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Review

Animal models of working memory: A review of tasks that might be used in screening drug treatments for the memory impairments found in schizophrenia

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ABSTRACT

The Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) meeting on "Selecting Promising Animal Paradigms" focused on a consideration of valid tasks for drug discovery in non-humans. This consensus review is based on a break-out session with experts from academia and industry which considered tasks that tap working memory in animals. The specific focus of the session was on tasks measuring goal maintenance, memory capacity, and interference control. Of the tasks nominated for goal maintenance, the most developed paradigms were operant delayed-non-matching-to-position tasks, and touch-screen variants of these may hold particular promise. For memory capacity, the task recommended for further development was the span task, although it is recognized that more work on its neural substrates is required. For interference control, versions of the *n*-back task were felt to resemble the deficits found in schizophrenia, although additional development of these tasks is also required.

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In schizophrenia, difficulties in learning and memory are associated with impairments in learning basic life skills, social problem solving, and the capacity for work or schooling (Green et al., 2000). The development of therapeutics to address these difficulties would be facilitated by identifying robust, high-throughput cognitive tasks that could be used for screening drugs in pre-clinical tests. As a first step towards identifying such tasks, this review will provide a critical consideration of selected cognitive paradigms that tap working memory in non-humans.[1]

A challenge in considering animal paradigms for assessing working memory is that this domain has been defined in a different way in different species. One of the dominant models of working memory in humans is that of Baddeley and Hitch (1974) (Baddeley, 2003). In their model, working memory is comprised of three limited capacity stores for information, and a central executive that, among other things, allocates attention.

In non-humans, however, working memory is often synonymous with short-term spatial or visual-spatial memory. In pigeons, for example, Honig (1978) used the term working memory to refer to tasks in which the birds had to retain, over a delay interval, memory for stimulus that was no longer present.[2] In these tasks, only memory for the immediately preceding stimuli on a given trial was relevant; the birds had to ignore representations of the stimuli from preceding trials. In rats, the standard working memory task is the eight-arm radial maze of David Olton (Olton and Samuelson, 1976). Here, on a given trial the animal gathers a food reward from each of the eight maze arms, and typically does so without re-entering previously visited arms (which are not re-baited during the session). This ability to remember previously visited locations indicates that the rat possesses short-term spatial memory for multiple places. Working memory that allows efficient collection of rewards within each maze session is distinguished from "reference memory" that is relevant for multiple test trials in a task (for example, the location of arms in the maze that are never rewarded; Olton et al., 1979).

For non-human primates, working memory has been referred to as the capacity to hold "on-line" a stimulus that is no longer present (Goldman-Rakic, 1994). Here the prototypical task is a delayed response task, and the oculomotor variant of this task requires the monkey to remember where a visual stimulus was presented on a TV monitor over a delay period when the stimulus is no longer present. After the delay period, the monkey is reinforced for making a saccade to the location of the previously presented stimulus. Compelling neural substrates of this memory have been demonstrated with the identification of neurons in the principal sulcus of the prefrontal cortex that fire specifically during the delay period of these types of tasks (Kubota and Niki, 1971; Fuster and Alexander, 1971; Funahashi et al., 1989).

As this brief summary indicates, working memory has been conceptualised in different way in humans and non-humans, and it has been operationalized in different ways in non-human primates and rodents. In animals, generally, a common feature of working memory tasks has been that performance decreases as the delay over which a memory is held increases. Thus, working memory in animals has been viewed as having a limited lifetime or being task-relevant for only a brief period.

1. Working memory in schizophrenia

A consideration in selecting useful animal tasks for drug development in schizophrenia, however, is that the working memory impairments are not delay-dependent. Lee and Park (2005), in a meta-analysis of 124 studies on working memory and schizophrenia, found that working memory impairments were reliable across different methodologies, but did not get worse with delays longer than 1 s.

The purpose of this review, then, is not to select tasks solely on how working memory has been traditionally measured in animals. Rather, it is to identify tasks that map to the impairments observed in schizophrenia. This can be done by considering two questions. First, what features of working memory tasks do patients with schizophrenia have difficulty? Second, are there analogous tasks in non-humans? In an earlier CNTRICS meeting, the first question was evaluated. Two features of working memory were identified as most suitable for immediate translational work: *goal maintenance* and *interference control* (Barch and Smith, 2008). Goal maintenance was defined as

> The processes involved in activating task-related goals or rules based on endogenous or exogenous cues, actively representing them in a highly accessible form, and maintaining this information over an interval during which that information is needed to bias and constrain attention and response selection. (p. 13)

An example of a task that taps goal maintenance in humans is the expectancy AX paradigm, developed by Jonathan Cohen and co-workers (Servan-Schreiber et al., 1996). In this task the participant responds to the presentation of the target "X", but only if it is preceded by the presentation of the letter "A". X is not a target if it is preceded by a different letter, B. A is also presented before another letter, Y, but this again does not serve as a target. Thus, the participant has to learn the rule – X is a target if it follows A – and remember which letter was presented initially on a trial, A or B. Barch et al. (2003) have shown that patients with schizophrenia make more errors on A–X and B–X trials than control participants.

Interference control, a second feature of working memory that was viewed as ready for translation, is defined as "the processes involved in protecting the contents of working memory from

[1] This review of tasks is based on deliberations that took place at the Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) meeting, which met on 27 April, 2011.

[2] Even in these tasks there are important differences. In a traditional delayed matching-to-sample task, like that of Roberts (1972), a bird might be presented with a green key in the sample phase of the trial, and it has to remember this stimulus over a delay period where no key are illuminated. After the delay period, a choice phase ensues where both a green key and a red key are illuminated. The bird is reinforced for pecking at the green key and not the red key.
In Honig's advance-key procedure, the to-be-remembered stimuli are associated with different responses. One stimulus indicates that the bird should peck at the red light after the delay period; the other stimulus indicates that the bird should refrain from pecking after the delay. So, the sample stimulus may initiate preparations to respond or to not respond over the delay period.

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interference from either competing representations or external stimuli" (Barch and Smith, 2008, p. 13). An example of this construct is found in a study by Brahmbhatt et al. (2006). Patients with schizophrenia were tested on a 2-back memory task–where a stimulus is a target if it matches a stimulus presented before the last stimulus (e.g, key–dog–*key*). The patients were impaired at this task, and were poor at rejecting repeated (1-back) stimuli.

From the first CNTRICS meeting, the task nominated to assess interference control in humans was the recent-probes test. In this task, participants are asked to memorise four words, and then after a 3 s delay, recognise whether a given word was one of the four presented on that trial. The interference here comes from the presentation of words on the recognition phase of the trial that had been presented on earlier trials. Thus, the participant has to focus on the stimuli from the current trial, and tune out stimuli from preceding trials.

A third feature of working memory that will be considered in the current review is *memory span capacity*. This refers to the amount of information that is maintained in working memory. At the time of the previous CNTRICS meeting, this construct was identified as requiring more basic research before being suitable for translation (Barch and Smith, 2008). Recent work by Gold et al. (2010), however, has highlighted the importance of this feature of working memory in schizophrenia. They tested patients with schizophrenia on a task in which they had to remember arrays of 3 or 4 color patches, presented on a video screen, over delays of 1 or 4 s when these stimuli were not present. After the delay, one of the patch locations on the screen was highlighted, and the participant's task was to select the color that had appeared at this location from a continuous color wheel. The authors reasoned that if the color patch was in working memory, then the color selected should be similar to the stimulus's actual color. However, if it was no longer in memory, then the color selected should be random. They found that patients remembered fewer stimuli, relative to a control group of healthy volunteers, and that this impairment was similar at both the 1 and 4 s delays. Importantly, the precision of the responses (how close the selected colors were to the true colors) did not differ between patients and the control group. Thus, the impairment seen in patients did not reflect less precise memory, but rather a reduced memory capacity.

2. Promising animal paradigms for testing working memory

In the CNTRICS meeting on which this review is based, a breakout session comprised of experts from academia and industry considered animal paradigms for assessing the working memory constructs described above: *goal maintenance*, *memory capacity*, and *interference control*. Below the nominated and the consensus tasks for each construct are considered.

