CNTRICS Final Task Selection: Long-term Memory

Abstract Word Count: 163

Text Body Word Count: 8,910

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Abstract

Long-term memory (LTM) is a multi-factorial construct, composed of different stages of information processing, and different cognitive operations that are mediated by distinct neural systems, some of which may be more responsible for the marked memory problems that limit the daily function of individuals with schizophrenia. From the outset of the CNTRICS initiative, this multidimensionality was appreciated, and an effort was made to identify the specific memory constructs and task paradigms that hold the most promise for immediate translational development. During the second CNTRICS meeting, the LTM group identified *item encoding and retrieval* and *relational encoding and retrieval* as key constructs. This manuscript describes the process that the LTM group went through in the third and final CNTRICS meeting to select nominated tasks within the two LTM constructs and within a *reinforcement learning* construct that were judged most promising for immediate development. This discussion is followed by each nominating authors' description of their selected task paradigm, ending with some thoughts about future directions.

Key Words: episodic memory, schizophrenia, relational memory, item memory

Introduction

From the outset, the CNTRICS initiative appreciated that long-term memory (LTM) is a broad and multidimensional construct, encompassing multiple stages of information processing, and engaging distinct neural systems, some of which are likely to be more central to the memory problems that limit the daily function of individuals with schizophrenia. Accordingly, during the second of three CNTRICS meetings two LTM domains[1] were identified as the most promising constructs for immediate translational development: 1) *relational encoding and retrieval*, defined as, "the processes involved in memory for stimuli/elements and how they were associated with coincident context, stimuli or events.", 2) *item encoding and retrieval*, defined as, "the processes involved in memory for individual stimuli or elements irrespective of contemporaneously presented context or elements." The LTM group was also assigned the construct of *reinforcement learning*, defined as, "acquired behavior as a function of both positive and negative reinforcers including the ability to (a) associate previously neutral stimuli with value, as in Pavlovian conditioning; (b) rapidly modify behavior as a function of changing reinforcement contingencies and; (c) slowly integrate over multiple reinforcement experiences to determine probabilistically optimal behaviors in the long run." At the end of the second meeting, a call went out to the scientific community to engage in an on-line submission process to nominate tasks that assess these three constructs, to be considered for ongoing development.

As part of the nomination process, scientists were asked to provide evidence for each task's construct validity, link to neural circuits, clarity of cognitive mechanisms, availability of an animal model, link to neural systems through neuropsychopharmacology, amenability for use in neuroimaging, evidence of impairment in schizophrenia, and psychometric characteristics. In the third CNTRICS meeting the LTM working group was asked to select the two most promising

tasks within each construct based on these same criteria, with an understanding that although all tasks may not meet all requirements (e.g., animal model, psychometric characteristics), tasks without clear evidence of construct validity and link to a neural circuit should not be given further consideration. The purpose of this manuscript, is to report on the outcome of this deliberation process, and provide the reader with the nominating authors' description of the one item encoding and retrieval, two relational encoding and retrieval, and three reinforcement learning tasks that were judged to be ready for immediate translational development.

For the construct of relational encoding and retrieval two tasks – Associative Inference Paradigm (AIP) and Relational Encoding and Retrieval (REaR), were judged ready for further development and will be described below. The third nominated task was a Transitive Inference Paradigm (TIP). Working group members were impressed with TIP's link to neural circuits, availability of an animal model, link to neuropsychopharmacology, and evidence of impairment in schizophrenia. However, the greater complexity of the TIP versus AIP resulted in a somewhat lower score for construct validity, and led to a decision to select the AIP over the TIP for immediate development. Two tasks were considered for the item encoding and retrieval construct – Relational Encoding and Retrieval (REaR) and Inhibition of Current Irrelevant Memories Task. Of these, only the REaR (which assesses both item and relational memory) was chosen. The nominating author's acknowledgement that the Inhibition of Current Irrelevant Memories Task has "unknown" construct validity precluded it from further consideration. Within the reinforcement learning construct, the complementary nature of several of the nominated tasks lead the working group to recommend three tasks for further development – the Probabilistic Reward Task, the Probabilistic Selection Task, and the Probabilistic Reversal Learning task. The Weather Prediction Task was the fourth task nominated. Because the nominating author

described three different possible learning strategies, questions arose about the task's construct validity and it did not receive further consideration. Below are the nominating authors' descriptions of the selected tasks within each of the three LTM constructs.

Relational Encoding and Retrieval

Associative Inference Paradigm (AIP)

Description: Relational representations bind distinct elements of an event into a memory representation that captures the relationships between the elements.[2,3] Relational representations are thought to underlie mnemonic flexibility that allows for the generative use of stored knowledge about elements of experience to address new questions posed by the environment. The AIP provides a means to examine mnemonic flexibility and the nature of the relational representations that support the use of memory in novel situations.

In the AIP, participants receive explicit training on two sets of paired associates (e.g., AB and BC) and are then tested on whether they can infer from these associations the relationship between A and C. Specifically, participants learn an initial set of AB associations, where each A might consist of a unique face and each B a unique house (Figure 1a). Then, participants learn an overlapping set of associations consisting of the same B stimuli (e.g., the same houses) paired with a new set of C stimuli (e.g., another unique set of faces). Thus, during learning, each B stimulus (a house) is associated with two different stimuli, A and C (two unique faces), though the A and C stimuli are not directly experienced together.

During a subsequent memory test, participants make two-alternative forced-choice judgments that depend on memory for the learned associations (AB and BC) and the inferential relationship between A and C. For all test trials, the incorrect choice item (foil) is a stimulus that had been studied in another pairing, ensuring that the two choice stimuli are equally familiar.

This aspect of the design provides construct validity, because performance requires memory for the relations between stimuli rather the memory for individual items. That is, memory judgments for trained pairs (AB, BC) cannot be determined from stimulus familiarity and must be made based on learned associations. Similarly, for inferential pairs (AC) whose relationship was not studied, participants must retrieve the relation between the A and C stimuli that emerges from the overlapping associations with the same B stimulus.

Figure 1 About Here

Construct Validity: The logic of the AIP rests on the theoretical argument that relational representations separately code elements of an event, maintaining the compositionality of the elemental representations and organizing them in terms of their relations to one another.[2,3] The compositional nature of these relations allows for reactivation of representations from partial input (pattern completion),[4,5] a process thought to underlie event recollection. Further, maintenance of the compositionality of elements in relational representations allows flexible use of learned information at retrieval, making it possible to infer relations across stimuli without explicit training. This flexibility is important for associative inference decisions that putatively require inference to solve novel (untrained) stimulus configurations at test (AC retrieval decisions). However, relational representations may also contribute to inferential decisions through pattern completion at encoding.[5-7] When learning an overlapping set of pairs, AB and BC, pattern completion to AB during presentation of BC would enable an AC relation to be encoded. At test, inferential logic is not required to make an AC decision because a stored AC relation exists and can be directly retrieved.

