control should measure the ability to use internal representations to guide responding (Nuechterlein et al, 2009). CNTRICS defines two task essential task elements to address this; a baseline task (e.g. detection of a signal in the context of non-signals, guided mainly by “bottom-up” processing) and an addition to the baseline task that requires further cognitive recruitment to maintain performance (e.g., a flanker distractor, guided mainly by “top-down” processing). The CPT task fulfils these criteria for measuring attentional control.

The touchscreen rodent CPT (Mar et al, unpublished; Mar et al, 2012 poster; Mar et al, 2013 poster; Lei et al, 2014 poster) provides a translational measure of selective and sustained visual attention in the rodent. The task is designed to be highly analogous to the human CPT, versions of which have proven sensitive to detect impairments in patients with schizophrenia independent of clinical state (Asarnow and MaCrimmon, 1978) and in non-affected relatives (Grunebaum et al, 1974; Rutschmann et al, 1977; Erlenmeyer-Kimling and Comblatt 1992; Nuechterlein 1983; Mirsky et al, 1992; Franke et al, 1994; Laurent et al, 1999). The task has shown predictive power for disorder development (Cornblatt and Malhotra, 2001), with attentional impairments preceding clinical signs and symptoms of the illness (Cornblatt et al, 1997).

In the simplest human version of CPT, the subject must detect a target (e.g. the letter X) amongst non-targets (e.g. the letter Y) presented sequentially in one location on the screen. The rodent task utilises patterned stimuli rather than letters (e.g. vertical and horizontal stripes), but is otherwise identical in that animals must detect

and respond directly to the target stimulus and withhold responding from non-target stimuli presented sequentially in a central location on the screen (see Fig 2). This allows rodent task performances to be analysed using signal detection theory, a measure of target detection in the context of noise analogous to human CPT measures. The use of both non-targets and the possibility of touching a blank screen during the inter-trial-interval (ITI) allows for measures of inhibitory control. A major advantage of the rCPT is the ability to include flanker distractors, in which congruent or incongruent stimuli are presented either side of the target area during stimulus presentations. Furthermore, the stimulus duration, probability of a target presentation, ITI, contrast of visual stimuli and the number of non-targets used can all be varied to create a wide and flexible tool set for probing attentional and perceptual functioning.

A number of studies have been conducted to validate the rCPT in terms of its sensitivity to detect performance alterations following brain lesions, within various rat and mouse models proposed to relate to schizophrenia, as well as to detect cognitive enhancements following treatment with nootropic compounds. Both rats and mice show impaired attentional performance following fibre-sparing, neurotoxic lesions of the medial prefrontal cortex (mPFC) observed as a reduction in d' (i.e. sensitivity of targets to non-target stimuli), mirroring early human CPT data on patients with frontal lobe damage (Mar et al, unpublished). A comparison of commonly used mouse strains trained on the rCPT illustrates typical acquisition and performance levels for the mouse, and demonstrates sensitivity of the task to enhancements in performance following systemic administration of Donepezil (Kim et al, this issue). In NR1 knock-out mice of GABAergic interneurons (Belforte et al, 2010), the task is sensitive to impairments whereas the same mouse model is unaffected on the 5CSRTT (Hvoslef-Eide et al, 2013 poster), supporting the interpretation that these two attentional paradigms assess different aspects of attention. Moreover, using three rat models

proposed to model aspects of schizophrenia, a differential pattern of effects was observed between the offspring of dams injected with methylazoxymethanol acetate on embryonic day 17 (MAM-E17), rats that had been neonatally-treated with phencyclidine (neo-PCP) and animals subchronically administered PCP in adulthood (sub-PCP), relative to their respective controls (Mar et al, 2013 poster; Mar et al, unpublished). MAM-E17 rats showed marked elevations in false alarm rate and "blank" touch responses relative to sham controls, suggestive of deficits in inhibitory control. These MAM-E17 deficits have been demonstrated to be differentially modulated and in certain cases, selectively improved, following acute treatment with a variety of cognitive enhancers targeting monoaminergic, cholinergic glutamatergic or GABAergic systems (Mar et al, unpublished). In contrast to MAM-E17 rats, sub-PCP rats were largely unimpaired (Mar et al, 2013 poster) and neo-PCP rats actually showed improved target hit rates relative to their respective control animals (Mar et al, unpublished). However, both PCP-treated groups were differentially affected from their respective controls when the task stimuli were reduced in contrast which may suggest perceptual deficits similar to those observed in schizophrenic patients (Calderone et al, 2013).

The touchscreen 5-Choice Serial Reaction Time Task (5CSRTT)

An overlapping, but arguably separate form of attention is the ability to monitor in parallel a number of potential inputs, and allocate appropriate resources to each stimulus (Robbins, 1992; 2002). This type of divided attention is frequently assessed using dual-task performance paradigms in humans, whilst tasks such as the 5CSRTT may represent a suitably selective measure of spatial divided attention in the rodent.

The 5CSRTT has been employed as the main assessment of divided spatial attention in rodents for three decades and has shown robust construct and predictive

validity for modelling attentional and impulsive symptoms of human psychopathologies in the rodent (Young et al 2004; Hoyle et al, 2006; Siegel et al, 2011). The original, non-touchscreen version of the task has previously been discussed at length elsewhere (Robbins 2002; Chudasama and Robbins 2004; Young et al, 2009; Lustig et al, 2013). The 5CSRTT is also a component of the human CANTAB battery (http://www.cambridgecognition.com/academic/research). The 5CSRTT has been used widely for measuring divided spatial attention, and contrasts with the CPT which focuses on visual selective attention. In addition, the 5CSRTT allows for the specific measurement of premature and perseverative responding, and is as such better suited for the assessment of impulsivity and compulsivity as separate constructs. A separate human 4CSRTT has been developed explicitly to measure premature responding (e.g. in human drug abusers; Voon et al, 2014; Worbe et al, 2014). The rodent 5CSRT task has been successfully transferred to the touchscreen, and now offers measures of divided spatial attention, impulsivity and compulsivity within the same testing environment as the other tasks in the battery (thus allowing for cross-task comparisons when adopting a battery approach).

The task is administered similarly to the standard operant chamber, with the exception that responses are made directly to the brief presentation of a white square (presented in one of 5 locations) on the touchscreen rather than by nose poking in response to a light flash (see Fig. 3). Response accuracy is taken as a measure of attentional ability, whilst perseveration and premature responding are considered indicative of compulsivity and impulsivity respectively. A recent analysis (Mar et al, unpublished) shows that signal detection theory can also be employed to extract the relevant parameters of discriminability and response bias for this task.

The touchscreen 5CSRTT has been used widely with mice, and has proven sensitive to models of a range of disorders. When assessing genetic models of

Alzheimer's disease, Romberg et al (2011) found impaired accuracy, vigilance and perseveration of correct responses in the 3xTg mouse (Tau-P301L, APP-Swe and PS1-M146V), as well as impaired accuracy in the APP(695) model with Swedish and Indiana mutations (Romberg et al, 2013). The attentional impairment in 3xTg mouse could be rescued using the cholinesterase inhibitor Donepezil (Romberg et al, 2011) in a comparable manner to the rescue of attentional deficits of patients with Alzheimer's disease following administration of the anticholinesterase drug tetrahydroaminoacridine (THA) measured using the CANTAB 5CSRTT (Sahakian et al, 1993). The touchscreen 5CSRTT is further sensitive to cholinergic manipulations as Bartko et al (2011) demonstrated using a global muscarinic (M1) acetylcholine receptor knock-out mouse. This model was not impaired on the task's attentional measures (accuracy), but showed both compulsive and impulsive tendencies demonstrated as reduced omissions, and increased perseverative and premature responding. When reducing vesicular acetylcholine transporter (VAChT) in the prefrontal cortex specifically, a more subtle profile emerged in which VAChT deficient mice showed impaired acquisition, and increased omissions at short stimulus duration probes of high attentional demand (Kolisnyk et al, 2013b). When VAChT was overexpressed, mice displayed a profile of both impaired attention and impulsivity at shorter stimulus durations, with reduced accuracy and increased premature responding respectively (Kolisnyk et al, 2013). The task has also been used to assess a model of autism, the inbred BTBR T+tf/J mouse, which also showed reduced levels of prefrontal acetylcholine (McTighe et al, 2013). As in Kolisnyk et al (2013b), these mice showed impaired acquisition. In addition, an impulsivity phenotype was detected, as well as decreased accuracy at short stimulus durations.