2.1. Goal maintenance

2.1.1. Tasks considered

Within the area of goal maintenance several tasks were proposed, including the contextual control of response task (operant rodent stroop task; Haddon and Killcross, 2007), touch-screen based visual discriminations (e.g., Bussey et al., 2008), discrimination reversal learning, operant delayed non-match to position (DNMTP)/operant delayed match to position (DMTP) (Dunnett et al., 1988), and 8-arm delayed win-shift (Olton and Samuelson, 1976). The contextual control of response task (described in the *interference control* section below) was determined to lack the necessary memory component to be included within the category of goal maintenance. The contextual element negated the need for working memory per se. All agreed that touch-screen based visual discriminations as typically performed (Bussey et al., 2008) required a high degree of restrained attention, however this task was not thought to require the necessary malleable memory component during acquisition or recall to qualify.

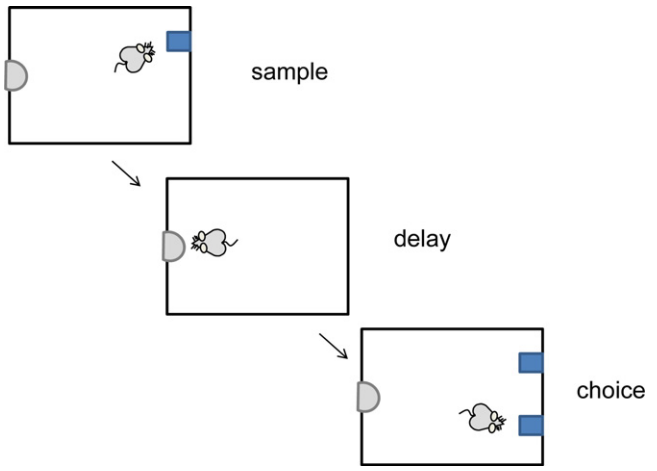

Fig. 1. Schematic of the operant delayed-non-matching-to-position (DNMTP) task. In this task the rat is presented with one of two levers as the to-be-remembered stimulus. The rat samples this stimulus by pressing it, after which it is typically retracted and the rat obtains a food pellet reward at the opposite end of the operant box. A delay period ensues over which the rat must remember which lever was presented. After this delay, both the left and right levers are presented, and the rat must respond to the lever that had not been presented during the sample phase of the trial.

The area of discrimination reversal learning generated substantial debate. It was agreed by all present that a slow reversal, over several days, clearly fell outside of the definition of goal maintenance, but this distinction was not clear for a serial reversal (within a session, for example see Boulougouris et al., 2007). In the end it was agreed that this might require a malleable memory, but that the memory demands were still insufficient for inclusion here.

Finally, operant delayed non-match, operant delayed match, and 8-arm delayed win-shift procedures were considered. Though the operant non-match task and the 8-arm maze task are run on different apparati, they were felt to entail a similar requirement for memory of a location over a short delay. Delayed match and non-match paradigms were considered approximately equal. However it was acknowledged that certain manipulations may result in an apparent pro-cognitive profile in one paradigm and not in the other in instances where manipulations influenced an animal's tendency to perseverate or switch behavioral responses (for example see Sahgal, 1987). Indeed, testing compounds and disease models in both matching and non-matching paradigms will likely provide a more complete picture of the influence of the selected manipulation, and avoid false positive results. Despite substantial differences between how maze and operant DNMTP tasks are executed, it was thought that they were dependent upon similar domains, and from a neurobiological perspective differed primarily in the load placed upon relevant cognitive substrates. Both tasks require the ability to flexibly adapt a rule in response to incoming stimuli, and then maintain this across a delay to achieve a goal. While the group decided both tasks should be considered, it was also agreed that the operant version was the more practical of the two variants because of its high-throughput, ease of blinding, sensitivity of timing, and standardization (see Fig. 1). As such, the focus here will be on the operant version (primate versions of delay tasks are considered in a separate section below). However, in certain situations the temporally distinct acquisition, consolidation, and recall periods of the maze version may present distinct advantages. The win-shift radial

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arm maze also requires the hippocampus, whereas the data on this for the operant tasks are more ambiguous.[3] Finally, despite a great deal of similarity with DNMTP, delayed alternation will not be considered as a DNMTP task. Although it is similar to DNMTP with regards to its working memory component, the lack of an inter-trial interval (ITI) may result in a very different role for memory "interference" between the two tasks.

DNMTP and related paradigms (Dunnett et al., 1988) have a long history in the drug discovery process. Existing in several forms, the task was quick to catch on because it could be used in a high-throughput fashion in an operant box, and similar procedures could be used in humans or non-human primates. A traditional view of rodent DNMTP is that it is requires the hippocampus for recall of the sample across the delay, and the prefrontal cortex (PFC) for execution of the rule. As such, delay-dependent impairments or enhancements have traditionally been interpreted as memory effects, whereas manipulations that affect all time points have been proposed to influence executive function. However it is also possible that manipulations that affect all time points could be the result of changes in motivation, motor function, attention, or other non selective processes (Chudasama and Muir, 1997), especially in instances where response latencies or omissions also increase.

2.1.2. Neural substrates

Although it is often argued that DNMTP is partially dependent upon the hippocampus and frontal cortex, the literature on this is mixed. For example, Sloan et al. (2006b) found that lesions of the hippocampus caused no impairment on an operant DMTP task, whereas Porter et al. (2000) reported a delay-independent impairment. This is in contrast to the work of Chudasama and Muir (1997) and Winters and Dunnett (2004), who describe delay-dependent deficits after fornix lesion, effectively preventing output from the PFC from reaching the HPC (albeit this manipulation is not equivalent to destruction of the HPC). Interestingly, a lesion of the perforant path to the hippocampus was also capable of inducing a delay-dependent impairment in DMTP performance, suggesting that input into the hippocampus is also required for successful task completion, and not just the structure itself. Using a conditional match/non-match paradigm Sloan et al. (2006a) found a substantial impairment across short and long delays, although this impairment could have been related to other task demands. Talpos et al. (2010) also describe substantial delay-dependent impairments after a hippocampal lesion in an operant trial unique non-match to location task using a touch-screen equipped operant box (see Fig. 2). Both of these novel paradigms use procedures that likely reduce, or alter, the ability of the rodent to use mediating strategies which may substantially alter task demands, and delay dependency.

From a single-unit recording, there is also evidence that the hippocampus and hippocampal formation is involved in the rodent DNMTP and DMTP tasks. Unlike the primate prefrontal cortex, robust memory delay firing has not been typically observed in rodent hippocampal recordings in these tasks. However, Samuel Deadwyler, Robert Hampson, and colleagues have reported that individual neurons in the hippocampus fire with respect to multiple phases (sample, match, and reinforcement delivery) of delayed-matching or non-matching trials (Hampson et al., 1993; Deadwyler et al., 1996). They also suggest that neurons encoding aspects of a DNMTP task are clustered within portions of the dorsal hippocampus (Hampson et al., 1999), although such clustering has not been shown in the analyses of other place cell recordings (Redish et al., 2001). Neurons in the subiculum also show task-related correlates in the DNMTP task, particularly for the sample phase and early part of the delay for each trial (Hampson et al., 2000; Hampson and Deadwyler, 2003; Deadwyler and Hampson, 2004). Some evidence of delay firing in the hippocampus has been observed in an operant delayed alternation task (Takahashi et al., 2009) and in the parahippocampal region in an odor non-matching-to-sample task (Young et al., 1997).