Neural Systems: Neuroanatomical and computational models have proposed that the medial temporal region, and the hippocampus in particular, is essential for pattern completion processes that support performance in the AIP.[5,8,9] Recent neuroimaging work with humans has revealed activation in anterior hippocampal regions at retrieval during inferential judgments relative to explicitly learned associations (Figure 1b).[10]

Pharmacological and Behavioral Manipulation: Medial temporal lobe function has also been associated with performance on a related relational memory task in humans.[11-13] In this hierarchical (or transitive) inference paradigm (TIP), participants incidentally learn, via feedback, relationships between pairs of stimuli that are hierarchically organized (A > B, B > C, C > D, D > E). At test, participants make recognition judgments for trained relationships (e.g., B > C, C > D) as well as decisions about untrained, inferential relationships (e.g., B > D). Successful performance on BD trials has been argued as evidence for the formation of a relational hierarchy (A > B > C > D > E) that allows untrained judgments to be inferred from learned information. However, others have proposed that successful BD performance in this hierarchical inference task can be explained by reinforcement learning processes that do not depend on relational representations that rely on medial temporal lobe processing.[5,6] The benzodiazepine midazolam, which is thought to disrupt hippocampal function, actually enhances BD performance in this hierarchical inference paradigm, suggesting that learning in this task may rely on striatal mechanisms that support feedback-based habit learning.[14] Thus, important differences may exist between the AIP and TIP, with different neural systems being recruited depending on task demands.

Behavioral variation in performance has been observed in the AIP, with awareness of the overlapping relationships between stimuli during encoding perhaps being essential to inferential

performance at test. For example, participants who are explicitly informed about the overlapping relationships between stimuli prior to learning or who spontaneously acquire such awareness during learning perform more accurately on AC judgments than uninformed or unaware subjects.[15] Similar awareness-dependent performance differences are observed in the TIP. While above chance inferential performance can occur in unaware participants,[16,17] aware participants demonstrate greater accuracy on AC judgments than unaware participants.[16,18]

Animal Models: Complementary animal work has documented impaired associative inference judgments following hippocampal lesion. In rats, lesions of hippocampus proper impair AC judgments without disrupting the ability to encode or retrieve the explicitly trained associations (AB and BC).[19] Medial temporal lobe function has also been associated with task performance in the TIP in rats.[20]

Performance in Schizophrenia: How schizophrenia affects performance in the AIP is currently unknown. However, in the hierarchical transitive inference paradigm, schizophrenia impairs relational judgments (BD) with performance on nonrelational judgments (AE) remaining intact.[21] Functional neuroimaging has further demonstrated that impaired memory performance in schizophrenia during conscious recollection[22] and the hierarchical inference task[23] is associated with decreased activation in hippocampal regions.

Psychometric Data: These data are not yet available for the AIP.

Item Encoding and Retrieval and Relational Encoding and Retrieval

Relational Encoding and Retrieval Task (REaR)

Description: The REaR task combines two paradigms previously used to study item-specific and relational episodic memory in schizophrenia. The first is a levels-of-processing task designed to control for group differences in item-specific encoding strategies and, thereby,

generate equivalent recognition and source memory performance between schizophrenia patients and controls.[24,25] The second is a relational encoding task,[26] that produces a significant recognition deficit in patients with schizophrenia. During the encoding phase of REaR, participants are presented with two trial types in separate blocks. During 'item-specific' encoding blocks, participants are presented with a series of trials in which they are shown a single object and asked to rate whether it is pleasant or unpleasant. During 'relational' encoding blocks, participants are presented with a series of trials in which three objects are shown and they must judge whether the objects are in the correct order in terms of weight (from lightest to heaviest). In each study block, participants encode 12 objects, and a total of 3 blocks are completed for each encoding condition. The sequence of encoding blocks is counterbalanced to minimize order effects. During the retrieval phase of the task, participants first complete a yes/no item recognition test consisting of a random sequence of 72 previously studied objects (36 from item-specific and 36 from relational) and 72 previously unseen foil objects. Next, participants are given an associative recognition test consisting of objects that were previously studied on relational trials. The test includes 18 "intact" pairs consisting of objects that were originally studied on the same trial and 18 "recombined" pairs consisting of objects that were originally studied on different trials. Subjects are asked to indicate if the pairs are intact or rearranged.

Construct Validity: Behavioral research has distinguished between item-specific and relational encoding strategies.[26-28] Common item-specific encoding strategies involve making a semantic decision about an item (e.g., "pleasant"/"unpleasant", "abstract"/"concrete"), whereas relational encoding strategies include imagining two or more items interacting, or linking two or more words in the context of a sentence or story. It is thought that relational encoding promotes memory for associations amongst items, whereas item-specific encoding enhances the

distinctiveness of specific item.[27-30] In the episodic memory literature, relational encoding has been linked to the function of the hippocampus, which is thought to support the binding of novel representations.[31-33] The distinction between relational versus item-specific encoding has also been supported by neuroimaging studies of working memory (WM) that have revealed dissociations between brain regions involved in item-specific WM maintenance and regions involved in manipulation of relationships between items while they are being maintained. Research has shown that DLPFC is selectively activated on trials in which relationships among items are processed.[34] Moreover, engagement of the DLPFC during relational WM processing predicts successful long-term memory (LTM) retrieval.[26,35,36] Several studies have shown that, although both relational and item-specific encoding tasks are effective, they tend to have different effects on memory performance.[27-30] For example, relational encoding is optimal when memory for associations between items will be tested (e.g., paired associate learning), whereas item-specific encoding is optimal when memory for item-details is tested.[37] The available evidence therefore indicates that the construct of relational encoding and retrieval has validity at both the cognitive and neural level of analysis, and that it is supported by both hippocampal and DLPFC mediated mechanisms.

