Neuroscience and Biobehavioral Reviews 37 (2013) 2141–2148

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review

Testing long-term memory in animal models of schizophrenia: Suggestions from CNTRICS

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ARTICLE INFO

Article history:
Received 29 November 2012
Received in revised form 30 April 2013
Accepted 10 June 2013

Keywords:
Episodic memory
Hippocampus
Mouse
Object recognition
Neuropsychiatric disease
Prefrontal cortex
Rat
Relational memory
Rodent
Paired-associate learning
Touchscreen

ABSTRACT

This paper reports the results of discussions at the fourth meeting of Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) meeting, held over two days in Washington, DC in April 2011. The meeting focused on animal paradigms for assessing the cognitive constructs relevant to schizophrenia identified in previous CNTRICS meetings. This report focuses on the outcome of discussions in the general area of long-term memory. A number of candidate animal paradigms were discussed. Two of these – one for rodents and one for non-human primates – were recommended as particularly promising for further development.

Contents

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http://dx.doi.org/10.1016/j.neubiorev.2013.06.005

1. Introduction

The aim of the CNTRICS (Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia) initiative is to develop tasks from cognitive neuroscience with a view to development of treatments for impaired cognition in schizophrenia. It is recognized that animal models must play an indispensable role in this enterprise (e.g. Nestler and Hyman, 2010). Thus, at the fourth meeting of CNTRICS, held over two days in Washington, DC in April 2011, discussion focused on animal paradigms for assessing the cognitive constructs targeted in previous CNTRICS meetings. The procedure was that first, prior to the meeting, the CNTRICS steering committee surveyed the field for nominated tasks. Then, at the in-person meeting, the meeting delegates discussed each task. Tasks that were not nominated were not discussed. This report summarizes the outcomes of discussions in the general area of long-term memory; these outcomes do not necessarily represent the opinions of the authors. Related constructs such as working memory will be summarized in separate articles. Nominated tasks for human research in the area of long-term memory are described in Ragland et al. (2009a,b).

2. Long-term memory

Fig. 1 shows the standard, text-book 'taxonomy of memory'. There is some debate regarding some of the elements within the taxonomy and how, or even whether, these divisions map neatly onto brain structures. Working memory is affected in schizophrenia, and is dealt with in a separate CNTRICS meeting report. Within long term memory, declarative memory, especially episodic memory, is thought to be most affected in schizophrenia. The cognitive and neural substrates of episodic memory deficits in individuals with schizophrenia have been reviewed in several previous papers stemming from prior CNTRICS meetings (Ranganath et al., 2008; Ragland et al., 2009a), and so will not be repeated here. Two structures implicated in episodic memory are the hippocampus and the prefrontal cortex (PFC). The contribution of these two structures to long-term memory impairments in schizophrenia can be discussed separately.

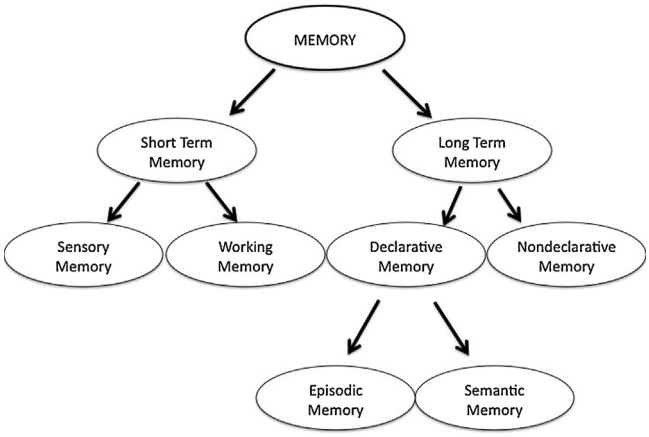

Fig. 1. The standard, text-book 'taxonomy of memory'. There is some debate regarding some elements in the taxonomy, and how or even whether these divisions map neatly onto brain structures. Working memory is also affected in schizophrenia, and is dealt with in a separate CNTRICS meeting report. Within long term memory, declarative memory, especially episodic memory, is thought to be most affected in schizophrenia. See text for discussion.