Another approach to identifying the neural substrates for the DNMTP task has been to use direct infusion procedures. However, these have done little to clarify whether the hippocampus is necessary for DNMTP task performance. In a series of papers Mao and Robinson demonstrated that MK-801 infused into the DHPC, but not the VHPC, causes a non-delay-dependent impairment in accuracy (Robinson & Mao, 1997; Mao and Robinson, 1998). However no effect on accuracy was observed after an infusion of several concentrations of scopolamine, even though non-specific behavioral changes were observed (Robinson and Mao, 1997). This effect was in contrast to that seen by Dunnett et al. (1990), who observed a delay-independent impairment with scopolamine. Furthermore, in the Mao and Robinson studies, no effect of the GABA-A agonist muscimol was seen after infusion into the dorsal or ventral hippocampus. This result was unexpected, as muscimol infusions are generally considered to be equivalent to lesion of the area of interest, and MK-801 infusions have been shown to cause an impairment. To conclude, despite disparities in the literature, there is evidence that the HPC is necessary for DNMTP task performance, although the extent and nature of its involvement remains unclear. However procedures designed to reduce mediation appear to recruit HPC involvement in DNMTP type tasks.

Most studies agree that the prefrontal cortex is necessary for successful completion of the task, but the issue of delay-dependence remains unresolved. For instance Sloan et al. (2006b) report a delay-dependent impairment after lesions of the PFC, whereas Porter et al. (2000) observed delay-independent impairments, and Chudasama reports a delay-independent impairment after lesions to the pre-limbic area. Furthermore, in a series of studies designed to look at the influence of direct injection of dopaminergic compounds into ventral medial prefrontal cortex, Broersen et al. (1994, 1995) report a lack of specific effects on a DMTP task. For instance the DA agonist apomorphine appeared to cause only non-specific side effects, whereas D1 antagonist SCH-23390, and the non-specific DA antagonist cis-flupenthixol induced non-specific side effects and delay-independent accuracy deficits. Direct injections of scopolamine into the pre-frontal cortex were reported to cause a delay-independent decrease in accuracy by Dunnett et al. (1990) without the presence of side effects (scopolamine is known to induce hyperactivity). Herremans et al. (1996) also report that scopolamine injected into the PFC can induce impairments without non-specific side effects (DMTP). Intriguingly, the effects they observed could be delay-dependent or -independent, depending upon the behavior of the animals. In animals using a high number of mediating strategies, delay-*dependence* was observed after scopolamine administration. However, delay-*independence* was observed in animals committing few mediating strategies. Yet considering the findings of Lee and Park (2005), delay-dependence may be of less importance when modeling cognitive deficits associated with schizophrenia.

[3] Delayed non-matching to position tasks in rodents and non-human primates may appear to tap different neural substrates – the hippocampus and the dorsolateral prefrontal cortex, respectively. However, this difference may relate to the type of space assessed in each task. For rodents, particularly on mazes, to-be-remembered positions are locations in an environment through which rats must locomote. (That this is less so in an operant chamber may help to explain why the effects of hippocampus disruption are more mixed.) For primates, to-be-remembered positions are locations on a touch screen or a table top, within reach of a stationary animal. This distinction between table-top space and navigational space has been noted previously (Maguire et al., 1999). When freely-moving monkeys are tested in a task that is more comparable to a rodent maze, a delayed-matching-to-position task in an open room, damage to the hippocampus produces a substantial impairment (Hampton et al., 2004).

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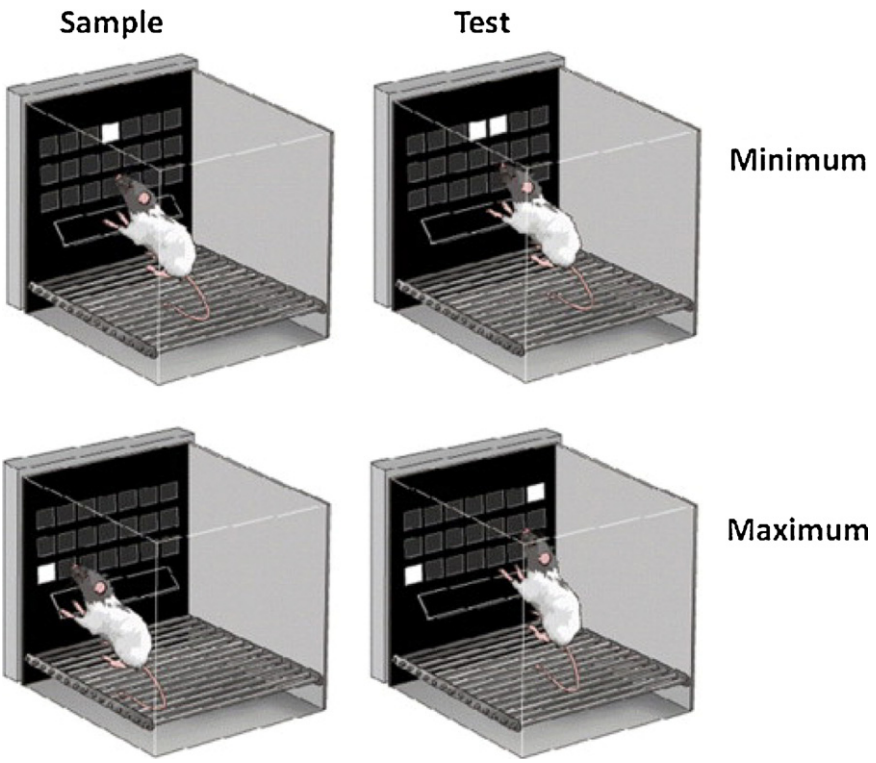

Fig. 2. Schematic of the trial-unique, delayed nonmatching-to-location (TUNL) task. In this task the rat is presented with a light in a specific location on a touch screen. When the rat nose-pokes this stimulus, it is turned off, and the rat receives a food pellet on the opposite wall of the operant box. After a short delay, the test phase of the trial begins, and the rat is presented with a light in the previously sampled location, and a new location. The rat is reinforced if it responds to the light in the new location. Performance under the minimum light separation condition (top right figure) is lower than when the test stimuli are separated by more space (bottom right figure). In contrast to the lever-based DNMTP task, the animal cannot predict where the non-match stimulus (the new light) will appear, and is thus unable to bridge the memory delay with a postural bias.

2.1.3. Pharmacology

DNMTP has a long history as a tool for pharmacological research with the effects of scores of compounds having been characterised on it. Perhaps the most prevalent model used is a cholinergic blockade induced by scopolamine. As a disease model this approach would certainly be more applicable to Alzheimer's disease then schizophrenia. Although popular in the literature, scopolamine is a difficult challenge model with little margin between selective effects on cognition, and non-specific side effects, with some groups failing to show any differentiation between these two elements. Moreover scopolamine has been shown to induce a wide array of behavioral changes and side effects within the dose range used as a cognitive challenge model (for a comprehensive review on the subject see Klinkenberg and Blokland, 2010). However, numerous cholinesterase inhibitors have been tested in this model, typically showing a reversal of the scopolamine-induced deficit. A similar approach has been used with selective and partially selective muscarinic receptor antagonists. More recently, scopolamine has also proved effective as a tool for studying pro-cognitive effects with non-cholinergic compounds. For instance recent studies have demonstrated that delay-dependent deficits induced by scopolamine could be reversed by mGlu2/3 antagonists (Woltering et al., 2010; DMTP) and a GABA-A alpha5 inverse agonist (Ballard et al., 2009; DMTP). This data suggests a potential utility beyond the cholinergic system.

Outside of the cholinergic system, NMDA antagonists are the best described class of compounds in DNMTP, largely as a result of two independent studies. In the first, Willmore et al. (2001) tested a series of compounds including "PCP" site antagonists, competitive NMDA antagonists, a glycine site antagonist, and one NR2B antagonist. Interestingly, regardless of the observed side effect profile, the authors were only able to observe deficits in accuracy with the "PCP" site antagonists (PCP, MK-801, and memantine). This is a profile of effects not dissimilar to that reported by Smith et al. (2011) on DMTP. In this series of studies the authors report small selective deficits with PCP (delay-dependent) and MK-801, while non-selective impairments were seen with memantine, SDZ 220,581, and Ro 25-6981. Owing to possible cross-site variability, these studies testing numerous related compounds under highly similar conditions are a great aid. Other compounds have been tested, however, unlike the studies by Willmore et al. (2001) and Smith et al. (2011), the range of compounds used have not been extensive (for examples see Cole et al., 1993; Campbell et al., 2004; Ballard et al., 2005; Pitkanen et al., 1995; Higgins et al., 2004, 2005).