With relevance to schizophrenia, Nithianantharajah et al (2013) assessed mice with mutations in Discs Large homolog (Dlg) family of synaptic scaffold proteins, which

are implicated in the disorder. On the 5CSRTT, Dlg2-/- mice were impaired in acquisition and accuracy, and displayed reduced premature responding. In contrast, Dlg3-/+ mice showed increased accuracy and elevated premature responding compared to controls, indicating that these two genes have opposing regulatory functions. This highlights the ability of the task to detect both facilitation and impairment of performance.

In another demonstration of cross-species validation, the touchscreen 5CSRTT has recently been back-translated into a human touchscreen 4CSRTT (Worbe et al, 2014). This task is designed specifically to measure premature responding. Following serotonin depletion (through dietary tryptophan depletion) in human volunteers premature responding increases, a highly similar pattern to that observed following serotonin depletion in rodents (Harrison et al, 1997a; Winstanley et al, 2004a). These data highlight the potential value of back-translation of tasks established in the pre-clinical literature.

When used together, the rCPT and the 5CSRTT offer a comprehensive attentional assessment that covers both spatial divided attention, as well as selective and sustained visual attention. These have been used together in a battery approach in our research, and should be combined with an assessment of visual ability using a standard visual discrimination task (with care taken to avoid stimulus bias).

Visual discrimination and reversal (2 or 3-stimulus versions)

Measures of visual processing have been highlighted by CNTRICS (Green et al, 2009) in light of increasing awareness of impairments in patients with schizophrenia in this domain (Butler and Javitt, 2005). Visual discrimination measures associative learning and perceptual ability, and underpins successful performance in cognitive touchscreen tasks involving complex stimuli, including paired-associates learning (PAL), CPT and

reversal learning. The visual discrimination task involves the simultaneous presentation of two visual stimuli. Responses to one stimulus are rewarded (S+) while responses to the second stimulus are non-rewarded (S-). The spatial location of the S+ is counterbalanced across trials. Over multiple trials, the rodent learns which stimulus is rewarded and develops a preference for selecting the S+ (see Fig. 4).

Visual discrimination in the touchscreen operant chambers offers good versatility relative to generally employed olfactory or spatial discrimination learning assays. Stimuli can be replaced across repeated discriminations to decrease proactive interference and repeatedly probe discrimination performance, for example in instances when varying degrees of perceptual difficulty of discriminations is desired. The set-up also allows for manipulations of perceptual load by altering stimulus size and stimulus contrast. Visual discrimination acquisition and performance is highly stable across laboratories, as is demonstrated by the multi-site study in the current issue (Talpos et al, this issue). Other more complex tasks can be built upon simple two-choice discrimination learning, including transverse patterning (Bussey et al, 1998) and transitive inference (Silverman et al, 2013). Importantly, the acquisition of a visual discrimination allows for the assessment of cognitive flexibility through reversal learning, as once a standard visual discrimination has been acquired, the reward contingencies can be reversed to assess a central aspect of cognitive dysfunction in schizophrenia.

Reversal learning as measured in the reversal phases of the CANTAB ID/ED-task of executive functioning is sensitive to deficits in patients with schizophrenia, independently of generalised intelligence (Leeson et al, 2009). These reversal learning deficits likely represent underlying abnormalities in fronto-striatal circuits, as these structures have been linked to reversal learning through imaging studies in humans (O'Doherty et al, 2003) as well as through excitotoxic and neurotransmitter-selective

lesion studies in experimental animals (Bussey et al, 1997; Schoenbaum et al, 2002; McAlonan and Brown, 2003; Chudasama and Robbins, 2003; Kim and Ragozzino, 2005; Bissonette et al, 2008; Ghods-Sharifi et al, 2008; Burke et al, 2009; Graybeal et al, 2011). Specifically, intact 5-HT signalling in the orbitofrontal cortex (OFC) and dopamine signalling in the caudate nucleus (primates) or dorsomedial striatum (rodents) is critical for successful reversal learning (Clarke et al, 2004; O'Neill and Brown 2007; Boulougouris et al, 2010; Clarke et al, 2011; Groman et al, 2013). The basolateral amygdala also plays an integral role in reversal learning (Stalnaker et al, 2007; Izquierdo and Murray, 2007). However, less is known about the contribution of specific 5-HT and dopamine receptor subtypes, and there is demand for improved rodent reversal-learning paradigms that allow for the identification of novel drug targets outside of these neurotransmitter systems and the evaluation of putative cognitive enhancers in animal models of schizophrenia. Human and non-human primate assays of reversal learning commonly employ touchscreen methods to study visual reversal whereas rodent versions have often used alternative sensory modalities, such as the bowl-digging task (Birrell and Brown, 2000; McAlonan and Brown, 2003). Whilst this method is widely used and has provided important findings, it is more labour-intensive and more sensitive to experimenter interference than operant reversal learning assays. Importantly, tasks with vastly different testing apparatus lack the ability for cross-task comparisons, further emphasising the need for touchscreen-based reversal learning as part of a wider battery of touchscreen tasks.

The test battery presented in this review suggests two complementary reversal learning tasks for the assessment of visual reversal learning in the rat, namely the (2- or 3-stimulus) visual reversal task, and the visual serial reversal task. Generally, successful reversal learning requires the subject both to suppress prepotent responses at the now non-rewarded, previous S+ and to overcome the avoidance of

the now rewarded, previous S-. These two processes might require separate forms of plasticity at the neural as well as behavioural levels; for instance, 5-HT depletion of the OFC in marmoset monkeys was linked to a lack of inhibition of a previously learnt response (Clarke et al, 2007), whereas the lesioned subjects performed at control levels when the previously correct stimulus was excluded. Another strategy, previously employed by Jentsch and colleagues (Jentsch et al, 2002; Lee et al, 2007) and now adapted to the touchscreen for rodents (Mar et al, 2012 poster; Alsiö et al, this issue), is to employ the simultaneous presentation of three visual stimuli (one S+, two S-). This paradigm gives the opportunity to analyse incorrect responses at a previously correct stimulus and responses at a never-reinforced stimulus (Fig. 5) and allows the dissociation of specific stimulus-perseveration (e.g., rats continues to respond at the 'previous S+' but there is no increase in the number of errors at the 'constant S-' stimulus) from an overall impaired performance (increased number of errors both the 'previous S+' and at the 'constant S-' stimulus). In addition, the difficulty of this paradigm (3-stimulus instead of 2-stimulus discrimination learning) increases the dynamic range within which to detect performance improvements.

2-stimulus visual serial reversal learning

The second reversal learning task included in the test battery is the visual serial reversal learning task. Whereas most rodent operant discrimination and reversal assays – including touchscreen tasks - require multiple sessions to reach the criterion for successful reversal learning (a single reversal can extend >14 days and therefore requires extended periods of daily testing; Mar et al, 2013), the visual serial reversal task offers an alternative wherein reversal learning data can be obtained within 3 sessions. The difference in training time to reversal criterion may be acceptable for chronic manipulations (e.g., genetic modifications or excitotoxic lesions) and/or

systemic treatment (e.g., serotonergic manipulations; Boulougouris et al, 2008), but the tasks have less utility for neuropsychopharmacological investigations due to the high number of required intracerebral microinfusions. Moreover, whereas there are large differences between individuals in their visual reversal performance (regardless of testing apparatus), performance does not vary much across reversals within each subject in either non-human primates (Groman et al, 2013) or in rats (Barlow et al, in press). The problem of between-subject variability in performance can be avoided by focusing on within-subject manipulations across reversals to increase statistical power. To exploit this, the serial visual reversal task requires each rat to complete a number of reversals, allowing for measures of stable performance across serial reversals (Alsiö et al, this issue). The task is optimised to produce significant perseveration behaviour after each contingency shift; that is, each reversal allows for measures of perseveration as you would obtain in a single reversal design. This highly versatile task was validated by pharmacological inactivation of the OFC (Alsiö et al, this issue) and will allow further investigation of the neural circuitry and neuropsychopharmacology of visual reversal learning in rats (Fig 6).