3. Structures implicated in long-term memory in schizophrenia

A common theme in theories regarding the role of the hippocampal formation in long-term memory is the idea that it is critical for the rapid binding of novel configurations of information (Squire, 1987; Eichenbaum and Cohen, 2004). Consistent with this view, individuals with schizophrenia may show evidence for a greater impairment in associative as compared to item memory (Achim and Lepage, 2003), though there are some psychometric and construct validation issues that may influence such findings. More recently, researchers have begun to use tasks for humans that are derived from the animal literature, such as the transitive interference or transitive patterning tests. This research has shown that individuals with schizophrenia are impaired in the ability to learn the relationships among hierarchically arranged stimulus pairs (Weiss et al., 2004). Very recent work has also shown that individuals with schizophrenia are impaired on eye-movement measures of relational memory (Hannula et al., 2010), which have also been shown to be impaired in individuals with hippocampal lesions (Hannula and Ranganath, 2009). There is also research suggesting greater deficits in recollection than familiarity measures of long-term memory in schizophrenia, which could also be interpreted as reflecting hippocampally mediated relational memory impairments (van Erp et al., 2008). Hippocampal dysfunction is observed during relational memory performance in schizophrenia (Hanlon et al., 2011). All of these types of deficits in long-term memory in schizophrenia have been taken as evidence potentially suggestive of deficits in medial temporal lobe function, with most of the emphasis on hippocampal dysfunction.

With respect to PFC, a number of lines of research suggest that PFC damage alters long-term memory by impairing strategic contributions to memory formation and retrieval (Janowsky et al., 1989a,b; Shimamura et al., 1990). For example, studies have shown activation of ventral PFC regions such as Brodmann's areas 45 and 47 when participants are asked to process verbal information using semantic elaboration strategies (Spaniol et al., 2009), or relational strategies (Blumenfeld et al., 2011). Despite such impairments, individuals with schizophrenia were able to benefit when provided with strategies that enhance long-term memory encoding (Barch, 2005; Bonner-Jackson et al., 2005). In addition, a recent meta-analysis of brain activity during long term memory performance in schizophrenia showed clear evidence for reduced activation in both ventral and dorsal regions of prefrontal cortex (Ragland et al., 2009b). There is also intriguing work showing impaired dorsal prefrontal activity during relational memory performance in schizophrenia (Ragland et al., 2012). Taken together, these findings suggest that both hippocampus- and PFC-mediated memory functions are impaired in schizophrenia, and thus it would be desirable if tasks used in schizophrenia research in animals were dependent on brain regions including, but not limited to, these structures.

4. Specific tasks discussed by CNTRICS

The long-term memory working group discussed paradigms nominated by CNTRICS participants. Several tasks became the focus of the discussion, at the end of which two were nominated as being particularly promising for further development. Here we will first describe some of the tasks that were extensively discussed but which were not, in the end, strongly recommended, before turning to the recommended tasks.

4.1. Spontaneous object recognition

Spontaneous object recognition (SOR), also called novel object recognition (NOR) – among other things – has been considered

by some to be a model of episodic memory, chiefly on the basis that it can be acquired within a single 'trial', meaning exposure to the to-be-remembered item. In the standard version of this task an object or pair of objects is presented during the first, 'sample' phase. The animal is allowed to explore the object(s) for a predetermined amount of time (either actual object exploration time or time spent in the apparatus). Following a variable delay the animal is then confronted with a copy of the sample object (the 'repeated' object), along with an object the animal has not previously encountered. Normally a rat or mouse will explore the novel object more than the repeated one, and failure to do so is usually interpreted as a failure of memory. (An alternative "decoupled" version has been developed which allows analysis of responses to the repeated and novel objects separately (2010).) Thus SOR has been proposed to map onto the MATRICS 'visual learning and memory' domain (Young et al., 2009). A plethora of schizophrenia-relevant studies have used SOR; for reviews of these studies see Lyon et al. (2012) and Dere et al. (2007). The advantages of SOR have been described elsewhere (Dere et al., 2007; Young et al., 2009; Lyon et al., 2012) and include parameter variation (i.e., delay) to load on the construct of interest; manipulations of other parameters such as similarity of objects (Norman and Eacott, 2004; Bartko et al., 2007a,b, 2010; Burke et al., 2011); it is non-aversive; no 'rule' needs to be acquired by the animal; enough data can be gathered from a single trial to allow the study of encoding, consolidation/storage and retrieval operations separately (Winters and Bussey, 2005; Winters et al., 2006; Nilsson et al., 2007); animals can be tested on multiple occasions using different sets of objects; and finally the task can work well with both rats and mice, humans (Manns et al., 2000) and non-human primates (Nemanic et al., 2004).