Few studies have been published investigating the effects of dopaminergic compounds in DNMTP paradigms. In a study by Baron et al. (1998) comparing the effects of drugs of abuse on memory, neither cocaine nor D-amphetamine was observed to cause an acute impairment, even at doses that disrupted an operant delayed alternation procedure. This is in line with observations by Sahgal (1987) who reported that amphetamine induced a bias in responding, but not an impairment in memory per se. As several compounds that have been suggested for cognitive enhancement in schizophrenia have recently shown to be active in DMTP (Woltering et al., 2010; Ballard et al., 2009; Prieto and Taboada Martinez, 2011), it is surprising that little work has been published investigating the effects of established anti-psychotics within DNMTP. In a study by Gemperle et al. (2003), a striking delay-dependent enhancement in performance was seen after administration of the atypical antipsychotic iloperidone (atypical, DNMTP). In the same study, the typical antipsychotic haloperidol caused a small impairment at the longest delay and the highest dose tested, while clozapine (atypical antipsychotic) was shown to have no effect on accuracy. In a more recent study, Marston et al. (2009) also observed

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a small delay-dependent enhancement with risperidone (atypical), whereas asenapine and olanzapine (both atypical) had no effect on accuracy (DNMTP). Taken as a whole it appears that in some instances anti-psychotics are capable of improving accuracy in DNMTP, a finding counter to their typical clinical profile. This pro-cognitive effect in normal rats is perhaps also surprising considering that stimulation of the dopaminergic system did not induce clear cognitive impairments, as discussed above. However, additional work would be required to rule out a simple change in bias towards/away from a match or non-match rule. An excellent example of such a misinterpretation is highlighted by (Sahgal et al., 1990) who described a response bias induced by vasopression that could be interpreted as a cognitive impairment or enhancement, depending on whether a match or non-match procedure is used.

2.1.4. Impairment models

Few disease models not based on acute pharmacology have been tested in operant DNMTP paradigms. An exception to this is the development methylazoxymethanol (MAM) model, based upon the inhibition of mitosis on gestational day 17. In a study by Flagstad et al. (2005) no deficit was found in DNMTP, although deficits were present in active avoidance and in latent inhibition. A study with reeler mice, proposed as a model of schizophrenia, found no difference between heterozygous animals and wild type controls on DNMTP performance (Krueger et al., 2006).

2.1.5. Psychometrics

It can easily take a rat three months to learn DNMTP in an operant box, which is slow when compared to many other paradigms. However the automated nature of DNMTP, and the ability to reuse animals, makes it ideal for the drug discovery process. Throughput is almost entirely dependent upon the number of operant chambers, making it easily scalable for use in a small laboratory, or to support a large drug discovery effort. Typically, animals are trained once a day with sessions varying in length from 30 to 60 min. Once trained the number of studies performed in a set of animals is only limited by life span, ethical considerations, and confidence in reusing animals after multiple treatments. For example, one set of 16 operant boxes being used by one experimenter for half a day could deliver nearly 40 dose response curves ($n = 12$) in a year with once-weekly testing (3 months training, 9 months testing with 3 test sessions of 16 animals), while statistical analysis is also typically straightforward. Performance level can also be easily manipulated by adjusting the delay between sample and choice phase. The majority of animals show clear signs of delay-dependent memory, with higher performance at shorter delays than at longer delays (and chance level performance at delays between 20 and 60 s). As such, DNMTP has adequate dynamic range to detect enhancing or impairing effects. Since delays can be adjusted there is little worry of over-training occurring. If a cohort of animals begins to show insensitivity to the delays being used, then the delay can be increased to achieve an ideal level of baseline performance. Similarly, performance stabilizes quickly when delays are adjusted. Although less frequently used, a second means of manipulating performance is through the inter-trial interval (ITI). Since DNMTP uses only two positions, and each is seen on every trial, there is a very high interference component (trial one causes a proactive interference for trial two). Accordingly, the shorter the ITI the more difficulty an animal will have remembering the current sample location as a distinct entity from the previous sample. As such, animals are expected to perform better with longer ITIs (Dunnett and Martel, 1990; van Hest and Steckler, 1996). This variable is rarely manipulated, but perhaps could be used to distinguish memory effects from interference effects.

2.1.6. DNMS/delayed response tasks in non-human primates

Historically, procedures similar to DNMTP have been used in monkeys, with both spatial and nonspatial stimuli. Monkeys can learn that the location of a reward alternates between two locations on a test tray (left and right wells) within a test session. This spatial alternation task is impaired by ablations of the dorsolateral prefrontal cortex, specifically the cortex lining the banks of the principal sulcus (Goldman and Rosvold, 1970). Object alternation, in which the monkey must alternate choices of 2 objects across trials (and the objects randomly vary spatial position between left and right) is also impaired by lateral prefrontal lesions in monkeys, but can be re-acquired by monkeys with lesions of the dorsolateral (but not ventrolateral) prefrontal cortex (Mishkin et al., 1969). However, the delayed response task and variations thereof have been used much more commonly, perhaps because of the demonstration in this task of neurons with "memory fields" in prefrontal cortex (Kubota and Niki, 1971; Fuster and Alexander, 1971; Funahashi et al., 1989), providing a compelling neural correlate of working memory.

In the delayed response task, the monkey is essentially performing a spatial delayed matching-to-sample procedure. In the manual testing format the monkey watches while one of two wells (left or right) is baited by the experimenter, then the wells are covered and an opaque screen is lowered between the monkey and the test tray for a brief delay interval. When the screen is raised, the monkey is allowed to displace the cover over the well and retrieve the food reward, remembering the baited location during the delay on each trial. In the automated versions of this task, a visual cue signals the to-be-remembered location rather than the event of the experimenter baiting the well. Performance of this task is devastated by lesions of the dorsolateral prefrontal cortex (Bachevalier and Mishkin, 1986; Alexander and Goldman, 1978). Notably, monkeys with ventromedial prefrontal ablations also fail in acquisition of the delayed response task, albeit at a later stage of training than monkeys with dorsolateral lesions (Bachevalier and Mishkin, 1986), so impairments in this task are not strictly diagnostic of dorsolateral prefrontal dysfunction. With regard to the neurochemical regulation of this task, dopamine depletion with the dorsolateral PFC impairs spatial delayed response (Brozoski et al., 1979), as does cholinergic depletion of lateral and orbital PFC (Croxson et al., 2011). Systemic administration of muscarinic cholinergic antagonists impairs delayed response performance (Bartus and Johnson, 1976) and cholinesterase inhibitors such as physostigmine may produce improved performance in a narrow dose range (Bartus, 1979). Iontophoretic administration of an alpha-2 noradrenaline agonist (guanfacine) increases the firing rates of prefrontal delay neurons in older rhesus monkeys, as do compounds which inhibited cAMP signaling, or which block HCN or KCNQ channels (Wang et al., 2011). Systemic administration of guanfacine also improves delayed response performance in aged monkeys (Arnsten et al., 1988).