Self-Ordered Working Memory (rSOWM) task

A central cognitive domain impaired in patients with schizophrenia is working memory (Piskulic et al, 2007). This refers to the ability to maintain and utilise information appropriately over a short time period, without allowing irrelevant information to interfere with this process (Barch et al, 2009). Working memory deficits in patients with schizophrenia do not appear to be modality specific, as they are detected using auditory and visuospatial stimuli (Forbes et al, 2009). Impaired working memory is observed in first-degree relatives of patients (Park et al, 1995), suggesting that there is a genetic contribution to the phenotype of spatial working memory deficits regardless

of whether the potential genetic vulnerability to schizophrenia the first-degree relatives of patients may be carriers of is expressed or not.

The CNTRICS recommendations for tasks measuring working memory deficits in patients with schizophrenia are the AX-Continuous Performance Task/Dot Pattern Expectancy task and the recent probes and operation/symmetry span task (Barch et al, 2009). Whilst these tasks are highly valuable in a clinical setting, there are challenges associated with developing rodent analogues due to the complex nature of the task designs and the types of stimuli used (e.g. maintaining a span of read words or mathematical operations). Furthermore, the AX-CPT task may be sensitive to patient impairments partly because of the combined load on both attention and working memory. In contrast, the battery approach adopted in the current review aims to dissect cognitive function accurately, and for this tasks should load predominantly on a single construct of interest. We therefore chose to attempt to isolate working memory by focusing on the touchscreen CANTAB spatial working memory (SWM) task, which utilises nonmatching-to-sample rules and a number of distinct, illuminated screen locations, two features commonly used in pre-clinical behavioural tasks such as the Trial-Unique Non-matching to Location (TUNL) task, which was highlighted by the Selecting Promising Animal Paradigms meeting of CNTRICS focused on working memory (Dudchenko et al, 2013). The novel rSOWM test has the added strengths of requiring a series of self-generated choices (in which strategic responding can aid performance and is sensitive to prefrontal disruption) across a variable number of choice options (an important parameter taxing working memory load), more akin to human SWM paradigms. Importantly, the CANTAB SWM task has repeatedly detected spatial working memory impairments in patients with schizophrenia (Pantelis et al, 1997; Elliott et al, 1998; Joyce et al, 2002; Hutton et al, 2004; Badcock et al, 2005; Joyce et al, 2005), including ‘at-risk’ patients (Wood et al, 2003). Moreover, this task is

also sensitive to the performance-enhancing effects of modafinil both in healthy volunteers (Muller et al, 2013) and in first episode patients with schizophrenia (Scoriels et al, 2012). The CANTAB SWM requires subjects to collect tokens hidden beneath boxes on a touch sensitive screen. The number of boxes varies based on determined task difficulty and the subject is free to search the boxes in any order. Once a token is found, the next token is available at a different location. A box is never baited with a token more than once, requiring subjects to remember boxes that have been visited (non-match rule).

The rodent self ordered working memory task (rSOWM; Mar et al, unpublished; Mar et al, 2012 poster; Gamallo-Lana et al, 2014 poster) aims to provide a rodent analogue of the CANTAB spatial working memory (SWM) task. The basic paradigm measures the capacity to monitor and correctly remember self-generated choices of stimuli presented on a touchscreen. In this task, rats are presented with a series of trials in which either 2, 3 or more “white square” stimuli are displayed at different positions on the monitor (Fig 7). Within each trial, rats are rewarded each time they select a stimulus they have not previously selected. If a mistake is made, the animal must select again until a novel location is touched. Each trial ends when all stimuli have been selected once. Task performance is typically assessed using the percentage of perfect trials (in which each stimulus option was selected only once) and/or the number of errors (revisits to previously-selected stimuli). Response latencies can be examined as well as possible behavioural strategies based on the order/sequence in which stimuli are chosen within trials.

There are a variety of parameters that can be manipulated in the rSOWM. The delay between the opportunities for choice within trials can be lengthened to tax working memory, requiring the animal to maintain information about their previous choice “on-line” for a longer period of time. The interval between trials can be

manipulated to vary the amount of trial-to-trial interference. The physical distance between stimuli can be varied as a measure suggested to tax spatial pattern separation, a dentate gyrus (DG)-dependent process by which similar inputs are made more distinct to facilitate successful storage and retrieval of a representation (e.g. Leutgeb et al, 2007). Relevant molecular and cellular changes have been observed in patients with schizophrenia, suggesting that DG dysfunction may be of particular interest (Gao et al, 2000; Knable et al, 2004). Indeed, these changes appear to lead to behavioural dysfunction manifested as reduced pattern separation ability in patients with schizophrenia compared to healthy controls (Das et al, 2014). The number of stimuli can also be manipulated to increase memory load as in the CANTAB SWM task. By including trials having 3 or more locations/stimuli and by intermixing the number of stimuli and their positions between trials, the use of potentially confounding simple alternation strategies commonly observed in other working memory procedures (e.g., DNMTS) is largely prevented in the rSOWM. Additionally, potential sequencing strategies used by the animal can be probed by forcing the initial choice(s) on a given trial (e.g., present only one stimulus option to start a given trial – similar to the TUNL and cTUNL procedures described below).

This task has been demonstrated to be sensitive to the differential and detrimental effects of fibre-sparing neurotoxic lesions of specific hippocampal subregions (Mar et al, unpublished): DG lesioned rats show pronounced general impairments in task performance whereas CA3-lesioned animals are impaired when switched to sessions where delays precede stimulus presentation within trials. These effects mirror published reports implicating both the DG and the CA3 in working memory performance (Walsh et al, 1986; McLamb et al, 1988; Emerich and Walsh, 1989; Gilbert and Kesner, 2006). The task has also been demonstrated to be sensitive to the cognitive enhancing effects of low-moderate doses of modafinil (Mar et al,

unpublished; Gamallo-Lana et al, 2014 poster). Healthy adult male rats showed dose-dependent improvements in the percentage of perfect trials following systemic as well as intra-mPFC modafinil administration. These improvements were observed selectively on higher load, 3-stimulus trials (not on 2-stimulus trials), mirroring the recent results using the human CANTAB SWM test in healthy volunteers in which the cognitive enhancing effects of modafinil were only observed under higher load conditions (Muller et al, 2013).

Continuous Trial-Unique Non-matching to Location (cTUNL) and TUNL tasks

The prevalent automated spatial working memory in rodents has been an operant delayed-non-matching-to-position (DNMTP) task. This paradigm differs from the CANTAB SWM task in that the animal is required to remember a single location (left or right) across a delay and respond to one of two presented levers. The validity of automated DNMTP tasks has been questioned due to presence of mediating behaviours reducing the need to maintain information on line during the delay (Chudasama and Muir, 1997). In response to this criticism, we have developed novel variants of the previously published and validated Trial-Unique Non-matching to Location task (TUNL; Talpos et al, 2010; McAllister et al, 2013), which was been described in detail elsewhere (Oomen et al, 2013). Here we focus on the new NEWMEDS development of continuous TUNL for the rat (cTUNL; Oomen et al, this issue, Hvoslef-Eide et al, this issue, Howe et al, this issue) and a mouse version of the TUNL task (Kim et al, this issue). These tasks differ from the SOWM task in that there is no opportunity for self-selection of the order of responses.