In prior work,[26] it has been shown that the associative portion of the REaR task promotes LTM by building associations between triplets of words, whereas this evidence was not seen for a control task that involved passive rehearsal of words. Preliminary results (see below) suggest that performance is impaired in patients relative to controls. In contrast, item-specific semantic encoding has been shown to improve memory by facilitating encoding of distinctive item-specific information, as it does not encourage building of relationships amongst items.[28] As

described below, item-specific semantic encoding tasks promote robust levels of memory performance in patients with schizophrenia.[24,38,39]

Neural Systems: Several recent studies have demonstrated that DLPFC activation during relational encoding reliably predicts successful LTM.[26] However, DLPFC activity is generally not correlated with successful item-specific encoding (see[35] for review). For example, in a recent study from Dr. Ranganath's lab[26] using a variant of the relational encoding task used in the REaR paradigm, participants were scanned while performing the two WM tasks (Figure 2a). On 'rehearse' trials, subjects were required to rehearse a set of 3 words across a 12 second delay period, whereas on 'reorder' trials, participants were required to rearrange a set of three words based on the weight of the object that each word referred to over the delay. Although both conditions required maintenance across the delay, reorder trials also required participants to evaluate relationships between items in the memory set along a single dimension (weight). Analyses of subsequent LTM performance showed significantly more reorder trials in which all three items were recollected than would be expected based on overall item hit-rates alone (Figure 2b), but the same was not true for rehearse trials. This result suggests that, on reorder trials, participants successfully encoded relationships between the items in each memory set. Consistent with the idea that the DLPFC is involved in relational processing in WM, DLPFC activation was increased during reorder trials compared to rehearse trials (Figure 2c). Furthermore, DLPFC activation during reorder, but not rehearse trials, was positively correlated with subsequent LTM performance. No such relationship was evident during rehearse trials. In contrast, activation in the left VLPFC (BA 44/6) and in the hippocampus was correlated with subsequent memory performance on both rehearse and reorder trials. Results from this study and others[36] suggest that

the DLPFC may be specifically recruited during relational encoding, adding support to the validity of this neural construct.

Figure 2 About Here

Pharmacological and Behavioral Manipulation: Data on pharmacological manipulation effects on the REaR are not yet available. As noted above, when patients are provided with an item-specific encoding strategy there are no longer group differences in item recognition and source retrieval performance,[25,25] or in fMRI activation in the VLPFC.[38,39]

Animal Models: The kinds of relational encoding processes that are manipulated in the REaR paradigm have not been extensively investigated in animal models, in part because it is difficult to directly manipulate encoding strategies in non-human animals. Some relevant evidence, however, comes from studies of working memory tasks in monkeys. For example, a single-unit recording study[40] showed that neurons in the monkey dorsal prefrontal cortex encoded information about temporal order relationships between a series of items presented in a working memory task. In contrast, ventral prefrontal neurons tended to encode the physical features of objects to be maintained. Another study demonstrated that lesions to mid-dorsolateral prefrontal cortex impaired memory for sequences of actions.[41]

Performance in Schizophrenia: Research by Dr. Ragland and others has revealed consistent evidence of episodic memory deficits in schizophrenia linked to impaired organizational processes. During initial experiments, subjects were studied with explicit word list encoding tasks where no strategy was provided.[42,43] During debriefing, controls were more likely

to engage in item-specific semantic processing, and we suspected that patients were employing a less effective strategy. A levels-of-processing (LOP) paradigm[44] tested whether providing a semantic, item-specific encoding strategy could improve patients' performance and prefrontal function. As predicted, patients showed the same benefit as healthy controls from item-specific semantic processing on both recognition[38,39] and source memory tasks,[25] and showed robust activation in the ventrolateral portions of the prefrontal cortex.[38] These results suggest that item-specific encoding processes may be relatively spared compared to relational encoding, and motivate inclusion of a semantic item-specific encoding condition in the REaR paradigm to address issues of generalized deficit.

In contrast, pilot data from Dr. Ragland and Dr. Ranganath using the relational encoding condition from the REaR task, suggests that when individuals with schizophrenia are provided with a relational encoding strategy, they may perform more poorly than controls (Figure 3). Specifically, preliminary data from a sample of 12 individuals with schizophrenia (4 females) and 12 demographically-matched healthy volunteers showed that recognition accuracy was significantly lower in patients (red triangles) versus healthy controls (blue circles) for relational encoding [$t(23)=-1.73$; $p<.05$], but not for item-specific encoding [$t(23)=-1.24$; $p=.12$].

Figure 3 About Here

Psychometric Data: These data are not yet available for the REaR.

Reinforcement Learning

Probabilistic Reward Task

Description: This task is based on a differential reinforcement schedule that provides an objective assessment of participants' propensity to modulate behavior as a function of reward history.[45] The task, which was modified from an earlier paradigm described by Tripp and Alsop,[46] is rooted within the behavioral model of signal-detection[47] and the generalized matching law.[48,49]

Figure 4 About Here

Figure 3 provides a summary of the probabilistic reward task (adapted from[45]). The task includes 300 trials, divided into 3 blocks of 100 trials, which are separated by a 30-sec break. A trial starts with the presentation of an asterisk for 1400 msec, immediately followed by a schematic mouthless cartoon face presented for 500 msec. Next, either a short (11.5 mm) or long (13 mm) mouth is briefly presented on the screen for 100 msec. The mouthless face remains visible until the participant makes a response. For each trial, participants are asked to determine which mouth stimulus was presented by pressing either the "z" key or the "/" key on a PC keyboard (counterbalanced across subjects). For each block, the two mouth stimuli are presented equally often using a pseudo-randomized sequence allowing up to three consecutive presentations of the same stimulus. Within each block, only 40 correct trials are followed by reward feedback (e.g., "Correct!! You won 5 cents"), presented for 1500 msec immediately after a correct response. If a reward feedback is presented, an additional blank screen is presented for 250 msec. For non-rewarded trials, a blank screen is presented for 1750 msec.

Critically, an asymmetric reinforcer schedule is used to induce a response bias.[50] Thus, correct identification of one mouth ("rich stimulus") is rewarded three times more frequently

than correct identification of the other mouth ("lean stimulus"). Only 40 correct trials are rewarded in each block (30 rich, 10 lean) to ensure that each participant is exposed to the same (or a very similar) number of rewards. To achieve this goal, a controlled reinforcer procedure is used: if a participant makes an incorrect response on a trial scheduled to be rewarded, the feedback is delayed until the next correct response of the same stimulus.