With all these advantages it is no wonder this task and its variants was discussed extensively at the CNTRICS meeting. However there have been criticisms of this task. For example, some researchers have raised caveats regarding predictive validity (e.g., Young et al., 2009) (although predictive validity is difficulty to assess in schizophrenia, for which there is no approved treatment for the cognitive symptoms). One particular suggestion has been that the task is subject to false positives, with some compounds (e.g., α7 nAChR agonists e.g., Freedman et al., 2008) producing positive results in rodent SOR but not in clinical trials. However it is a rather stringent criterion to base assessment of a task on the results of a clinical trial, particularly when such studies can be limited in terms of critical factors such as appropriate control conditions and sample sizes. Furthermore improvements in cognition have been reported in schizophrenia clinical trials using agents that also improve rodent performance in SOR (reviewed in Lyon et al., 2012), and it is not clear that other tasks definitively out-perform SOR in their ability to avoid false positives while maintaining a high 'hit' rate. Another problem with criticizing any task for failing to predict results in the clinic is the validity of the animal disease model that was used to assess the task. This is a particular problem in schizophrenia, in which the validity of a pharmacological (e.g., PCP) or genetic (e.g., DISC 1) model is itself a matter of debate.

Another common misgiving about this task that was discussed is that the method can yield high variability. It has certainly been our observation that inadequately trained experimenters can yield poor data with this task. To circumvent this problem the group recommended the automation of this task. Some advances have already been made in this area (e.g., Dere et al., 2007; Romberg et al., 2012).

A more serious concern regarding this task is that the construct SOR is thought to measure may not be the right one to target in schizophrenia research. It has been suggested that SOR in rodents preferentially taps familiarity-based, rather than recollection-based, recognition memory (Aggleton and Brown, 1999); this idea is consistent with common ideas regarding the role of hippocampus in episodic recollection, and the fact that SOR is sensitive to, e.g., perirhinal cortex lesions, but not, if at all, to hippocampal dysfunction (Winters et al., 2004). Recollection-based memory is more like the 'episodic memory' that researchers noted to be impaired in schizophrenia, and which SOR was assumed to model. Indeed, this assumption may have been naïve, heavily based as it on the "one-trial" nature of the task. First, it has been argued that one-trial acquisition may be necessary, but certainly not sufficient, to model episodic memory (Clayton et al., 2003), and second, the concept of 'one-trial learning' may not be useful in this regard: the 'one-trial' in this task is actually usually several minutes in the presence of the object(s), consisting of multiple bouts of stimulus-sampling. It has been argued that schizophrenia patients are not generally impaired on such familiarity-based single-item recognition; instead memory impairments are thought to emerge when the task encourages 'recollection' of the item along with contextual or 'relational' information (Achim and Lepage, 2003; Danion et al., 2007; van Erp et al., 2008; for a recent review see Libby et al., 2012). For these reasons, the discussion at the CNTRICS meeting turned to tasks that might better measure recollective, associative or relational memory. We consider some of these tasks now.

4.2. Tasks measuring associative or relational memory in rodents

There are a number of variations on the SOR procedure that may more closely model episodic memory in humans, a construct sometimes referred to as "episodic-like" memory in animals (Clayton and Dickinson, 1998; Griffiths et al., 1999; Clayton et al., 2001). For example, a slight variation in the SOR procedure permits testing of memory for temporal order: instead of testing object recognition by exposing rats to a pair of identical objects (A A) and then examining exploratory behavior during a test with a familiar object and a novel object (A B), rats may be given sequential exposures to multiple pairs of objects (A A/B B) and then tested with two familiar objects, one that was experienced more recently than the other (A B). This task is more reliably affected by hippocampal damage than the standard SOR task (Good et al., 2007; Hoge and Kesner, 2007; Hunsaker et al., 2008; Kesner and Hunsaker, 2010; Langston and Wood, 2010; Barker and Warburton, 2011). More complex variations on this procedure are possible that test memory for conjunctions of object, location, and context, or object, location, and time (Eacott and Norman, 2004; Eacott et al., 2005; Good et al., 2007; Easton et al., 2011; Devito and Eichenbaum, 2010). These tasks in particular ("what–where–which" or "what–where–when" memory) are thought to relate more closely to human episodic memory because they require temporal and spatial precision of object memories and cannot be solved based simply on familiarity with the stimuli. These tasks were not nominated for consideration at the CNTRICS meeting, and thus were not discussed extensively by the long-term memory group. Furthermore with respect to measurement and methodological issues, these tasks would be subject to many of the concerns brought up during the discussion of SOR. It was noted that these variants of SOR tend to show smaller absolute effect sizes in terms of discrimination index scores than the basic SOR task itself (e.g., Dix and Aggleton, 1999), which would exacerbate many of these concerns. Moreover, it is also not obvious that memory for temporal order is specifically impaired in schizophrenia (see next section).