In all the variants of this task, one can parametrically vary both the delay between sample and choice, and the physical distance between the stimuli on the screen. The TUNL task has a standard Sample and Test phase, whereby one of 15

possible locations on the screen is illuminated with a white square at Sample. Touching the sample results in reward on 1/3rd of trials to maintain motivation to respond. After a delay, the same location is re-illuminated, along with a novel location at Test. The animal is required to non-match to location by selecting the novel location (S+). Given the number of locations on the screen, the ability of the rat to predict which of the remaining 14 locations will be illuminated as novel is greatly reduced, and indeed, detailed behavioural analysis of TUNL performance indicated minimal advantage from use of mediating strategies (Talpos et al, 2010).

cTUNL differs from TUNL in a number of ways. Firstly, the trial structure is continuous in nature, so that the S+ location on the previous trial becomes the S- location on the current trial (Fig 8). This results in all trials being choice trials (i.e. data are collected from every trial, as opposed to 50% of touches as in TUNL). This structure has the advantage of halving the time it takes for the animal to acquire the task, a practical, but important concern. Secondly, (and more theoretically important), the continuous nature of the task allows one to vary the similarity (separation) of locations at both the encoding and retrieval stages of the task. In other words, because there are always two stimuli on the screen, the successful encoding of a location as unique on the previous trial depends on the proximity of that location to the other (“encoding phase”), and the ability to avoid that location on the current trial depends on the proximity of the S- to the novel S+ (“retrieval phase”). This is important because pattern separation is hypothesised to be a process active at the encoding stage (i.e. representations are made more unique to allow for successful storage and retrieval, rather than retrieved as two overlapping representations that are then made more unique to allow for accurate use of a single representation). The effects of manipulations that affect pattern separation (e.g. knock-down of adult neurogenesis; e.g. Clelland et al, 2009; Nakashiba et al, 2012) are therefore hypothesised to have a

greater effect at encoding than retrieval in such a task (Bekinschtein et al, 2013), which can now be measured using cTUNL. The cTUNL task has been validated as sensitive to dysfunction of the dentate gyrus subregion of the hippocampus, but interestingly leaves performance unaffected when the CA3 region is targeted (Oomen et al, this issue). The task has also been used with disease models of schizophrenia, demonstrating impaired acquisition and performance of MAM-E17 rats (Howe et al, this issue), mirroring reports of deficits in MAM-E17 on hand run hippocampus-dependent tasks, such as the Morris water maze, the T-maze and the Y-maze (Gastambide et al, 2015).

A final task feature of cTUNL is the ability to increase the number of stimuli on the screen to manipulate the amount of proactive interference in the task, as was originally implemented in the rSOWM (Mar et al, unpublished) to resemble the human CANTAB SWM task. For example, if the 3-stimulus version of the task is used, the two most recently touched (but both S-) locations will be presented on the screen alongside a novel location (S+), rather than a single S- as in the 2-stimulus version (Fig. X). In this issue, we demonstrate that both the 2- and 3-stimulus version of cTUNL is impaired following permanent inactivation of the DG (Oomen et al, this issue). Furthermore, the task has been validated as dependent on prefrontal function in a delay-dependent manner, as temporary inactivation of the medial prefrontal cortex (mPFC) in rats impairs performance at long, but not short delays (Hvoslef-Eide et al, this issue). The task can also detect facilitations in performance of young, healthy rats following infusions of phenylephrine into mPFC, an important task attribute for preclinical drug discovery.

At this time, it is clear that both rSOWM and cTUNL are sensitive to DG dysfunction, whilst TUNL is sensitive to full lesions of the hippocampus. In terms of medial prefrontal cortex contributions, cTUNL performance is modulated by adrenergic

and GABAergic agonists infused into PFC, whilst rSOWM is sensitive to both microinfusions and systemic delivery of modafinil into PFC. However, as validation work is a continuous process, these tasks may emerge as dissociable based on other neurocognitive and neuropharmacological manipulations. Certainly, they differ in practical aspects which may be relevant when selecting a touchscreen task for spatial working memory. For example, the rSOWM task has high face validity when compared to the CANTAB spatial working memory task, as they both allow the rodent/participant to select the order of responses to stimuli. In addition, stimulus load and the inter-trial interval (ITI) can be independently manipulated. However, if one is searching for a spatial working memory task not influenced by the element of self-selection of stimuli, TUNL or cTUNL offers alternatives, with the possibility of manipulating stimulus load in cTUNL, and the ITI independently from delay in TUNL.

Mouse TUNL

The assessment of spatial working memory in mice has relied heavily upon maze-based tasks, although lever-based operant chamber methods for the assessment of this construct are available (e.g. Estapé and Steckler, 2001). It has been argued that the acquisition of lever-pressing behaviour in mice is slower to establish than nose-poke based operant behaviour due to a murine preference for holes compared to levers (Crawley, 2000; Baron and Meltzer, 2001). We have developed a mouse version of the published rat touchscreen TUNL task (Talpos et al, 2010) that allows for the manipulation of both separation between the sample and test location, as well as the delay between sample and test choice. This may have advantages in terms of the readiness of mice to nose-poke touchscreens in response to visual stimuli, as well as enabling the assessment of spatial working memory in the mouse within a touchscreen battery (enabling cross-task comparisons of performance). The mouse

TUNL task uses a simplified grid of 5 locations (Fig. 9) and a somewhat different training approach compared to the rat outlined in detail in Kim et al (this issue). Despite the reduced number of grid locations, no mediation behaviours were observed, and mice were encouraged to engage with the magazine during the delay (thus avoiding body positioning as a strategy) using intermittent rewards. Control mouse performance is delay dependent, and the task is sensitive to dorsal hippocampal lesions (Kim et al, this issue).

Paired-associate learning (PAL)

Long-term memory impairments in patients with schizophrenia manifest as deficits in declarative memory, indicating the prefrontal cortex and the hippocampus as central structures of dysfunction (Aleman et al, 1999; Simons and Spiers, 2003). Tasks based on forming associations between stimuli (such as object and place) rely upon concurrent activity between these regions (Eichenbaum, 1999, 2000; Milner et al, 1997; Owen et al, 1995; Simons and Spiers, 2003). The CANTAB object-location paired-associate learning (PAL) task is highly sensitive to impairments in patients with schizophrenia (Barnett et al, 2005; Chouniard et al, 2007; Donohoe et al, 2008, Aubin et al, 2009) and performance correlates with symptom severity (Prouteau et al, 2004, 2005; Ritsner and Blumenkrantz, 2007). The task is also sufficiently sensitive to detect patients with schizophrenia from individuals with schizo-affective disorder (Stip et al, 2005).

The rodent touchscreen PAL task is available for both rats and mice (Talpos et al, 2009; Horner et al, 2013; Bartko et al, 2011), and assesses memory for associations between visual stimuli (A, B, C) and specific locations on the screen (1, 2, 3; see Fig 10), although see Kim et al (this issue) for an alternative version of PAL for

mice. The task was recommended by CNTRICS for the assessment of long term memory in rodents (Bussey et al, 2013).

On every trial, two patterns are presented; one pattern is in its correct position (e.g. A in 1, S+), whilst the other pattern is in one of its two incorrect positions (e.g. B in 3, S-). The third location is left blank, and is illustrated by an empty, white frame. Touchscreen rodent PAL requires activation of AMPA and NMDA receptors in dorsal hippocampus to maintain performance (Talpos et al, 2009), whilst an intact prefrontal cortex is necessary for control-level acquisition of the task (Bussey et al, this issue). The current version of the task (Horner et al, 2013) utilises luminance matched patterned stimuli as displayed in Fig. 10, as this results in a more homogenous acquisition curve of the 3 object-location associations (Hvoslef-Eide et al, unpublished). Traf2 and NcK interacting kinase (TNiK), linked to both NMDA and AMPA receptor function, also impairs acquisition of PAL when knocked out in mice (Coba et al, 2012), whilst adult neurogenesis in the dentate gyrus has no effect on PAL acquisition (Clelland et al, 2009). Performance appears linked to the cholinergic system, as scopolamine and dicyclomine cause impairments in mice (although note that effects in rats may differ), whilst Donepezil facilitates performance (Bartko et al, 2011b). Furthermore, PAL performance is impaired by phencyclidine (PCP) and amphetamine when administered systemically (Talpos et al, 2014).