Before the task, participants are instructed that the goal of the task is to win as much money as possible, and that not all correct responses will receive a reward feedback. Importantly, participants are not informed that one of the stimuli will be rewarded more frequently. Note that due to the probabilistic nature of the task, participants cannot infer which stimulus is more advantageous based on the outcome of a single trial; instead, in order to optimize their choices, participants need to "integrate" reinforcement history over time. Depending on the monetary reward used for each trial, participants earn approximately $6 (5 cent/trial)[45] or approximately $24 (20 cent/trial).[51]

The main variable of interest is response bias, which can be computed[46,47] as:

$$\log b = \frac{1}{2}\log\left(\frac{Rich_{correct} * Lean_{incorrect}}{Rich_{incorrect} * Lean_{correct}}\right)$$

As evident from the formula, a high response bias emerges when participants tend to correctly identify the stimulus associated with more frequent rewards (rich hits) and to misclassify the lean stimulus (lean misses). To examine general task performance, secondary analyses consider hit rates [(number of hits)/(number of hits + number of misses)], reaction time, and discriminability. Discriminability, which assesses the subjects' ability to perceptually distinguish between the stimuli and can thus be used as an indication of task difficulty), is computed as:

$$\log d = \frac{1}{2}\log\left(\frac{Rich_{correct} * Lean_{correct}}{Rich_{incorrect} * Lean_{incorrect}}\right)$$

In addition to these variables, the probability of specific responses as a function of the immediately preceding trial can be computed to evaluate the strength of a response bias as a function of (a) which stimulus had been rewarded in the preceding trial; and (b) proximity of reward delivery. For example, the probability of selecting "rich" or "lean" in trials immediately following a correctly identified, rewarded rich trial vs. a correctly identified, non-rewarded rich trial may be computed.[52] Finally, in several studies we have found that reward learning, which can be measured by subtracting response bias in block 1 from response bias in block 3, showed strong construct and predictive validity.[45,52]

Construct Validity: Initial construct validity comes from studies evaluating samples hypothesized to be characterized by dysfunctional reinforcement learning.[53,54] Subjects with elevated depressive symptoms,[45] unmedicated patients with major depressive disorder (MDD),[55] and medicated euthymic patients with bipolar disorders[52] showed reduced response bias toward the more frequently rewarded stimulus (Figure 5a). Moreover, trial-by-trial probability analyses revealed that MDD subjects were impaired at expressing a response bias toward the more frequently rewarded cue in the absence of immediate reward (manifested as increased miss rates), whereas they were responsive to delivery of single rewards. Increased miss rates for the more frequently rewarded stimulus correlated with anhedonic symptoms ($r = 0.52$, $p < 0.05$), even after considering anxiety symptoms and general distress.[55] In prior studies, reward learning (response bias in block 3 minus response bias in block 1) negatively correlated with self-reported anhedonic and/or melancholic symptoms in non-clinical samples ($r = -0.28$, $p < 0.05$;[45] $r = -0.33$, $p < 0.05$)[56] and euthymic bipolar patients ($r = 0.51$, $p < 0.030$),[52] and predicted these symptoms

one month later ($r = -0.41$, $p < 0.05$).[45] Additional analyses indicated that reward learning predicted anhedonic symptoms more than one month later (on average, 38.28 days later) after controlling for initial anhedonic symptoms and general negative affectivity.[45]

Figure 5 About Here

Neural Systems: In a recent study, event-related potentials (ERPs) were recorded in 30 healthy controls performing the probabilistic reward task.[57] Feedback-related negativity (FRN) was measured in response to reward feedback, and compared between subjects who developed a response bias toward the more frequently rewarded stimulus ("learners") versus subjects who did not ("non-learners"). Relative to non-learners, learners were characterized by smaller (i.e., more positive) FRNs (Figure 6a). In light of recent findings indicating that the FRN is smaller (i.e., more positive) when participants learn a stimulus-response association[58] or can predict outcomes, including positive ones,[59] larger FRN in the non-learners was interpreted as an electrophysiological marker of blunted reinforcement learning. Consistent with this interpretation, compared to learners, non-learners showed significantly lower activation in response to reward feedback in dorsal anterior cingulate cortex (dACC) regions that have been previously implicated in integrating reinforcement history over time (Figure 6b).[60,61] Moreover, the ability to develop a response bias toward the more frequently rewarded stimulus correlated with dACC activation ($r = 0.40$, $p < 0.030$). A final feature of this study was that some of the participants performed a monetary incentive delay (MID) task[62,63] during functional magnetic resonance imaging. Relative to non-learners, learners showed larger basal ganglia responses to reward feedback (monetary gains) in the MID task (Figure 6c). These findings suggest that

participants developing a response bias toward the more frequently rewarded stimulus had stronger dACC and basal ganglia responses to reward outcomes.

Figure 6 About Here

Pharmacological and Behavioral Manipulation: Two studies have shown that response bias in the Probabilistic Reward task is modulated by pharmacological manipulations affecting dopamine (DA) either directly[51] or indirectly.[64] In the first study, a single 0.5 mg dose of the D2/3 agonist pramipexole or placebo was administered to healthy volunteers 2 hours before performing the task.[51] Consistent with predictions based on animal evidence,[65-67] pramipexole impaired reinforcement learning (see[68] for a prior human study postulating similar effects). Compared to placebo, subjects receiving pramipexole showed lower response bias toward the more frequently rewarded stimulus (Figure 5b).[51] Control analyses confirmed that reduced response bias was not due to transient adverse effects.

These behavioral findings were extended by analyses of event-related potentials (ERPs) collected while participants performed the probabilistic reward task by the application of computational modeling to test whether presynaptic inhibitory mechanisms might explain the reduced response bias in the pramipexole group. Two sets of findings emerged. First, blunted reward learning in participants receiving pramipexole could be simulated by reduced presynaptic DA signaling in response to reward in a neural network model of striatal-cortical function.[69,70] Second, compared to the placebo group, participants receiving pramipexole were characterized by larger (i.e., more negative) FRN to probabilistic rewards, indicating reduced reinforcement learning.[58,59,70] Replicating and extending findings from an independent study,[57] source

localization at the time of maximal FRN indicated that, relative to the placebo group, the pramipexole group was characterized by significantly lower activation in dACC regions previously implicated in integrating reinforcement history over time.[70] Collectively, these findings are in line with prior evidence that phasic DA signaling plays an important role in reinforcing actions leading to reward,[71-73] and indicate that performance in the probabilistic reward task is sensitive to DA challenges.

The aim of a second pharmacological study was to test the hypothesis that nicotine might increase responsiveness to reward-related cues,[64] based on prior findings that nicotine increases appetitive responding through activation of presynaptic nicotinic receptors on mesocorticolimbic DA neurons in animals,[74,75] and increases the incentive value of monetary reward in humans.[76] Using a randomized, double-blind, placebo-controlled crossover design, Barr and coworkers administered a single dose of transdermal nicotine (7-14 mg) to 30 psychiatrically healthy adult non-smokers. Nicotine increased response bias toward the more frequently rewarded stimulus, and this effect persisted over time, as demonstrated by a greater response bias during the placebo session in participants who received nicotine in the first compared to the second session (one week later).