Other innovative 'one-trial' tasks attempt to model more closely episodic recall by examining choice behavior in a situation where the to-be-remembered items are not present at the choice point: the cued recall task of Day et al. (2003) and the "E-maze" designed by Eacott et al. (2005). These tasks require the rat to make an explicit discriminative response that signals memory, either searching in a particular location for a previously encountered flavor (Day et al., 2003) or choosing which arm of a maze to explore that contains a

relatively novel object (Eacott et al., 2005). Both of these tasks are sensitive to hippocampal damage or inactivation. However, both tasks suffer from the fairly serious problem that normal control rat performance is about 60% correct at relatively short delays, and this level of performance does not improve with training in the case of the cued-recall task. It is not clear whether this reflects a feature of the task design or an innate limitation on the memory abilities of rats, but from a psychometric standpoint, this allows for a very limited parametric space in which to probe impairments.

4.3. Other tasks discussed

Trace conditioning – a classical conditioning paradigm in which a brief unfilled interval (the "trace interval") separates the conditioned and unconditioned stimuli – is impaired by hippocampal damage in animals (Solomon et al., 1986; Kim et al., 1995) and in humans with medial temporal lobe amnesia (McGlinchey-Berroth et al., 1997). Thus, trace conditioning of the eyeblink response may represent a simple paradigm for testing the integrity of the hippocampus that does not engage verbal or visual memory. One study has reported disrupted trace conditioning in schizophrenia (Marenco et al., 2003) although the interpretation of the data in this study were complicated by increased blink rates and post-CS responding in the subjects with schizophrenia. This task was not discussed or recommended for further consideration on the basis that even though this task engages the hippocampus, it involves retention of information only over a second or two, and thus does not measure long-term memory in the sense intended by CNTRICS. Classical conditioning paradigms in general will be considered by the Motivation and Reinforcement Learning Group.

A continuous active avoidance task (Pastalkova et al., 2006) was also nominated and discussed. Although this task possesses some interesting characteristics, it was considered that it did not have a close human analog and thus was not suitable for translation. It was also noted that this task and variants of it was proposed by one CNTRICS member as a candidate task for several other cognitive domains, suggesting that it might be difficult to ascribe impaired performance in the task to a specific cognitive domain such as long-term memory.

Transitive inference procedures have been implemented in studies with both animals and humans to specifically probe nonspatial aspects of relational memory. In these tasks a sequential/hierarchical sequence of discrimination problems is learned, such that the stimuli form an ordering relative to each other. For example, in the sequence of problems A+ B−/B+ C−/C+ D−/D+ E−/E+ F−, the relationships among the stimuli can be represented as A > B > C > D > E > F. This paradigm results in several behavioral phenomena. First, performance on "middle" pairs (for example B C and C D) may engage relational memory mechanisms, because knowing whether to select an individual stimulus depends on the identity of the other stimulus present on that trial. Second, critical test probes may be given between stimuli that are never encountered together. An A F probe (following the above example) tests behavior toward a novel discrimination that can be solved purely based on reinforcement history, because A is always rewarded and F is never rewarded. But a B E probe cannot be solved this way, because the stimuli in the middle of the sequence have roughly equivalent reinforcement histories, each having been reinforced approximately 50% of the time. Animals and humans older than age 6 years reliably choose B most of the time in these probe trials over D, presumably based on a representation of the relationships between these stimuli. Other explanations for this behavior exist, however (Bryson and Leong, 2007). Third, "symbolic distance" effects occur that mirror the separation between the stimuli in the hierarchy, such that reaction times to B E probes are longer than those to B D probes, presumably because the greater separation in the sequence requires more processing to make the comparison (e.g., Rapp et al., 1996). Critically, humans with schizophrenia are impaired in transitive inference learning (Titone et al., 2004; Weiss et al., 2004) and this task activates the hippocampus in humans (Heckers et al., 2004). However this task was also not recommended for further consideration because of concerns that only a very few probe trials could be given before new learning about the specific probes could support behavior, limiting opportunities for drug testing. Furthermore, some studies have reported that hippocampal damage impairs acquisition of the training pairs (e.g., Smith and Squire, 2005), complicating interpretation of the probe data.