In a cross-species study, Nithianantharajah et al (2013) assessed mice and human carriers of the *Dlg2* mutation, which is implicated in schizophrenia. The *Dlg2* mice were impaired on the rodent PAL task, whilst humans carrying the *Dlg2* mutation were impaired on CANTAB PAL. In more recent (as yet unpublished) work, the same human participants were assessed on the rodent PAL task with no modifications, and found to display the same phenotype as the mouse model. This important demonstration of successful translation from rodent to human is one that will be

pursued further using other tasks in the battery as validation work continues beyond the specific boundaries of the NEWMEDS project.

Challenges and limitations

It is evident that the touchscreen method has many advantages. However as with any method there can be limitations. For example, certain rodents may present with visual impairments that may preclude the use of at least some of the tasks in the battery. One of the challenges of the NEWMEDS project has been the development of touchscreen operant chamber tasks for rodents that fulfil the requirements of both academia and the pharmaceutical industry, whereby the task “wish lists” do not necessarily perfectly overlap. For example, the speed of acquisition of a particular task, as well as the stability of a performance baseline for repeated drug testing can be desirable task criteria for drug development, and some tasks meet these criteria more readily than others (e.g. cTUNL and rCPT, as compared to PAL). Although the NEWMEDS project has formally completed, the communication between the industrial and academic partners will continue, and in parallel, continued efforts to further optimise both the implementation and further development of the task battery for drug discovery.

Future directions

Whilst the rodent touchscreen battery presented here focuses on cognitive domains, there are a range of additional psychological constructs that could be assessed in the touchscreen operant chamber to form a wider battery for schizophrenia-relevant behaviour, such as motivation, attentional set-shifting and perceptual processing.

Motivation and reinforcement learning was highlighted by a CNTRICS working group (Markou et al, 2013) as a reflection of extensive evidence of impairments in patients with schizophrenia (e.g. Gard et al, 2007; Gold et al, 2008; Weiler et al, 2009; Barch and Dowd, 2010; Kasanova et al, 2011; Dowd and Barch, 2012; Yilmaz et al, 2012; Gold et al, 2013; Barch et al, 2014; Gard et al, 2014; Griffiths et al, 2014). Some of the tasks proposed by the working group are already established in the touchscreen, such as autoshaping, which has been successfully used in both rat and mouse models (Bussey et al, 1997b; Parkinson et al, 2000, 2000b; Dalley et al, 2005; Ito et al, 2005; DePoy et al, 2013; Horner et al, 2013). Others, such as progressive ratio (Heath et al, this issue), probabilistic (selection) learning task (rPST; Mar et al, unpublished; Trecker et al, 2012 poster; Markou et al, 2013) and notionally a version of an operant probabilistic reversal paradigm that can assess bias to negative and positive feedback (Bari et al, 2010) are the focus of current development and validation, and will together form a battery to screen for motivational and reinforcement learning-related deficits to complement the current range of preclinical touchscreen tasks.

Furthermore, we and others have made strides towards a rodent intra- and extra-dimensional set shifting task in the touchscreen using two visual dimensions (Brigman et al, 2005; Dickson et al, 2014), a valuable contribution for cross-species comparisons with both monkey (e.g. Roberts et al, 1988) and human literature (e.g. Downes et al, 1989; Owen et al, 1993) including schizophrenia, (Pantelis et al, 1999; Barnett et al, 2010).

Another future avenue for development is the assessment of complex visual perceptual processes in the rodent. This would be of significant value, given the occurrence of alterations in visual perception in schizophrenia such as deficient perceptual organisation (Giersch and Rhein, 2008; Giersch et al, 2011; Silverstein and Keane, 2011). Despite frequent reports of poor visual ability in these species (e.g.

Kumar et al, 2015), work from our laboratory has previously shown that even rats of the non-pigmented Sprague-Dawley strain are proficient at successfully discriminating between two complex visual stimuli presented on the touchscreen (Bussey et al, 2008). Furthermore, accumulating evidence suggests that rodents likely possess the computational capacity necessary for higher-order visual processing thought unique to primates (Huberman and Niell, 2011; Niell, 2011; Zoccolan, 2015). The touchscreen approach can therefore be readily leveraged to examine higher-order visual processing and perceptual mechanisms in rodents for which the number of available experimental manipulations is considerably greater than in the cat or primate conventionally used in vision research. This is exemplified by the recent development of a rat touchscreen paradigm (Ward et al, 2013) to assess perceptual organisation through evaluation of contour integration (Feigenson et al, 2014). Performance in this paradigm is sensitive to acute administration of the NMDA receptor antagonists PCP and ketamine (Ward et al, 2013) suggesting that it may be of use in mechanistically assessing changes in visual perception associated with a psychosis-like state. The present CPT task is also in fact sensitive to selective perceptual deficits caused by PCP treatment based on its contrast sensitivity component (Mar et al, 2013 poster).

Summary

The rodent touchscreen cognitive test battery presented represents the NEWMEDS WP02 consortium's contribution to pre-clinical schizophrenia research, focused heavily on improving the interlinked concepts of construct and predictive validity. Following on from the efforts of MATRIC and CNTRICS, our goal has been to develop a set of tasks that tap into cognitive constructs highly relevant to schizophrenia that are in a position to predict compound success in a clinical population, in addition to evaluating models of disease. The model of academic task development and validation followed by

further validation and utilisation by pharmaceutical partners will continue to come to fruit following the end of this project. One important validation effort will be demonstrations of back-translational studies reproducing specific cognitive impairments found in patients with schizophrenia in animal models, as well as effects of cognitive enhancing compounds. Whilst highly valuable as positive controls, such effective compounds are challenging to identify in humans. Nevertheless, modafinil could serve as a good candidate for back translational studies, as it has been effective in enhancing cognition in both healthy volunteers (Winder-Rhodes et al, 2010; Muller et al, 2013) and patients with schizophrenia (Turner et al, 2004). With this approach in mind, we hope that the developed battery will aid in bridging the gap between rodent and human cognitive testing, with the ultimate goal of aiding drug discovery for novel treatments of schizophrenia.

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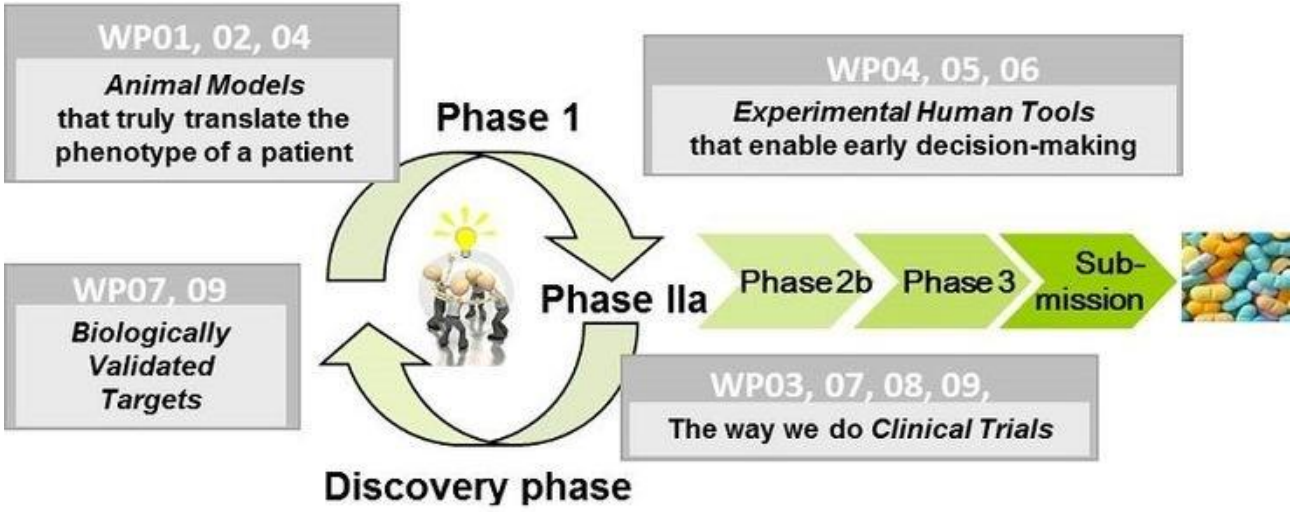


Fig. 1 An overview of the NEWMEDS initiative. The current review focuses on work carried out within work package 2 (WP02).