Two additional studies investigated the effects of stress on reward responsiveness,[77,78] and were motivated by a large body of animal work and limited human findings indicating that stress might exert depressogenic effects by reducing hedonic capacity.[79,80] In a first study, the hypothesis that non-clinical participants reporting elevated levels of stress – assessed by the Perceived Stress Scale (PSS)[81] – would show reduced response bias toward the more frequently rewarded stimulus was tested. Consistent with this hypothesis, in two independent samples (n = 88 and n = 80), individuals reporting elevated stress had reduced reward responsiveness and

elevated anhedonic symptoms. Moreover, PSS scores predicted reduced reward responsiveness above and beyond symptoms of general distress and anxiety.[78] These correlational findings were extended by a second study that tested the effects of an acute laboratory stressor on reward responsiveness in healthy participants.[77] Eighty female participants performed the probabilistic reward task under both a stress condition (threat-of-shock, n = 38 or negative performance feedback, n = 42), and a no-stress condition. The acute stress manipulation (particularly threat of shock) reduced reward responsiveness (Figure 5c). Notably, the deleterious effects of stress on reward responsiveness were largest in individuals reporting elevated anhedonic symptoms in their daily life.[56] Preliminary analyses of an independent sample replicated these findings, and indicated that stress-induced decreases in reward responsiveness might be largest in psychiatrically healthy subjects who might be at increased genetic risk for depression,[82] suggesting that stress-induced hedonic deficits might be a promising link between stressful experiences and depression.

Animal Models: In collaboration with Athina Markou at UCSD, Dr. Pizzagalli is developing a task analogous to the human Probabilistic Reward task for use in rodent studies.

Performance in Schizophrenia: In a recent study, Heerey and coworkers used the Probabilistic Reward task in a sample of 40 clinically stable and medicated outpatients with schizophrenia.[83] The authors found that, compared to healthy controls, patients with schizophrenia had a reduced ability to discriminate between the stimuli but similar response bias. The authors concluded that schizophrenia is characterized by intact sensitivity to reward and ability to modify responses based on reinforcements. Although intriguing, the interpretation of these findings is somewhat difficult because all patients were medicated at the time of testing. Moreover, no information was provided about the smoking status of participants, in particular

whether patients and controls were matched for this variable. In light of the recent finding that nicotine enhances response bias in the probabilistic reward task,[64] and given high rates of smoking in schizophrenia,[84,85] it is unclear whether the null findings reported in[83] might be partially due to group differences in smoking status and/or history. At present, there are at least four groups currently using or planning to study this task in individuals with schizophrenia.

Psychometric Data: The test-retest reliability of the Probabilistic Reward task over approximately 38 days was $r = 0.57$, $p < .004$. Satisfactory test-retest reliability of reward learning ($r = 0.56$ over an averaged period of 39 days period) also emerged in an independent sample.[57] In a recent study evaluating monozygotic ($n = 20$) and dizygotic ($n = 15$) twin pairs, the heritability of reward responsiveness was estimated to be 48%.[77] Due to the limited sample size of this twin study, these heritability estimates should be considered preliminary.

Probabilistic Selection Task

Description: The Probabilistic Selection Task[86,87] measures participants' ability to learn from positive and negative feedback, by integrating reinforcement probabilities over many trials. Three different stimulus pairs (AB, CD, EF) are presented in random order and participants have to learn to choose one of the two stimuli. Feedback follows the choice to indicate whether it was correct or incorrect, but this feedback is probabilistic: In AB trials, a choice of stimulus A leads to positive feedback in 80% of trials, whereas a B choice leads to negative feedback in these trials. CD and EF pairs are less reliable: stimulus C is correct in 70% of trials, while E is correct in 60% of trials. Over the course of training, participants learn to choose stimuli A, C and E more often than B, D, or F. Note that learning to choose A over B could be accomplished either by learning that choosing A leads to positive feedback, or that choosing B leads to negative feedback (or both). To evaluate whether participants learn more about positive or negative

outcomes of their decisions, performance is subsequently probed in a test/transfer phase in which all novel combinations of stimuli are presented and no feedback is provided. Positive feedback learning is assessed by reliable choice of the most positive stimulus A in this test phase, when presented with other stimuli (AC, AD, AE, AF). Negative feedback learning is assessed by reliable avoidance of the most negative stimulus B when presented with the same stimuli (BC, BD, BE, BF). The extent to which participants perform better in choose-A or avoid-B pairs has been associated with a "Go" or "NoGo" learning bias, and is very sensitive to dopaminergic state, manipulation, and genetics.[68,88-91]

In addition to the probabilistic reinforcement learning biases, the task can also probe other aspects of reinforcement-based decision making. For example, the tendency to rapidly learn from a single instance of reinforcement in the initial trials of the task is thought to rely on distinct process from that involved in integrating feedback probabilities over trials.[89] Similarly, when faced with novel test pairs, participants adaptively modulate their response times in proportion to the degree of reinforcement conflict. High conflict choices involving stimuli with similar reinforcement probabilities are associated with longer response times than those associated with divergent reinforcement probabilities, a process thought to depend on interactions between dorsomedial frontal cortex and the subthalamic nucleus.[90]

Construct Validity: Performance on the Probabilistic Selection Task is defined by the ability to choose the probabilistically most optimal stimulus. Of course many factors can contribute to better or worse performance aside from reinforcement learning, including attention, motivation, fatigue, working memory, etc. However, the main measure of interest in the task is within-subject (i.e., the ability to choose the most positive stimulus is contrasted with that of avoiding the most negative stimulus), thereby controlling for overall performance levels and

specifically assessing the contribution of reinforcement. This relative positive to negative feedback learning measure is reliably altered by dopaminergic manipulation in a range of populations, and moreover, similar effects in positive vs negative learning have been observed in other tasks meant to measure similar constructs but using different stimuli, motor responses, and task rules (i.e., probabilistic Go/NoGo learning task,[68] and probabilistic reversal learning task[92]).