Tests of memory for temporal order in sequential learning tasks (e.g., Chiba et al., 1994, 1997) were also proposed, although were not discussed extensively as it was brought up that patients with schizophrenia do not display impaired memory for temporal order. Recall of serial order of word lists presented was impaired only to the extent that word recall itself was disrupted, suggesting that the temporal order impairment was secondary to a recall impairment (Elvevåg et al., 2000). Serial probe recognition is unimpaired in patients with schizophrenia when performance is unpaced (Hill et al., 2011).

5. Recommended tasks

5.1. Touchscreen object-location paired-associate learning

Patients with established schizophrenia are impaired on object-location paired-associate learning, tested using, for example, the 'PAL' task in the 'CANTAB' battery (Wood et al., 2002; Chouinard et al., 2007; Donohoe et al., 2008; Aubin et al., 2009). PAL performance can be correlated with symptom severity (Prouteau et al., 2004, 2005; Barnett et al., 2005; Ritsner and Blumenkrantz, 2007; Aubin et al., 2009) and individuals with an increased risk of developing schizophrenia can be impaired even during the prodromal phase (cf. Wood et al., 2002; Barnett et al., 2005; Bartók et al., 2005). Performance on PAL is able to differentiate between schizophrenia and schizoaffective disorder (Stip et al., 2005). It may be that impairments in object-location learning is a special case of schizophrenic patients' difficulties in recalling contextual information, which may in turn be reflected in errors in source monitoring (Johnson et al., 1993; Brébion et al., 1997; Vinogradov et al., 1997; Keefe et al., 1999; Waters, 2004; Diaz-Asper et al., 2008).

The rodent touchscreen version of object-location learning developed by Talpos et al. (2009) for rats and later used with mice (Clelland et al., 2009; Bartko et al., 2011a,b) is carried out in a touchscreen testing chamber like the one illustrated in Fig. 2a. This apparatus allows the presentation of shape, photographic, etc. stimuli on a computer screen; the animal selects a stimulus via a nose-poke toward the screen which is detected via an infra-red touchscreen assembly. Reward (e.g., pellet or liquid) is delivered at the back of the box, opposite the screen. The PAL task requires animals to learn to associate three different visual objects (shapes) with three unique spatial locations on a computer screen (see Fig. 2a). On a given trial the animal is confronted with two objects, in two of the three locations. One of the objects is in its correct location; the other object is in one of its two incorrect locations; thus a Flower shape may be correct on the left, a Spider in the center, and a Plane on the right. The three stimuli mapping on to three locations thus results in 6 possible trial types: if the shapes are Flower = F, Spider = S, and Plane = P, and a blank space = B, the trial types are FPB, FBS, PSB, BSF, SBP, and BFP. Rats require a mean of approximately 20–30 90-trial sessions to reach a criterion of 80% correct (Oomen et al., unpublished findings). Although this is relatively slow rate of acquisition, high throughput can be achieved because the task is automated and many animals (e.g., 20–40) can be tested