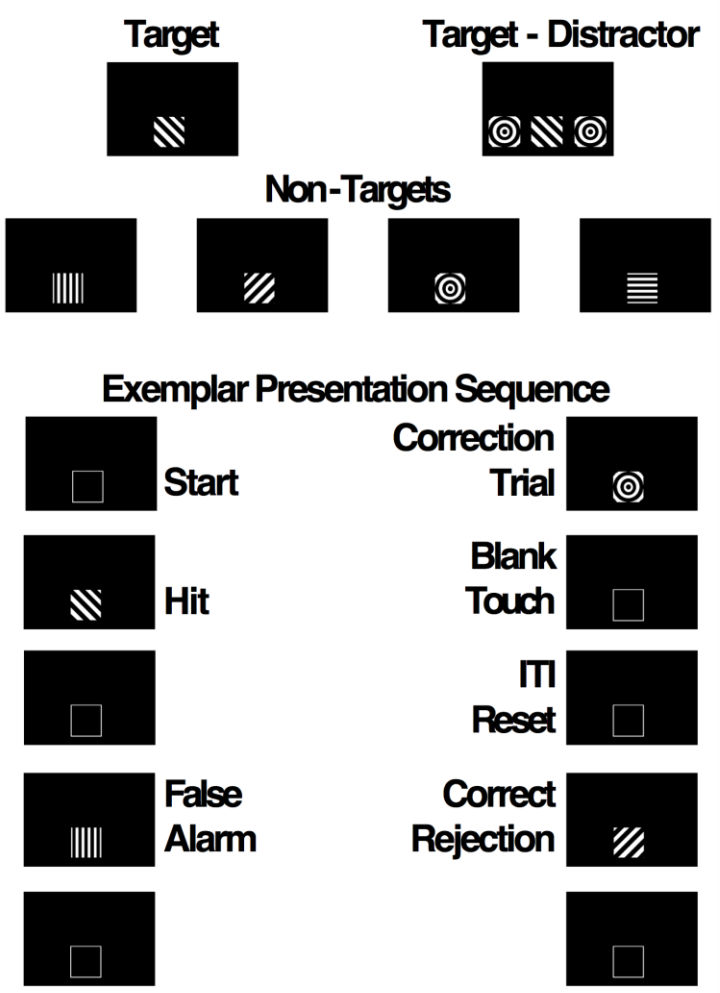


Fig. 2 A schematic of the rodent continuous performance test. One stimulus is assigned as the target (S+), and four stimuli are assigned as non-targets (S-). As

demonstrated in the exemplar presentation sequence on the left hand side, an empty white (unresponsive) square is present during the ITI. A response to the presence of the target is recorded as a hit. Responses to a non-target stimulus are recorded as a false alarm. A false alarm will result in the next stimulus being a non-target stimulus (correction trial; see exemplar presentation sequence on the right hand side). Touches to the empty white square resets the ITI. Inhibition of responding to a non-target is recorded as a correct rejection. Inhibition of responding to a target is recorded as a target omission (not shown). Central stimuli can be flanked by congruent or incongruent stimuli during distractor probes (see top right; incongruent example shown).

Fig. 3 A schematic example of four trials in the rodent touchscreen 5-choice serial reaction time task. In each trial, a white-square stimulus is presented in one of five horizontal response windows following a delay. A nosepoke response to the white-

square stimulus is scored as a correct response. A response to a blank response window during the presentation of the stimulus is treated as incorrect response. Response to the screen before the onset of the white square stimulus is treated as a premature response. Responses to the screen after the offset of the stimulus are treated as a perseverative response (to either correct or incorrect locations).

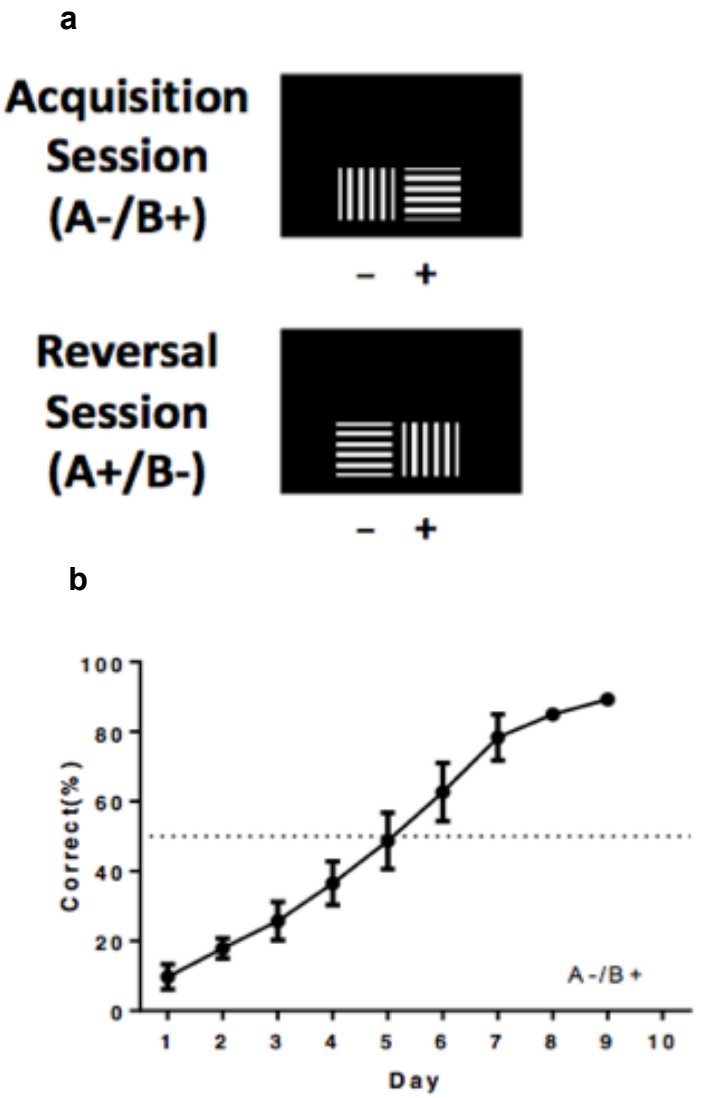


Fig. 4 A schematic of the rodent 2-stimulus visual discrimination and reversal task with representational 2-stimulus reversal learning performance. **A)** During visual discrimination acquisition, responses to one stimulus (S+) are rewarded while responses to the second stimulus (S-) are not. The spatial locations of stimuli are counterbalanced across trials, but reward contingencies remain unchanged. Following successful acquisition of a visual discrimination, the reward contingencies are reversed, resulting in the previous S- becoming the S+. **B)** In the initial stages, performance is below chance (50%) driven by a preference for the previously rewarded stimulus. After repeated exposure to the new reward contingencies, preference shifts to the now rewarded stimulus.