Neural Systems: Within the task paradigm, positive and negative feedback learning in this task are thought to rely on striatal D1 and D2 receptors, respectively. As described above, probabilistic positive and negative feedback learning are sensitive to dopaminergic manipulation. Increases in dopaminergic stimulation, likely in the striatum, lead to better positive learning but cause impairments in negative feedback learning.[68,89,90] Conversely, dopamine depletion is associated with relatively better negative feedback learning, but worse positive feedback learning. At the individual difference level, genes that control D1 and D2 dopamine function in the striatum are predictive of probabilistic positive and negative learning, whereas genes that control dopamine function in prefrontal cortex are predictive of rapid trial-to-trial learning from negative feedback.[88] Negative feedback learning is also associated with enhanced error-related negativity (brain potentials originating from anterior-cingulate cortex[69,93]) and activation of this same region in functional neuroimaging.[91] Lesions to medial prefrontal cortex are associated with both deficits in the acquisition of reinforcement contingencies (patients took longer to learn) and impaired negative feedback learning in the test phase.[94] Finally, the subthalamic nucleus (a component within the basal ganglia network) is believed to delay responses during high conflict decisions. Supporting this claim, deep brain stimulation of the subthalamic nucleus causes premature responding in these high conflict choices.[89]

Pharmacological and Behavioral Manipulation: As previously noted, the Probabilistic Selection task is sensitive to pharmacological manipulation. Dopamine agonists, including levodopa and D2 agonists, impair negative feedback learning in Parkinson's patients while sometimes improving positive feedback learning.[90] In ADHD, stimulant medications (methylphenidate and amphetamine), which elevate striatal dopamine, improved positive but not negative feedback learning.[93] In healthy participants, low doses of D2 agonists and antagonists, which may act presynaptically to modulate dopamine release, predictably alter positive and negative feedback learning.[68]

Animal Models: There is currently no available animal model of the Probabilistic Selection task. However, preliminary unpublished results from Claudio DaCunha's lab in Brazil suggest that rats can learn a reduced form of the task using odor discrimination and two pairs of stimuli. In a related project, Rui Costa and colleagues have developed a forced-choice task requiring mice to learn to choose and avoid behaviors associated with positive and negative tastants.[95] Mice with elevated striatal dopamine levels showed enhanced bias to approach rewarding tastants together with a reduced bias to avoid aversive tastants, similar to the data reported in humans. In monkeys, striatal D1 receptor blockade abolishes the normal response speeding observed when a large reward is available (a measure of Go learning), whereas D2 receptor blockade leads to greater response slowing when smaller than average rewards are available (a measure of NoGo learning).[96]

Performance in Schizophrenia: In a preliminary study, patients with schizophrenia showed large deficits in learning the standard version of the Probabilistic Selection task, which uses Japanese Hiragana characters as stimuli.[97] Subsequent testing using verbalizable stimuli (pictures of every day objects such as bicycles) showed that patients can learn the task, but show

selective deficits in early acquisition (thought to rely on prefrontal structures), which correlated with their negative symptoms.[97] In the test phase, patients showed intact "NoGo" learning, but selectively impaired "Go" learning. Further, all the genetic polymorphisms predictive of learning in this task are candidate genes for schizophrenia.

Psychometric Data: Practice effects for the Probabilistic Selection task have been assessed in Frank and O'Reilly.[68] Different stimuli are used across sessions. On average participants are faster to learn the task after multiple sessions, but this practice does not affect relative positive versus negative feedback learning.

Probabilistic Reversal Learning Task

Description: This task was developed by Trevor Robbins and Robert Rogers and first published in Lawrence et al.[98] and Swainson et al.[99] The task is administered using a touch-sensitive screen for recording responses, but a button box can also be used. On each trial, subjects are presented two visual patterns (rectangles of colored stripes; Figure 7). These patterns appear in two randomly chosen boxes out of four possible boxes. The task consists of two stages, starting with a simple probabilistic visual discrimination, in which subjects have to make a two-alternative forced choice between two colors. The 'correct' stimulus (which is always the first stimulus touched) receives an 80:20 ratio of positive:negative feedback and the opposite ratio of reinforcement is given for the 'incorrect' stimulus. After completing 40 trials of this initial discrimination, the task proceeds to the second, reversal stage in which contingencies are reversed, without warning, so that the previously 'incorrect' color is now correct and vice versa for the previously 'correct' color. The instructions for the task are: "On each go, the same two patterns will be presented. One of the patterns is correct and the other pattern is wrong and you have to choose the correct pattern on each go. However on some goes, the computer will tell you

that you were wrong even if you chose the correct pattern. Your task is to stick to the pattern that is usually correct. So in other words, always choose the pattern that is correct more often than the other pattern. At some point during the task, the rule may change so that the other pattern is now usually correct. You then have to follow this new rule and choose the new pattern. It is important that you only start choosing the other pattern when you are sure that the rule has changed."

Figure 7 About Here

Although all subjects receive a total of 80 trials, a learning criterion of eight consecutive correct trials is generally imposed for the purposes of analysis. Main performance measures are failure or success at each stage, mean errors to criterion and mean latencies. Failure/success rates are analyzed using the likelihood-ratio method for contingency tables.[100] Subjects failing stage 1 are excluded from subsequent analyses of error rates and latencies at stage 2. They are included when error rates and latencies at stage 1 are analyzed (to obtain a measure of acquisition). Square-root transformed errors to criterion [(x + 0.5)1/2] (or total errors if criterion is not reached) and response latencies (log-transformed if necessary) are analyzed using one-way ANOVAs. If the assumption of homogenous variances is violated, then the error measures are analyzed using the nonparametric Kruskal-Wallis and/or Mann–Whitney tests.

Measures of perseveration and maintenance can also be obtained. Consecutive-perseverative responses refer to consecutive responses made, directly following reversal of the reinforcement contingencies, to the color that was correct during stage 1 but is now incorrect in stage 2. STAGE I-perseverative errors (in the terminology of Jones and Mishkin[101]) refer to

errors in blocks of eight trials (of the reversal stage), in which performance within these blocks falls significantly below chance (<=1 correct response). Both of these perseveration scores tend to correlate significantly with total errors made in stage 2 of the task. Therefore, each should be converted to a score indicating the proportion of total errors in stage 2. Maintenance errors refer to the errors made subsequent to criterion being reached (i.e. the number of responses to incorrect stimulus/total trials remaining), subject to there being at least 10 trials after criterion is reached.

Construct Validity: The Probabilistic Reversal Learning task gauges adaptive behavior, which requires anticipation of biologically relevant events, i.e. rewards and punishments, by learning signals of their occurrence. The ability to predict events interacts with the ability to strengthen and weaken actions when these actions are closely followed by rewards and punishments. These processes are often collectively referred to as reinforcement learning. Models of reinforcement learning use a temporal difference prediction error signal, representing the difference between expected and obtained events, to update their predictions based on states of the environment.[102] Probabilistic learning tasks are commonly used to assess reinforcement learning and neural activity associated with prediction errors.[103-105] For example, O'Doherty et al.[104,105] used probabilistic learning tasks to establish that activity in the (ventral) striatum and orbitofrontal cortex was positively correlated with the prediction error signal.