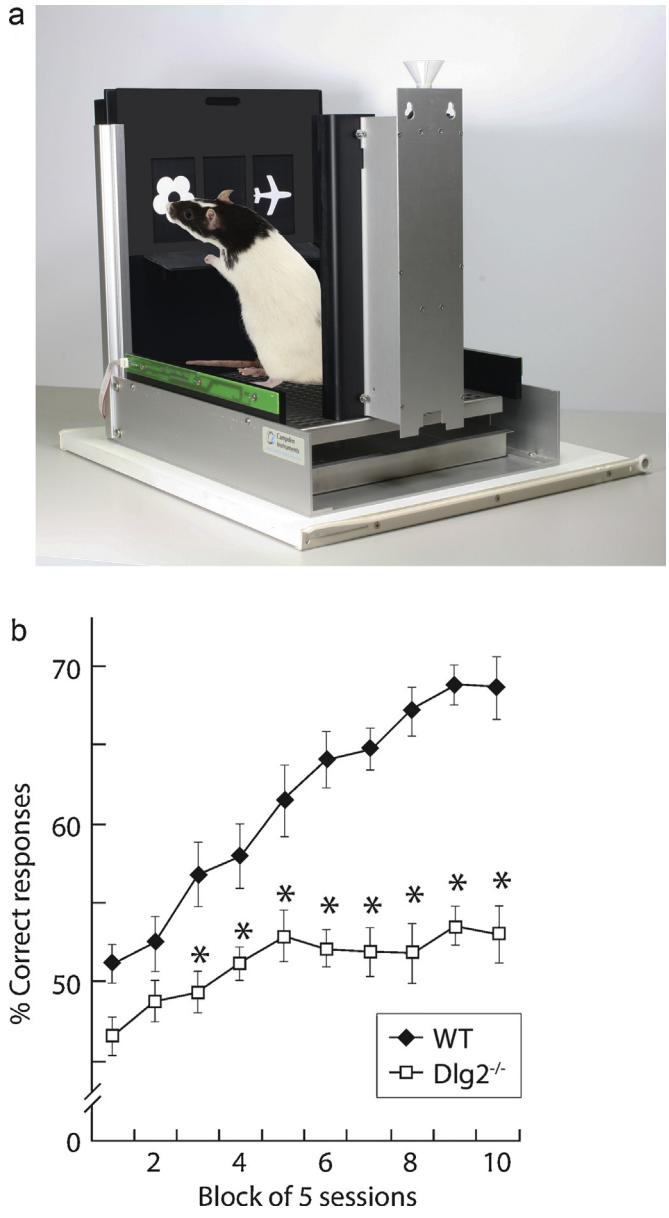

Fig. 2. (a) A rat performing the touchscreen object-location paired associates task. On each trial, the rat or mouse is presented with one of three shapes in that shape's correct location, and another shape which is in one of its two incorrect locations. Rats and mice learn over trials to map the three shapes on to their three locations. Photograph courtesy of Campden Instruments. (b) Example data from the touchscreen rodent object-location paired-associates learning task. Mice with deletion of the *dlg2* gene were severely impaired on acquisition of the task. Note that these mice were unimpaired on a 2-choice visual discrimination, suggesting that this impairment was not simply due to a difficulty discriminating objects. Data are from Nithianantharajah et al. (2013); reprinted with permission.

simultaneously. Because the task is acquired incrementally, it does not feature 'one-trial learning' and so cannot be considered a model of episodic memory. (However as discussed above, it is not clear that such a model exists for rodents, and certainly not one that has been validated and amenable to schizophrenia research). The utility of the task therefore lies more in the associative item-context/relational aspect which discussed above is a desired target construct for schizophrenia research. A certain amount of neurocognitive validation supports this idea: post-acquisition performance of this task is impaired by dorsal hippocampal dysfunction, for example via antagonism of intra-hippocampal NMDA or AMPA receptors (Talpos et al., 2009). Interestingly, a similar task with trial types FFB, FBF, SSB, BSS, BPP, and PBP, which we think is more likely to be solved by non-hippocampal conditional rules of the type "If Flower, go left" were not affected by these manipulations, providing a possible control task to test the selectivity of drug effects. Recent experiments in mice suggest that the task can be learned without the hippocampus (Horner et al., 2011), suggesting that the hippocampus is used to perform the task if the hippocampus is on-line during task acquisition. Acquisition of the task is sensitive to lesions of the medial prefrontal cortex (mPFC), with mPFC-lesioned rats attaining lower asymptotic performance levels than controls (McAllister et al., unpublished findings). Thus the findings from lesion studies so far, taken together, suggest that the hippocampus and prefrontal cortex may be operating in concert during the performance of this task. This finding is consistent with others showing that hippocampus and prefrontal cortex are thought to comprise a circuit underlying object-place memory (Barker and Warburton, 2011). Schizophrenia has been associated with deficient prefrontal–hippocampal interaction (Meyer-Lindenberg et al., 2005; Esslinger et al., 2009), and this may be why memory for object-location paired-associates learning (e.g., in CANTAB) is so sensitive to schizophrenia.