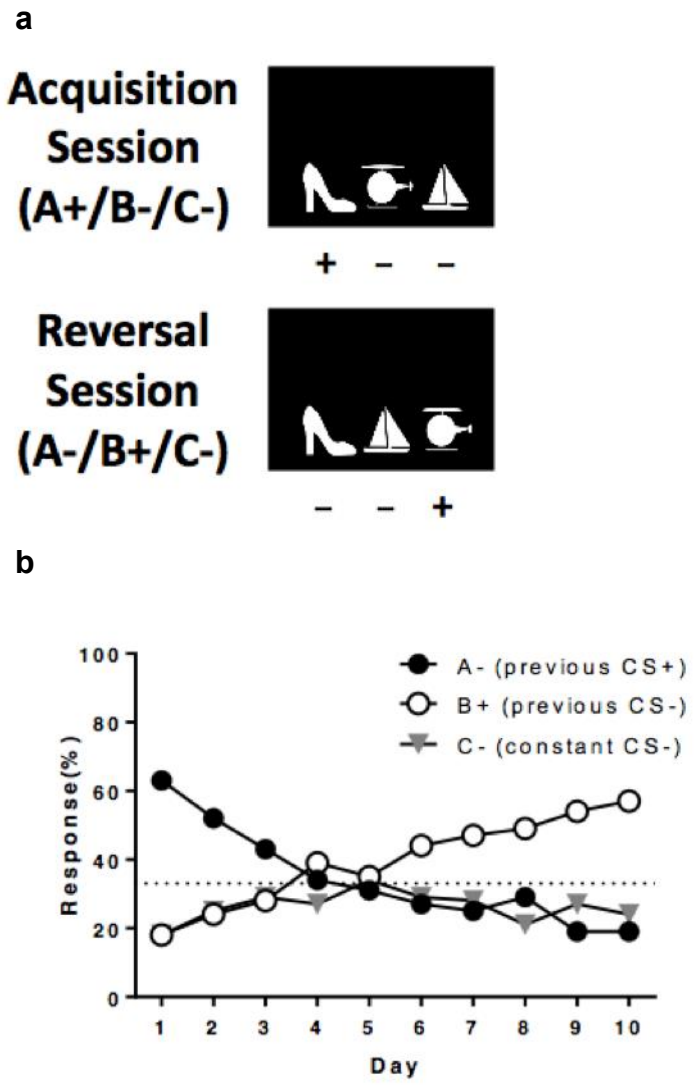


Fig. 5 A schematic of the rodent 3-stimulus visual discrimination and reversal learning task with representational 3-stimulus reversal learning acquisition curve. **A)** During visual discrimination acquisition, responses to one stimulus are rewarded while responses to the two other stimuli are non-rewarded. In the subsequent reversal sessions, responses to one of the previously non-rewarded stimulus become rewarded while responses to the previously rewarded stimulus become non-rewarded. Responses to the third stimulus remain non-rewarded in both discrimination and reversal learning. **B)** Data illustrating responses to the three stimuli over 10 reversal sessions in the rat. The responses to the constantly S- stimulus remain low throughout. The responses to the previous S+ are initially high, before gradually

reaching comparable levels to the constantly S- stimulus. The responses to the previously S- are initially high, before gradually becoming the preferred stimulus.

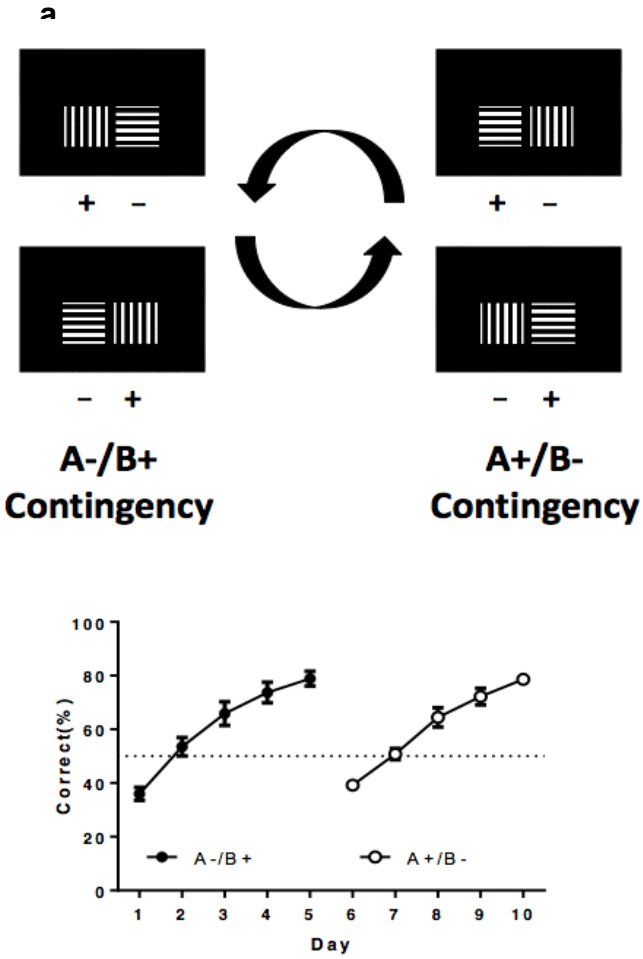


Fig. 6 A schematic of the rodent serial visual reversal learning task with representational 3-stimulus reversal learning acquisition curve. **A)** During visual discrimination acquisition, responses to one stimulus are rewarded while responses to the two other stimuli are non-rewarded. In the subsequent reversal sessions, responses to one of the previously non-rewarded stimulus become rewarded while responses to the previously rewarded stimulus become non-rewarded. Repeated reversals of the reward contingencies using the same stimuli results in a shortening of the number of sessions rats require to successfully reverse. **B)** Data illustrating responses two reversals of reward contingencies within 10 testing sessions in the rat.

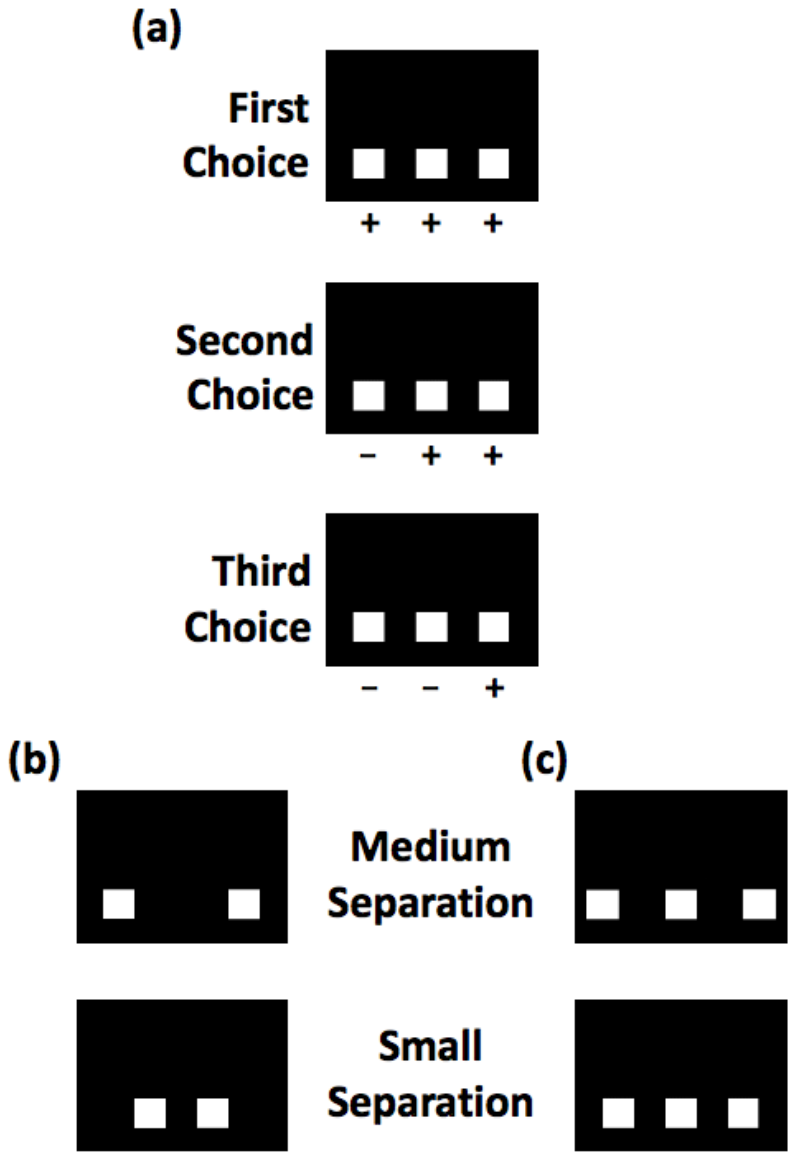


Fig. 7 A schematic of a perfect trial in the rodent self ordered working memory task. **A)** At the first choice, responses to any of the stimuli on the screen results in reward (all S+). After a delay, all stimuli are presented again. The previously touched stimulus is now a S-, and the animal must respond to either of the remaining stimuli for reward. After a delay, the two previously touched stimuli are now S-, and the animal must respond to the remaining stimulus for reward. A revisit to a previously touched stimulus results in an error, and all stimuli are presented again. This will continue until all stimuli have been touched once. **B and C)** The separation between stimuli on the screen can be manipulated on both the 2-stimulus (b) and 3-stimulus (c) trials.