Nonspatial working memory tasks in monkeys include the aforementioned object alternation task, which monkeys find very difficult to learn. Delayed nonmatching-to-sample (DNMS) is a common test of object recognition memory in monkeys in which the monkey encounters a sample object, and then after a delay is offered a choice between the sample object and a novel object and is rewarded for choosing the novel object. In the typical version of this task the objects are "trial-unique" in that they are drawn pseudorandomly from a pool of hundreds or thousands of objects. Acquisition of nonmatching to sample with trial-unique objects is much easier for monkeys than matching to sample with trial-unique objects, or either task with a repeated pair of objects from trial to trial (Mishkin and Delacour, 1975), presumably because the nonmatching rule takes advantage of the monkey's natural tendency to explore novelty, and because repeated objects lose their

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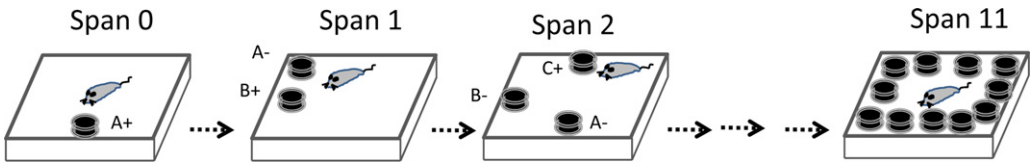

Fig. 3. Schematic of the odor span task. The rat is initially presented with a cup of sand scented with an odor (e.g., parsley). If The rat digs in this cup (A+), it will find a food reinforcement. On the next phase of the trial the animal again sees this odor, and a second odour (e.g., mint). Reinforcement is found only in the cup that the rat has not seen previously, B+. The task can continue In the same manner until several odors are presented. The number of odors the rat must remember is referred to as the memory span.

novelty very quickly so performance must rely solely on working memory. Importantly, this underscores the point that DNMS, in its standard, trial-unique format, is a test of recognition memory, rather than working memory; the monkey simply needs to recognize which object is less familiar at the choice trial, not maintain a memory of the sample object during the delay period. DNMS with repeated objects, which tests working memory rather than recognition memory (because the objects are equally familiar, therefore likely having more in common with operant DNMTP in rodents), has not been used extensively in cognitive testing of monkeys. It is notable that aged monkeys that are impaired on spatial delayed response, but show substantially intact recognition memory in DNMS tested with trial-unique objects, are dramatically impaired in DNMS with repeated objects (Rapp and Amaral, 1989). This points towards an impairment in working memory under conditions of high stimulus interference in aged monkeys (repetition of two objects or spatial locations) rather than a specific impairment in spatial working memory. Thus, this task may merit more attention for neuropharmacological testing in primates in the future, with regard to providing a test of nonspatial working memory (albeit one that is much more challenging for monkeys to learn than spatial delayed response).

2.2. Memory capacity

The task nominated for this construct was the rodent span task (Dudchenko et al., 2000; Young et al., 2007b). In this task, the rodent is presented with a cup of sand, in which a food reward is buried. In the odour version of the span task, this sand is scented with a small amount of a household spice, such as basil (odor A). The animal digs through the sand to retrieve the reward, and is permitted to consume it. The animal is removed from the platform while the initial cup of sand is removed, and two new cups are placed on the platform. One of the cups of sand contains sand scented with previous odor, odor A, and the other cup of sand contains a different odor (B). Reward is only found in the sand scented with odor B. The rodent thus has to remember which odor it had previously sampled, and select the one that it has not sampled previously. Through this stage, the task is identical to a delayed non-matching to sample task.

However, to test the capacity of the animal's memory, the trial does not end after the pair of odours, A and B, have been presented. Rather, this test comparison serves as the sample phase for the next test, where three odors, A, B, and C are presented (see Fig. 3). Here the rodent has to remember the two previously presented odors, and select the odor that it has not encountered before, odor C. Additional odors are then added up to a fixed number, for example 12, or until the rodent makes a mistake. The animal's span is the number of stimuli that the animal correctly remembers before making a mistake.[4] Alternatively, with the presentation of a fixed number of stimuli, the experimenter can consider the percentage of correct responses across days or animals at each span length.

Although the task has been described with odor stimuli and rats, this "span" approach also works with other stimuli and other species. For example, a spatial span can be assessed by requiring rats to remember the locations of previously visited cups of unscented sand (Dudchenko et al., 2000). Using a different approach, Steele and Rawlins (1989) showed that rats could learn remember at least 32 distinctive goalboxes. In terms of different species, Young et al. (2007b) have developed a version of the span task that works well in mice. Indeed, the original task was based on memory load manipulations in the assessment of hippocampectomised monkeys (Murray and Mishkin, 1998; Beason-Held et al., 1999).

2.2.1. Neural substrates

The neural systems that this task taps have yet to be fully identified. The odour span task in rodents does not require the hippocampus, although the spatial span version of the task does (Dudchenko et al., 2000). For other types of stimuli, the evidence implicating the hippocampus is mixed. For example, in monkeys with hippocampus and amygdala damage, no impairment was observed with memory for up to 40 objects (presented individually; Murray and Mishkin, 1998). Similarly, Heuer and Bachevalier (2011) found no impairments in object or spatial span in monkeys with hippocampal lesions. However, Beason-Held et al. (1999) found that monkeys with hippocampus damage had diminished memory spans for spatial locations, colours, and objects. Also, humans with hippocampus damage show smaller spans for line drawings and color patterns, but show only a modest impairment on an odor span task (Levy et al., 2003). It is possible, however, that the latter result could be related to semantic tagging of odours encountered.

Individuals with schizophrenia show reduced spans on a task which requires memory for the location of stimuli on a computer screen, and on a Corsi-type block tapping task (Chey et al., 2002). Diminished spans are also seen patients with schizophrenia on the visual memory span subtest of the Wechsler Adult Intelligence scale, a task in which one must remember a sequence of squares that the tester points to on a card (Pirkola et al., 2005).

2.2.2. Sensitivity to pharmacologic and genetic manipulations

To date, only a few studies have examined the effects of neurotransmitter manipulations on rodent memory span. Lesions of the cortical cholinergic system (with basal forebrain 192 IgG-saporin injections) produce a significant decrease in odor spans, although recovery is seen 3-4 weeks following surgery (Turchi and Sarter, 2000). In this study rats trained in a match to sample version of the span task with similar lesions did not exhibit any effect on performance, suggesting the lesions effects were specific to span capacity. Mice that over-express the apoptotic effecter caspase-3 exhibited age-independent deficits in span capacity that was remediated by nicotine (Young et al., 2007b). TG2576 mice that over-express the amyloid precursor protein incorporating the amyloidogenic Swedish mutation exhibit an age-dependent

[4] How the animal represents to-be-remembered odors is not yet known. However, as the same odors are used each day, the task is more comparable to the primate DNMS task with familiar objects, rather than trial-unique objects.

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working memory span deficit (Young et al., 2008). Alpha 7 nicotinic acetylcholine receptor knockout mice also exhibit a reduced span capacity (Young et al., 2007a), although this may have been mediated by attentional dysfunction (Young et al., 2004, 2007a; Hoyle et al., 2006). More recently the odor span task has been used to investigate the pro-cognitive effects of nicotinic agonists nicotine (mixed nAChR agonist), metanicotine (an alpha 4 beta 2 nAChR agonist), and (R)-N-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-pyridyl)thiophene-2-carboxamide) an alpha 7 nAChR agonist (Rushforth et al., 2010). The authors of this study found that all treatments increased the span capacity of rats in the task. Moreover, the nAChR antagonist mecamylamine and mAChR antagonist scopolamine impaired performance in the task.

2.2.3. Psychometrics

Rodents can be trained in the task in approximately 4–6 weeks, with retraining possible within 2 weeks. As such rodents can be repeatedly tested in the odor span task as evidenced in the age-related studies in caspase-3 over-expressing and TG2576 mice (Young et al., 2007b, 2008). At present, no data are available on the test-retest reliability of the task.

2.2.4. Role in the drug discovery process

More studies are required in the odor span task to identify the neural substrates mediating performance of the task. The task does appear to be useful in identifying compounds that can improve span capacity, and is easy to use in mice and rats. The mechanics of the task may limit its use however. To date, the odor span task has only been run manually, taking approximately 20 min to run each rodent. Thus, in a given 8 h workday, 15–20 rodents may be trained in the task. While study cohorts can be combined, the inability to test more may limit the use of the odor span task in the drug discovery process.

2.3. Interference control

The paradigms considered for this construct included (1) the stop-signal task, (2) the room–arena (R+A−) avoidance task, (3) a contextual control of response task, and (4) operant and radial arm variants of the *n*-back task. The consensus was that, of these, the *n*-back tasks held the most promise for this feature of working memory.