Pharmacological interventions can be done during acquisition – although this requires repeated daily dosing with different doses in different group of animals – or during post-acquisition performance, in which case a within-subjects design can be used. Systemic pharmacological manipulations in mice have revealed the dependence of touchscreen object-location memory on the cholinergic system and specifically muscarinic receptors, which have been linked with schizophrenia (Dean et al., 2003). For example the M1-preferring antagonists dicyclomine impairs post-acquisition performance of the task (Bartko et al., 2011b), although constitutive M1 receptor deletion does not impair acquisition (Bartko et al., 2011a), again suggesting a dissociation between mechanisms involved in acquisition versus post-acquisition performance (or retrieval). Scopolamine administration also impairs post-acquisition performance, whereas the anticholinesterase donepezil improves it (Bartko et al., 2011b), probably via extra-hippocampal mechanisms (Talpos et al., 2009). Another neurotransmitter frequently associated with schizophrenia is glutamate, with glutamatergic NMDA receptors having particular prominence in recent theories of schizophrenia pathology (e.g., Lisman et al., 2008). As mentioned above, intra-hippocampal injections of the NMDA antagonist MK-801 (or the AMPA antagonist CNQX) impairs post-acquisition performance of touchscreen object-location memory in the rat (Talpos et al., 2009). Recently mice with deletions of genes coding for NMDA receptor-associated proteins have been tested on the touchscreen battery (Nithianantharajah et al., 2013). It was found that mice carrying deletions of the schizophrenia-associated gene *Dlg2* (International Schizophrenia Consortium, 2008; Walsh et al., 2008) show severe impairments in acquiring this task (see Fig. 2b), and in CANTAB PAL (Nithianantharajah et al., 2013). These researchers are currently testing human participants and schizophrenic patients with deletions of the *Dlg2* on the identical version of the touchscreen object-location learning task used for mice and rats.

Thus, although further validation is necessary, the findings so far indicate that the touchscreen version of object-location learning has good potential for studies in schizophrenia. Another reason for recommending this particular version of the task is that object-location learning can be tested in the same apparatus, using the same types of stimuli, responses and reinforcers that are used in a number of other cognition tests in the rodent touchscreen apparatus, several of which have been recommended and/or discussed in other articles in the CNTRICS animal models series (e.g., Dudchenko et al., 2013; Markou et al., unpublished; Young et al., 2013), allowing a (flexible) 'battery approach' to the study of rodent models of schizophrenia.

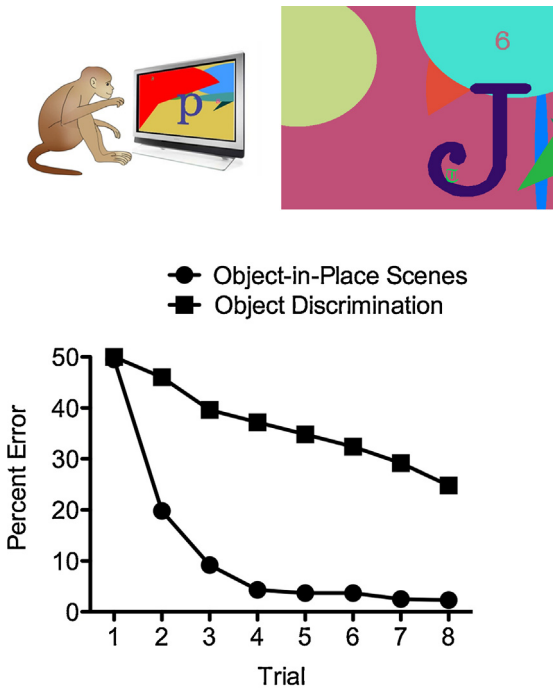

Fig. 3. Object-in-place scene learning in monkeys. Monkeys view the scene problems on a touch-sensitive screen. Each scene contains two small alphanumeric characters ("objects"), one of which is always rewarded and the other never rewarded, each unique to each scene. Monkeys can learn large numbers of these scene problems (20 or more) in a single test session, allowing learning curves to be drawn across trials, each consisting of a single presentation of each scene in the list. These curves ("object-in-place scenes") can be contrasted with learning visual discrimination problems between pairs of objects presented against a neutral background ("object discrimination"), which are learned much more slowly. The speed of learning conferred by placing the object discriminations in unique scene contexts likely engages mechanisms underlying episodic-like memory.