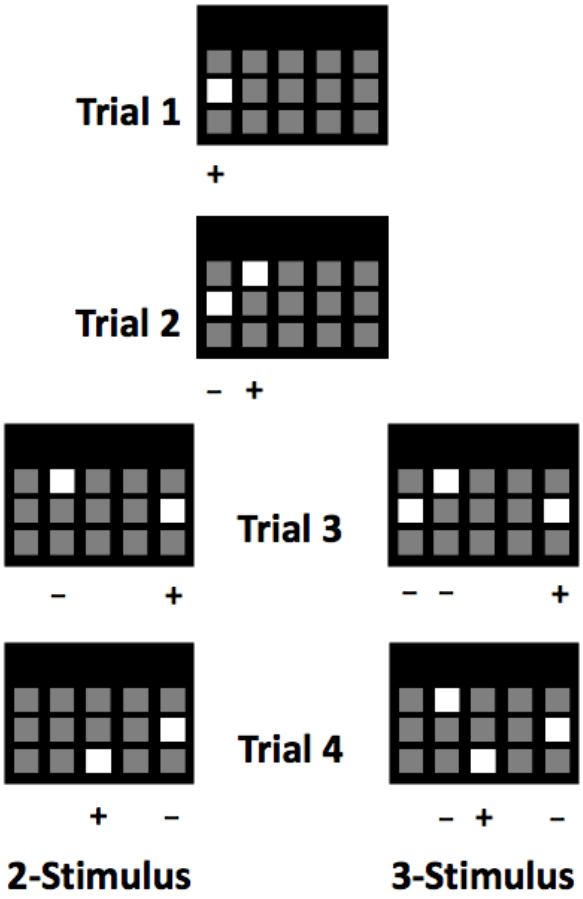


Fig. 8 A schematic of a four trials of the 2-stimulus and 3-stimulus version of the continuous trial-unique non-match to sample task. On trial 1, a single sample location is illuminated (S+). After a delay, the same location is presented again (S-), along with a novel location (S+). The separation between the two stimuli can be varied (presented is a separation 0 trial, in which no squares separate the S+ and the S-). In the 2-stimulus version of the task, the trials continue to display only two stimuli at a time, with the previously correct location always serving as the S-. In the 3-stimulus version of the task, the two previous S+ locations are presented (now both S-) alongside a novel location (S+). From the third trial onwards, every trial contains a choice of three locations, with the two previously correct locations always serving as the S-. Correction trials are utilised throughout the task, so that a response to a S- results in the re-presentation of the same spatial configuration on the screen until a correct response is made.

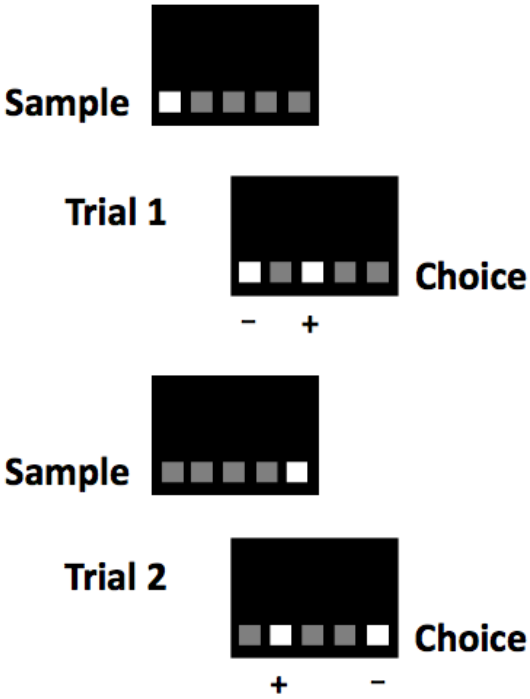


Fig. 9 A schematic of two trials of the mouse trial-unique non-match to sample task. A trial begins with a sample-phase where a white-square stimulus (occasionally rewarded to maintain responding) is presented in one out of five possible horizontally oriented response windows. Upon touch, a delay is implemented. After the delay, the sample location (now S-) and a novel location (S+) is presented. If a response to the sample location (S-) is made, a correction trial is implemented whereby the same two locations are presented again until a correct response (S+) is made. Following a correct response, an ITI is initiated. After the ITI, a second trial (sample and test phase) is initiated. The spatial separation between stimuli and the delay between sample and choice can be manipulated as in rat TUNL, cTUNL and SOWM.

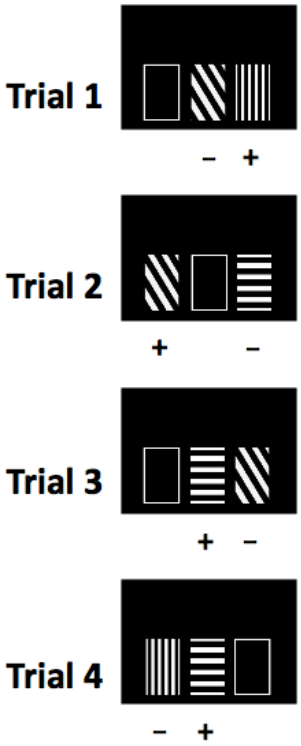


Fig. 10 A schematic of four trials of the paired-associate learning task. Across each trial the PAL task, two out of three possible stimuli appear on the screen in two out of three possible locations (giving six possible trial combinations). One stimulus is displayed in its correct location (S+) while the second stimulus is displayed in one of its two incorrect locations (S-). The third location is left blank. Responses to the S+ are rewarded while responses to the S- are not. In this example, the diagonal lines are correct (S+) when presented in the left-most response location, the horizontal lines are correct (S+) when presented in the central response location, and the vertical lines are correct (S+) when presented in the right-most response location.

	MATRICS domains	CNTRICS domains
1	Speed of processing	Perception
2	Attention/Vigilance	Attention
3	Problem solving/reasoning	Executive control
4	Working memory	Working memory
5	Verbal learning and memory	Long term memory
6	Visual learning and memory	Social/Emotional processing
7	Social cognition	

Table 1 An overview of the MATRICS and CNTRICS domains highlighted as relevant to schizophrenia (Marder and Fenton, 2004; Carter and Barch, 2007).

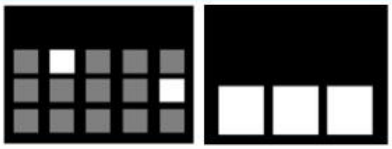
Rodent touchscreen tasks		Relevant MATRICS/ CNTRICS domains taxed by task
5CSRTT		**C2, M2, M1, C3**
CPT		**C2, M2, M1, C3, C1[1]**
Visual reversal learning (2 or 3-stimulus and serial version)		**C3,** (M5, C1[1], M3?)
cTUNL/TUNL/SOWM		**C4, M4**
PAL		**C5, M5, M3?**

Table 2 An overview of the rodent touchscreen tasks included in the battery for measuring cognitive function relevant to schizophrenia. Several MATRICS and CNTRICS defined cognitive constructs support performance on individual tasks (M = MATRICS, C = CNTRICS; see Table 1 for a numbered overview of domains). Constructs in brackets are not the primary construct for which this task would be recommended to test, but nevertheless supports general performance or acquisition of the task. M3 is highlighted with a question mark due to the challenges of applying this construct to animal cognition.