2.3.1. Tasks not considered for interference control

In the stop-signal task, the rat is required to press one lever, and then another, to receive a food reward on most trials. On some trials, however, a tone is sounded before the second lever is pressed. On these trials, the animal is rewarded if it refrains from responding to the lever. Thus, the tone is a signal to stop an on-going motor response, also referred to as 'action cancellation' (Eagle et al., 2008). Although this task has excellent translatability between animals and humans, and variants of it are disrupted in psychiatric conditions like ADHD, the consensus of the break-out session was that it did not have a clear working memory component.

In the room+/arena− task of Bures et al. (1997) (Cimadevilla et al., 2000) rats are trained to avoid a pie-shaped region of a circular platform. If they enter this region, they receive a mild footshock. The platform (arena) itself continually rotates, but the shock zone is stable in the room coordinates. Thus the rat must orient to extra-maze cues to avoid the shock zone, and ignore any intra-maze arena cues.

In its favour, this task approaches the interference construct, as the animal has to attend to one spatial reference frame, the room, and ignore a competing reference frame, the rotating arena floor. Deficits have been also been found with relevant models, including MK-801, PCP intoxication, and neonatal ventral hippocampal lesions (e.g., Vales et al., 2006). The potential limitations of this task, however, are two-fold. First, it appears that the task is most robust when the shock zone stays in the same location across days, as opposed to a new location each day (Cimadevilla et al., 2000). Thus, the representation of the shock location may be less of a working memory and more of longer term memory. Second, it is not clear that a human analogue of this task is available, and thus whether performance on it is sensitive to the disruptions in schizophrenia.

For the third task considered, the contextual control of response task, rats learn one set of stimulus-response contingencies in one environment, and a different set of contingencies in a second environment (Haddon and Killcross, 2006). For example, in one distinctive operant chamber, a tone may indicate that a response to the left lever yields a food pellet, and a click indicates that a response to the right lever will yield a pellet. In a second chamber, a flashing light and a constant light indicate which lever press will yield reinforcement. Compounds of these discriminative stimuli can then be presented in one of the two environments, and response to the "correct" stimulus indicates that the response is controlled by the context.

In its favour, the task is conceptually similar to the Stroop task (Haddon and Killcross, 2007), performance of which, in some forms, is impaired in patients with schizophrenia (Carter et al., 1997; Henik and Salo, 2004). The contextual control of response task has been shown to be sensitive to disruption of the prefrontal and the anterior cingulate cortices (Haddon and Killcross, 2006; Marquis et al., 2007), and to enhancement with a D1 agonist (Haddon and Killcross, 2007). However, as described under the goal maintenance construct, the task is based on competition between long-term associations. Thus, it was not felt to tap working memory per se.

2.3.2. Tasks recommended for interference control

Two types of tasks may satisfy the criterion for measuring interference control in rodents. Both tasks are conceptually based on the human *n*-back task (Kirchner, 1958), where subjects are presented a sequence of stimuli and are required to indicate when the current stimulus matches one from n steps earlier in the sequence. For example, a subject may be required to indicate that a stimulus is repeated immediately (1-back condition), or with one stimulus intervening (2-back condition), or with two stimuli intervening (3-back condition) (Gevins and Cutillo, 1993). This is a classic test of interference control as incoming stimuli interfere with the memory of previously presented stimuli, and thus a 1-back task is fairly simple while a 3-back condition is considerably harder. The task also requires monitoring and updating of information (Cohen et al., 1997). Patients with schizophrenia exhibit poor performance across all conditions, and worse performance in the harder conditions (Abi-Dargham et al., 2002; Glahn et al., 2005).

The first type of interference task for the rodent is an operant version of the *n*-back task developed by Ko and Evenden (2009). They attempted to measure *n*-back-like performance in rats using a 5-lever operant chamber, with either a 1-back or 2-back memory requirement. In both conditions rats were presented with an extended lever to which they were required to press and then nose-poke in the reward delivery area. This was repeated 3–5 times on different levers after which time a tone was presented and all 5 levers were presented until the rats selected a lever. In the 1-back condition they were required to press the lever they had last pressed, in the 2-back condition they had to press the 2nd to last lever they were presented with. Initially there was difficulty training the rats to perform the 2-back condition. Therefore, as an additional attempt to ensure lever encoding, the rats were required to press what would be the target lever 3 times during the lever sequences. Without this aid rats did not learn the task, although it also meant that the rats were cued as to which lever would be required to be pressed. Even with this cue, it took rats trained on

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the 2-back task 76 sessions to acquire the task (11 out of 16 met the >50% criterion) compared with 56 for rats in the 1-back task (14 out of 16 met the >60% criterion). Attempts to train rats on a 3-back task were apparently unsuccessful. Rats that had attained criterion were administered amphetamine (0.2 and 0.4 mg/kg), nicotine (0.1–1.0 mg/kg), and SKF38393 (1.0–10.0 mg/kg) in successive drug tests, but none were successful at improving performance. Impairments were observed at higher doses of amphetamine and nicotine (Ko and Evenden, 2009).

It was felt by the group that the reliance of cueing in the 2-back task limits this task to a 1-back task, essentially consistent with a short delay DNMTP. Although the approach is novel, and the task has a semblance to the *n*-back tasks used with patients, the difficulties of training rats in this task may limit its utility in the drug discovery process. With only one publication in the task, independent assessment of the utility of the task would be useful, but the group was pessimistic on positive results being obtained.

A second class of tasks for interference control include a series of paradigms which assess rodent spatial and object temporal order memory (Kesner and Dakis, 1997; Kesner and Giles, 1998; Kesner et al., 2001; Chiba et al., 1997, 2002; Jackson-Smith et al., 1993), and which have been described as working memory tasks (Kesner and Ragozzino, 1998). A wide variety of task apparati (object, holeboards, and 12- and 8-arm radial arm mazes) and experimental protocols have been used. Conceptually related tasks assessing memory for sequences of odors have been developed by Howard Eichenbaum and colleagues (Fortin et al., 2002; DeVito and Eichenbaum, 2011). The Kesner paradigms themselves can be subdivided into continuous and discrete temporal relational memory tests.

2.3.2.1. Continuous temporal relational memory test. This task resembles the *n*-back task whereby animals are presented with 8 (or 12) arms (or objects) in a specific sequence. The first time the rat samples a maze arm or an object, it obtains a food reward (either at the maze arm end or under the object). Within the presented sequence of stimuli (arms or objects), however, some stimuli are repeated, and repeated presentations are not reinforced. The degree to which the rodent remembers the stimulus is inferred by the difference in latencies between entering an arm that is novel (baited) vs. one that has been previously visited (and is thus not baited). The degree of separation from the initial presentation of a stimulus to it being repeated is the lag, and a stimulus that is repeated immediately has a lag of 0, while a stimulus that is repeated after 5 others has a lag of 5. The latency differences for repeat arm presentations are greater for the shorter lags (where stimuli are close together) as opposed to the longer lags (where there are a number of intervening stimuli), suggesting that there is a stronger memory after shorter as opposed to longer lags. This pattern of results may be similar to the better *n*-back memory in humans for 1-back as opposed to 3-back items.

2.3.2.1.1. Neural substrates. Hippocampus lesions (Jackson-Smith et al., 1993; Chiba et al., 2002), but not parietal cortex lesions (Chiba et al., 2002), impair performance in this task as indicated by a lack of latency differences at any lag (suggesting that the rodent does not recognise previously encountered stimuli). Perirhinal-, but not lateral- or medial-entorhinal cortical lesions, likewise abolish latency differences at all lags (Kesner et al., 2001). Intrahippocampal PCP injection disrupts acquisition of the task, but naloxone does not (Kesner and Dakis, 1997). Only the higher of the two doses of PCP impaired performance while the lower dose did not. With only one dose of naloxone tested, it is difficult to determine whether higher doses might also have impaired acquisition. The degree of impairment exhibited by the high-dose PCP-treated rats was not gradual, going from normal performance (gradual latency difference reductions with increasing lags) to a complete lack of latency differences at any lag.