Illustrations from Croxson et al. (2012), original data from Browning et al. (2005) and Gaffan et al. (2001a,b).

5.2. Object-location learning in nonhuman primates

Monkeys rapidly learn discrimination problems in which objects are presented against unique background scenes (Gaffan, 1994). The rate of learning of object discrimination problems presented against unique background scenes is much faster than that of discrimination problems presented against neutral backgrounds (Fig. 3), indicating that animals use the contextual information provided by the scenes to solve the problems. Lesions of the fornix impair learning of discriminations presented within unique scenes, but do not affect the rate of learning of discriminations presented against randomly varying backgrounds. In the "object-in-place" version of this task, in which the locations of the objects within the scenes are also held constant between presentations, monkeys and humans with damage to the fornix show comparable impairments in learning (Aggleton et al., 2000; Gaffan, 2002). The speed of learning of the unique scenes, combined with the item-place associative aspect, suggests this task may be considered at least a partial model of human episodic memory. Furthermore, the similarity of lesion results between humans and monkeys suggest that it possesses significant translational value.

Substantial lesion data on this task exist in the monkey which implicate frontal–temporal interaction as essential to rapid scene learning (Browning et al., 2005). Subregions of prefrontal cortex may make somewhat distinct contributions to scene learning (Baxter et al., 2007, 2008) but the involvement of the prefrontal cortex in scene learning appears to be integrative (Wilson et al., 2010). The fornix and prefrontal cortex appear to make distinct contributions, because frontal–temporal disconnection does not occlude the effects of fornix damage on this task (Wilson et al., 2008). The mediodorsal thalamus is also essential for rapid scene learning (Gaffan and Parker, 2000; Mitchell et al., 2007). Neurotoxic lesions of the hippocampus impair performance on a closely related task where the targets are signaled by dots (to indicate the response location) rather than objects (Murray et al., 1998). Unfortunately, no data on this task are available from animal models of schizophrenia, or from humans with schizophrenia. Furthermore, no analog of this task appears to exist for rats, which so far have not been shown to be able to learn new scenes rapidly. This may reflect either limitations on the episodic memory ability of rats (see section 4.1) or an inability of previous attempts at scene learning to present stimuli to rats in such a way that rapid learning was facilitated (cf. Gaffan and Eacott, 1997; Gaffan et al., 2001a,b). The achievement of similar object-location learning in rodents and primates would be a welcome advance. In the meantime the wealth of neuropsychological data for the 'scenes' task and the ability to test humans and monkeys with identical stimulus materials makes it a promising addition to the arsenal for translational investigations of episodic memory in the context of schizophrenia research, and future efforts to more fully develop the task with the study in schizophrenia in mind were encouraged.

6. Summary

This report has summarized the outcome of the CNTRICS discussions in the general area of animal models of long-term memory. Discussion was limited to those tasks nominated by CNTRIC members. Therefore the tasks summarized here should not be taken as the only possibilities for research in schizophrenia; different researchers will have different constraints and requirements that may be better met by tasks other than those recommended here. Nevertheless, guided by principles such as relevance to schizophrenia, potential for translation and practical considerations such as amenability to drug testing, some of the tasks discussed did not find strong support among the discussants, whilst others were more enthusiastically recommended. However it should noticed that even for these tasks, for example rat and monkey object-location learning, discussants felt that further development and validation would be highly desirable.

Acknowledgements

Thanks to Lisa M. Saksida for comments on an earlier version of this manuscript. Thanks to Campden Instruments for Fig. 2a, Jess Nithianantharajah for Fig. 2b, and Philip Browning and Paula Croxson for Fig. 3. TJB receives support from the Innovative Medicine Initiative Joint Undertaking under grant agreement no. 115008 of which resources are composed of EFPIA in-kind contribution and financial contribution from the European Union's Seventh Framework Program (FP7/2007–2013). TJB consults for Campden Instruments.

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