Furthermore, a recent EEG) study with healthy volunteers revealed that the FRN observed during punishment over the medial frontal cortex correlated significantly and positively with the reward prediction error signal during our serial probabilistic reversal learning task,[106] and was greatest during the probabilistic errors and was absent during the final reversal error. By contrast, a positive deflection in the signal (corresponding to the P300) was larger during the

final reversal error than during probabilistic errors, suggesting that the FRN correlates with the prediction error signal, but not necessarily with behavioral adjustment (but see[107]). Indeed, one of the strengths of the task is that it enables the separate investigation of punishment (i.e. prediction errors) and behavioral switching.

More generally, it should be noted that demands for reinforcement learning are particularly high in probabilistic reversal learning paradigms. However, reversal learning constitutes a special case of reinforcement learning, and adequate performance also depends on other processes including prepotent response inhibition and stimulus-switching. On a related note, it should be recognized that simple reinforcement learning models do not encompass all aspects of probabilistic reversal learning, as implemented in our paradigm. For example, Hampton et al.[108] have shown that behavioral performance on, and neural activity (in the ventromedial prefrontal cortex) during probabilistic reversal learning was fit better by a model that also simulated knowledge of the abstract task structure than by a simple reinforcement learning model that did not incorporate such a higher-order knowledge about interdependencies between actions.

Neural Systems: A number of neuropsychological studies have revealed that (probabilistic and deterministic) reversal learning is disrupted by frontal lobe lesions.[109-112] The deficits appear restricted to patients with ventromedial frontal lesions, do not to extend to patients with dorsolateral prefrontal lesions, and cannot be attributed to problems with initial acquisition of stimulus-reinforcement contingencies. Recently, Hornak et al.[111] observed deficits on the probabilistic reversal learning task in a small number of patients with dorsolateral prefrontal cortex lesions, but post-test debriefing revealed that these patients had failed to pay attention to the crucial feedback provided on the screen. In a further study, a group of patients

with frontal variant fronto-temporal dementia showed impairments on the probabilistic reversal learning task, while showing intact performance on executive functions associated with the dorsolateral prefrontal cortex.[113]

The first fMRI study of this task[114] revealed supra-threshold activity in the VLPFC, anterior cingulate cortex and posterior parietal cortex during the final reversal errors relative to the baseline correct responses. A priori hypotheses allowed more focused region of interest analyses, which revealed that the activity in the VLPFC was significantly larger on the final reversal errors than on the other (e.g. probabilistic) errors that did not lead to switching. It should be noted that, at a lower statistical threshold (uncorrected for multiple comparisons) the DLPFC was also active during the final reversal errors. Such additional (albeit relatively less) activity in the DLPFC was confirmed in later fMRI studies with this task,[115-117] and with a slightly adapted version of the task.[118] Finally, more recent studies that employed more optimal acquisition sequences, have also revealed reversal-related activity in the more anterior orbitofrontal cortex.[115,118] In our initial study, reversal-related activity was also observed in the ventral striatum, centered on the nucleus accumbens. Reversal-related activity was also observed in the nucleus accumbens in patients with Parkinson's disease (who had abstained from their medication[115]). However, the exact computation carried by the nucleus accumbens during probabilistic reversal learning is still under investigation.

Pharmacological and Behavioral Manipulation: Probabilistic reversal learning is sensitive to dopaminergic and serotoninergic manipulations, but not to noradrenergic manipulations in humans. Withdrawal of dopaminergic medication, such as levodopa and dopamine receptor agonists in patients with mild Parkinson's disease (PD) improves performance.[119] This effect is demonstrated by a greater number of patients OFF medication failing to reach learning criterion

on the critical reversal stage, relative to patients ON medication and to age- and education-matched controls. These results are consistent with Mehta et al.,[120] who showed that administration of the dopamine receptor agonist bromocriptine impaired performance on this task in young healthy volunteers while improving spatial memory. Additional support for the overdose hypothesis came from a recent pharmacological fMRI study, which revealed that dopaminergic medication in mild PD patients abolished reversal-related activity in the ventral striatum (particularly in the nucleus accumbens).[115] The effect of medication was particularly large on final reversal errors that led to behavioral switching. Interestingly, another pharmacological fMRI study in healthy volunteers revealed that administration of methylphenidate (60mg oral) also abolished reversal-related activity in the ventral striatum (particularly in the ventral putamen), an effect that was again particularly prominent on the final reversal errors.[116] Discrepancies in the precise localization of this effect within the ventral striatum indicate the need for further work.

Serotoninergic manipulation also affects performance on the task. However, the nature of the effect is qualitatively different from that observed after dopaminergic manipulation. Chamberlain et al.[121] observed that acute administration of citalopram, a selective serotonin reuptake inhibitor, but not atomoxetine, a selective noradrenaline reuptake inhibitor, increased the number of switches after probabilistic errors (i.e. misleading punishment). This effect was attributed to a presynaptic mechanism of action, paradoxically reducing serotonin levels. Consistent with this hypothesis, Evers et al.[122] found that the dietary acute tryptophan depletion procedure, which lowers serotonin synthesis, enhanced neural activity in the dorsomedial prefrontal cortex during punishment on switch and nonswitch trials. Thus, in contrast to dopaminergic medication, serotoninergic manipulation affected the processing of punishment

irrespective of switching. Interestingly, patients with major depression, which has been associated with serotoninergic abnormality, were found to suffer a deficit on probabilistic reversal learning that did not reflect perseverative responding, but rather reflected an inability to maintain responding to the usually correct stimulus in the face of misleading, probabilistic errors.[117,123] Finally, Taylor-Tavares et al.[117] observed an inverse correlation between suppressed activity in the amygdala during probabilistic, misleading errors and the tendency to switch after these misleading errors. Critically, this relationship was abolished in depressed patients. Additional pharmaco-fMRI studies examined different versions of the current task paradigm.[124-129]

Animal Models: There is a long history of animal work on the Probabilistic Reversal Learning task.[101,130,131] When assessing convergence between animal and human studies, it is important to consider subtle differences in task design. First, studies with experimental animals have used deterministic rather than probabilistic contingencies, so that animals never obtain 'misleading' punishment or reward. Second, the nature of reward and punishment is qualitatively different, with reward constituting prolonged periods of access to juice or food in animals, but (often) bonus points of positive feedback in humans. On the other hand, punishment may consist of periods of darkness or reward omission in animals, but bonus point loss or negative feedback in humans.