There are potential difficulties in interpreting manipulation-induced effects on the continuous temporal relations task. Essentially, all manipulation-induced impairments in performance described above produced the same deficit: a lack of latency differences at all lags. This has been interpreted as the animal not remembering where it had just been. However, no differences in latency have ever been observed at the 0 lag, where there is a minimal memory load as the animal had just emerged from that arm. This pattern of results is different from that shown by patients with schizophrenia, who exhibit memory of items they had immediately been presented with. It is also possible that impairments at all lags reflect a more general disruption of task performance, for example an impairment in the use of the task rule or a global disinhibition of responding. As differences in latencies are the sole measure of performance, it may also be difficult to determine whether a treatment reduces hyperactivity or improves memory.

2.3.2.2. Discrete temporal relational test. This task also presents the rodent with a series of baited stimuli (maze arms or objects) in an experimenter-controlled sequence (see Fig. 4). After a sequence of stimuli are presented, the rodent is presented with two previously stimuli and is required to select the stimulus that was first presented in the sequence. Consistent with the continuous task, the lag between the presented stimuli can be varied. However, the primary measure of the discrete task is the percentage of correct trials, which may allow performance effects to be more readily interpretable since both the accuracy of performance and the latencies to choose can be calculated. Also, unlike the continuous task, performance improves with increasing lag. This suggests that the maze arms or objects separated by more intervening items are more discriminable than those whose presentations are separated by fewer items. While these two tasks have been used to compare lesion effects in spatial vs. object recognition memory (Jackson-Smith et al., 1993), the different patterns of results with different lags suggest that they tap somewhat distinct memory processes. The discrete temporal relation task may assess the temporal discriminability of pairs of previously presented stimuli, whereas the continuous task assesses within-trial recognition of a previously sampled stimulus.

2.3.2.2.1. Neural substrates. Lesions of the mPFC produce a lag-independent impairment of performance with improvements still apparent with increasing lag (Chiba et al., 1997). This effect is reminiscent of mPFC lesion of the DNMTP which can produce delay-independent deficits in performance (Porter et al., 2000). Impairments with mPFC lesions have also recently been described with an odor version of a sequence memory (DeVito and Eichenbaum, 2011). Hippocampal lesions do not impair performance in this discrete choice task with objects (Jackson-Smith et al., 1993; Mumby et al., 1995), but deficits have been reported with sequence memory for odors (Fortin et al., 2002; DeVito and Eichenbaum, 2011). Acute systemic PCP-administration impairs performance in this discrete relational memory task (Long and Kesner, 1995).

2.3.3. Use in drug discovery

n-Back type tasks were viewed as having potential for the construct of interference control, although the existing paradigms have not seen widespread use. Thus, there is a lack of behavioral pharmacology in both of the maze tasks described above. Also, the lack of clear procedure and apparatus, as well their lack of use in other laboratories suggests more work is required before either task is ready for assessment. As with all maze-based tasks, the length of time taken to run a single subject, and the number of sessions required to generate data may limit the utility of both tasks in

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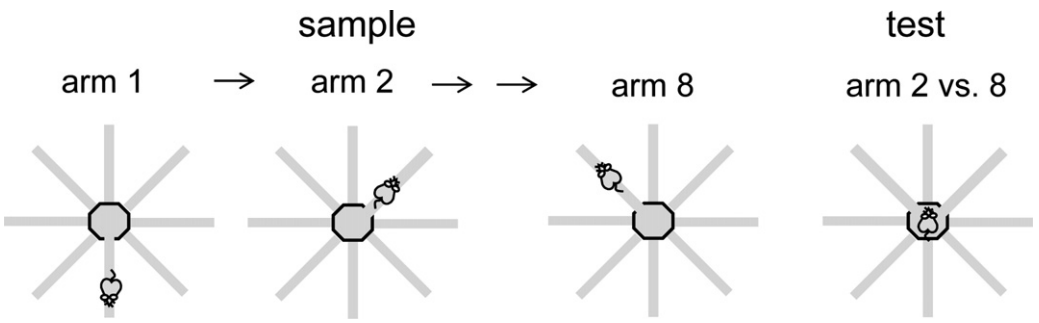

Fig. 4. Schematic of a temporal relations (*n*-back like) task. Kesner and colleagues have developed a maze version of a temporal memory task in which the rat is first presented with individual maze arms in a specified sequence. In the test phase of the trial, the rat is presented with a choice between two of the previously sampled arms, and is reinforced for selected the arm that appeared earlier in the sequence.

the drug discovery process. From an interpretational standpoint, a lack of lag-dependent effects in the continuous task with certain lesions and drug infusions suggests that some effects may not be memory-specific. Likewise, the use latency as the sole measure of behavior in the continuous task may limit its interpretability in terms of memory effects.

2.4. Next steps

2.4.1. Goal maintenance tasks

Despite being a mature task, DNMTP is still in need of refinement in several ways for application to schizophrenia. Foremost among these is the need for further characterization of antipsychotics in DNMTP. Existing publications suggest a pro-cognitive profile of antipsychotics, and the extent to which this can be replicated across compounds, laboratories, and procedural variants should be considered. Second, scopolamine remains the pharmacological challenge of choice, yet it is probably more appropriate as a model of general cognitive/attentional impairment, rather than a model of schizophrenia. Despite some flaws, Ketamine, or another NMDA antagonist, may be more appropriate as a closer translational model of schizophrenia, particularly as the same pharmacological challenge (Ketamine) is performed in some clinical settings. Accordingly, it would be of interest to see a comparison of existing anti-psychotics and novel compounds on NMDA and cholinergic antagonist challenges models. Similarly, additional work should be done with transgenic manipulations, sub-chronic NMDA antagonist models, as well as various developmental models of schizophrenia.

Despite its popularity, DNMTP has several well acknowledged shortcomings. Among these, as highlighted in the study by Sahgal (1987), is the ability for an induced bias towards match/non-match to be interpreted as a cognitive effect. Such a finding highlights the necessity of examining relative bias after a manipulation, but also demonstrates the utility of conditional match/non-match paradigms where both rule types can be considered in the same animal. While in the initial paradigm the trial type was signalled during the sample phase (Pache et al., 1999; Sloan et al., 2006a,b), more recent work indicates that this procedure works when the signal is only given at the choice phase (Fellini et al., 2011). This small change may have a marked influence on mediating strategies as the location of the correct stimulus (S+) can no longer be predicted at the sample phase, presumably requiring the animal to actively maintain the memory across the whole delay. One shortcoming with this procedure is that it is vulnerable to changes in use of the conditional rule. However, the need to combine the information about the sample phase with the required response rule at choice phase should also increase the "maintenance" component of goal maintenance. Furthermore, it also increases the similarity with the AX-continuous Performance Task/Dot Pattern Expectancy task, a task recommended for goal maintenance testing in humans.

A second alternative to standard DNMTP is the trial unique non-match to location (TUNL) paradigm for use in touch-screen equipped operant boxes (Fig. 2). In this procedure the screen is divided into a grid, and the sample and choice can be displayed any place upon the grid. In such a way it is impossible to predict the exact location of the S+ in the sample phase of the trial. In principle, the rats could attempt to bridge the delay by remaining at the sample location and then moving when the test phase of the trial begins. In practice, however, this has not been observed. This paradigm has been found to be sensitive to hippocampal lesions in delay- and separation-dependent manner (Talpos et al., 2010), whereas PFC lesions were observed to only have a delay-dependent effect only (Bussey et al., 2011). Future use of procedures of this type should be strongly considered to increase the construct validity of DNMTP tasks.

The consensus of the CNTRICS group is that both operant- and maze-based DNMTP procedures should be considered suitable for this domain. Here, the focus has been on operant paradigms for several reasons. The first of these is the benefits that come with automation (consistency in timing, accurate measurement of timing, comparatively high through-put, not dependent upon a single tester, automated scoring, etc.), all important in a drug discovery environment. Moreover there is little concern about the break down in the blinding procedure as there isn't the opportunity for experimenter bias during data collection. However little work has been done directly comparing the operant and maze based paradigms (Porter et al., 2000). While many differences are obvious, such as the need for ambulation, and a much "richer" spatial environment, perhaps one of the greatest differences is the interference component that exists in the operant version because of the massed trials. Indeed performance in operant DNMTP paradigms may be as much about forgetting the past, as remembering the past. As such, some emphasis should be placed on side-by-side comparison of these two paradigms to see if they yield the same pharmacological sensitivity. Finally, DNMTP appears to be at least partially dependent on the PFC and the HPC. However the relationship between these structures in task performance remains poorly understood. Work addressing the interactions and neuronal synchrony between the HPC and PFC was a point of particular emphasis by the group. Studying these interactions within a task like DNMTP may be particularly fruitful for schizophrenia research.

2.4.2. Memory capacity task

The consensus task for the memory capacity construct, the span task, holds promise, but requires additional work. First, the neural substrates of this task have yet to be fully identified. However, as the neuropathology in schizophrenia itself is likely not to be confined to one neural circuit (Shenton et al., 2001; Jarskog and Robbin, 2006), this may not be an insurmountable barrier to drug discovery. Also, it seems likely that somewhat different neural systems may

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be taxed by different types of the to-be-remembered stimuli (for example, the neural systems necessary for spatial location memory may differ from those underlying odor or visual stimuli). So, the specific version of the task employed may depend on the target of the intervention.

A related issue is the neurochemistry of this task. There is evidence that the cholinergic system is necessary for normal span memory. At the time of writing, however, there is a dearth of information on the sensitivity of this task to compounds that affect other neurotransmitter systems.

As stated above, the versions of the span task described in this review have been run by hand, and as such, may have a finite throughput. Automation for the odor span version of task may entail some engineering. However, other span stimuli, for example memory for a series of lights, may be amenable to testing in a 5-choice box or modifications thereof.

Lastly, a valid critique of the rodent span tasks is that they tap a slightly different capacity than that assessed in human tasks. In the latter, spans range from 4 to 9 items (e.g., Miller, 1956; Luck and Vogel, 1997), whereas in the rodent odor span task, capacities can be much higher. These higher spans in the rodent tasks likely reflect the re-presenting of the stimuli on each span trial, and thus may tap longer-term memory capacities. To bridge these differences, a next step may be to develop variants of the proposed tasks. For example, for odor-span type task, a match-to-sample procedure might be tried where a number of different odor cups are presented sequentially, followed by a test phase in which presented cups, and several distractors, are presented on the same table-top. The rodent would indicate its memory by digging in the previously presented cups, and refraining from digging in the cups that had not been presented. Another variant of the rodent span task might be a matching-to-sample task with a sequence of illuminated squares on a touch screen, comparable to the Corsi block test used in humans.

2.4.3. Interference control tasks

n-Back and sequence memory tasks relate to the impairments seen in schizophrenia, but likely require additional work before they can be adopted for drug discovery. An operant version of the task has been developed but, ideally, it would be preferable for the to-be-remembered stimuli to require the same response as that required for the distractors.

Maze versions of sequence and temporal order tasks may tap slightly different capacities. In the continuous version of the maze task, performance decreases as the number of intervening arms, or lag, increases. This suggests that visits to subsequent maze arms interfere with recognition of an arm visited earlier. However, it is possible that this task is solved on the basis of relative familiarity. In the discrete trial version of the task as used by Kesner and colleagues, interference takes the form of a diminished discriminability of stimuli presented near one another in time compared to those with a greater separation by intervening items.

These maze versions of interference control tasks may suffer from the low-throughput issue associated with many maze tasks. However, it seems likely that the continuous and discrete-trial tasks of Kesner and colleagues could be easily automated. Little behavioral pharmacology data have been published on these tasks, save for PCP-induced deficits in performance, so additional characterisation is needed.

As may be gathered from the preceding discussion, the selected tasks for the interference control construct likely require additional consideration. A valid critique of these is that they do not isolate interference specifically. However, variants of these tasks which resemble the recent-probes task (the task recommended for interference control assessment in humans) can be envisioned. For example, on a multiple-arm maze, rats might be trained on a match-to-sample rule, and then subsequently tested on trials in which 2–3 arms serve as the sample stimuli, with memory for these being tested by presenting a choice between one of these arms and a non-sampled arm. On a single trial, this is a simple memory task, but if repeated trials are presented, the non-sampled arm can be a sample from a previous trial, and thus yield interference.

2.4.4. Improving discriminant validity

From a practical perspective, the task recommendations in the current review will carry little weight unless the proposed tasks can be distinguished from other paradigms based on their pharmacological and neural system profile. At the moment, the evidence for such distinctions is suggestive, but not complete. For example, odor span performance is impaired by lesions of the forebrain cholinergic system, but such lesions do not typically impair novel object recognition memory (e.g., Savage et al., 2011). Further, hippocampal lesions do not affect odor span task performance, but such lesions are detrimental to delay-dependent memory performance as observed in the DNMTP. Further efforts to establish such task dissociations would be of inherent interest, and potentially of considerable value to researchers in industry.

2.4.5. Improving predictive validity

The approach to predictive validity implicit in this review is that of Sarter and colleagues (e.g., Sarter et al., 1992; Sarter, 2006). Essentially, it involves identifying behavioral tasks or models with good *construct* validity (that is, performance on the task depends on the construct of interest). With this view, one way of improving the predictive validity of working memory tasks would be to better specify the construct of interest. For example, if a reliable deficit in memory capacity can be demonstrated in schizophrenia, then the field would have a concrete target for which tasks can be developed or refined. From a preclinical perspective, a subsequent challenge may be balancing good construct validity with high throughput.

An obvious difficulty in the field is the lack of compounds that improve cognition in schizophrenia. Predictive validity entails an agreement between the animal model and patients: a drug works in both, or fails to work in both. Thus, a positive demonstration of validity has yet to be seen, but having a drug that works in patients also obviates the problem. Treatments that fail in both possess predictive validity, but may be uninformative. From a logical and practical perspective, this leaves situations where there are mismatches between the results in animal models and in patients. For example, some compounds have shown positive effects in novel object recognition tasks of memory in rodents, but have failed in patients with schizophrenia (for review see Young et al., 2009). Such a mismatch, or its converse, allows one to reject a particular animal model. So, a clear strategy to improve the predictive validity of animal tasks is to be mindful of clinical failures, and to use these to inform task selection. However, it may be unrealistic to insist on direct one-to-one relationship between a pre-clinical model and a human disorder. Rather, a positive pre-clinical finding should be a signal indicating an increased probability of a positive clinical result. A similar critical view should be taken of pre-clinical disease models. Observed deficits are only reflective of the disease model, and no disease model needs to capture every symptom of schizophrenia. For instance if a model disrupts synchronous neuronal firing, and induced a selective delay independent impairment in DNMTP, it may still have great utility in schizophrenia research even if failing to capture all elements of schizophrenia.

2.4.6. Summary

In this review tasks nominated for the working memory constructs of *goal maintenance*, *memory capacity*, and *interference control* in animals have been considered. The review has highlighted tasks for further development for each of these constructs, and reviewed what is known of their neural substrates

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and behavioural pharmacology. The most mature tasks, the delayed non-matching to position paradigms in rodents, have high throughput and a reasonable pharmacological characterization, though some work remains. One challenge to such traditional tasks is that, in patients with schizophrenia, memory deficits do not increase beyond a short delay. Thus, it may be that for goal maintenance, delay-dependence in its usual sense is not an absolute requirement. Rather, it may be necessary to show that delay performance is lower than no-delay performance, as has been observed in patients with schizophrenia (e.g., Gold et al., 2010). A translational challenge here will be to develop tasks where ceiling effects are not seen at short delays. Memory span tasks in rodents, or revisions thereof, may map to the capacity limits observed in patients with schizophrenia, though a lack of automation is a clear issue, and behavioral pharmacological work has been limited. Similar limitations apply to the maze-based interference control tasks. In general, an iterative process of task refinement based on the observed cognitive deficits in schizophrenia, of which this review is an initial attempt, should yield better tools for drug discovery.

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