Nevertheless, there is remarkable convergence. Consistent with neuroimaging studies in humans, animal work has implicated the orbitofrontal cortex in reversal learning. Lesions of the orbitofrontal cortex in rodents and non-human primates induce a perseverative response tendency to the previously rewarded stimulus, reflecting persistent interference from a prepotent response.[101,131,132] Single-cell recordings have also revealed that the firing of orbitofrontal

neurons changes with alterations in reward contingencies.[133,134] More recent single-cell recording studies suggest that the activity of orbitofrontal neurons reverses more slowly than that of neurons in the amygdala.[135,136] Based on these data together with (disconnection) lesion data from the same lab,[137] the authors concluded that the orbitofrontal cortex may indirectly facilitate flexibility in downstream regions (such as the amygdala) by signaling the expected value of outcomes rather than by directly inhibiting previously relevant responses.

In addition to orbitofrontal and amygdala findings,[101] animal studies have implicated the ventral striatum in reversal learning. Specifically, lesions of the ventrolateral part of the head of the caudate nucleus induced a perseverative response tendency during (object) reversal learning in monkeys.[130] Subsequent work with rodents and non-human primates indicates that lesions of nucleus accumbens also disrupts performance on (object and/or spatial) reversal learning tasks.[138,139] However, the impairment following nucleus accumbens lesions is generally not restricted to the reversal stages of the task, but extends to initial acquisition stages, suggesting a more general role in the learning of stimulus-reinforcement contingencies rather than in reversal specifically.[138]

Psychopharmacological work with marmosets supports human evidence that reversal learning is sensitive to serotoninergic manipulations. Clarke et al.[140-142] revealed that depletion of serotonin in the orbitofrontal cortex with the neurotoxin 5,7-DHT impaired reversal learning and induced perseverative responding to the previously rewarded stimulus. It might be noted that the perseverative nature of the deterministic reversal deficit after 5,7-DHT lesions in marmosets is qualitatively different from the inappropriate switching seen after tryptophan depletion in humans. This discrepancy may reflect differences in the task used in marmosets and humans

(probabilistic versus deterministic; emphasis on punishment) or, more likely, differences in the effect of the manipulation on the degree of serotonin depletion in the brain.[143,144]

Performance in Schizophrenia: Waltz and Gold[145] recently employed a modified version of the probabilistic reversal learning task in 34 patients with schizophrenia and 26 controls. Although patients and controls performed similarly on the initial acquisition of probabilistic contingencies, patients showed substantial learning impairments when reinforcement contingencies were reversed, achieving significantly fewer reversals.

Psychometric Data: These data are not yet available for the probabilistic reversal learning task.

Future Directions

In sum, all tasks selected for immediate translational development in the LTM domain demonstrate strong construct validity and evidence for neural systems. These criteria were viewed as central, as understanding the behavioral construct and neural underpinnings of that construct are central to interpretation of pharmacological effects and development and refinement of animal models. However, there were a number of other criteria that were not fully realized, and are important targets for future development. With the exception of the Probabilistic Reward and Probabilistic Selection tasks, psychometric characteristics have not been sufficiently established on most tasks. The issue of test re-test reliability, and the avoidance of practice effects is an especially thorny issue to deal with in LTM tasks, and is likely to necessitate development of parallel forms for many of the task paradigms.

Authors also identified several important areas of future development for their individual task paradigms. For the Associative Inference task it was noted that future studies should extend examination of the AIP to schizophrenia populations, and increase examination of

pharmacological affects on performance. In particular, medial temporal lobe regions that are thought to support relational memory performance in the AIP receive input from and provide feedback to dopamine releasing neurons in the midbrain that are associated with reward and motivation.[146] (Lisman & Grace, 2005). Alteration in medial temporal lobe–midbrain interactions may exist in schizophrenia given the abnormal transmission of dopamine observed in the disease, and these alterations may have important implications for relational memory function. Medications used to treat schizophrenia may also influence interactions between medial temporal lobe structures and midbrain dopamine regions thus impacting memory. Determining how medication affects medial temporal lobe function and performance in the AIP may yield new insights into disease treatment. For the REaR, an important direction for future development is initiation of pharamacological and pharmaco-fMRI studies and development of an animal model that dissociates item-specific and relational encoding and retrieval.

Within the reinforcement learning construct authors of the Probabilistic Reward Task see a need for ongoing studies to evaluate responsiveness to other types of feedback (e.g., punishments), which will allow researchers to pinpoint dysfunction in reinforcement learning with increased precision. Future research is also needed to investigate whether participants show reduced response bias due to (1) reduced learning that the rich stimulus is associated with more frequent reward (so called “Go” learning), and/or (2) reduced learning that the lean stimulus is not associated with frequent reward (“NoGo” learning). Finally, a more direct animal model of the Probabilistic Selection task was identified for future development to better define the precise mechanisms by which dopamine supports different aspects of reinforcement learning.

Acknowledgments

Appreciation goes to Dr. Cameron Carter and Dr. Deanna Barch, who spearheaded the CNTRICS initiative, and played a key role in guiding the work of the LTM group.

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Figure Legends

Figure 1. Associative Inference Paradigm a) Participants encode overlapping face-house pairs (AB, BC) and are tested on the inferential relationship between pairs (AC). b) Anterior hippocampal activation associated with inferential retrieval of AC pairs.[10]

Figure 2. Results from Blumenfeld & Ranganath.[26] a) Example stimuli and task timing for working memory trials, b) Difference between observed and expected numbers of recollected triplets from each memory set. The mean difference between the observed number of trials for which all three words were successfully judged as remembered and the expected number of such trials given the overall hit rate is separately plotted for reorder and rehearse trials. A positive difference indicated that subsequent memory performance was benefited by enhanced inter-item associations. Error bars depict the standard error of the mean (SEM) across subjects, and the asterisk denotes that the observed expected difference was statistically significant for reorder trials. c) Time course of activation in prefrontal regions of interest (ROI). The activity in the reorder and rehearse task is plotted separately for the left dorsolateral prefrontal cortex (DLPFC) and anterior ventrolateral prefrontal cortex (aVLPFC) was correlated with subsequent LTM performance specifically during reorder trials. In contrast, delay-period activation in the posterior ventrolateral prefrontal cortex (pVLPFC) was predictive of subsequent LTM on both rehearse and reorder trials. The error bars in the time courses reflect the SEM at each time point for the reorder and rehearse tasks for each ROI.

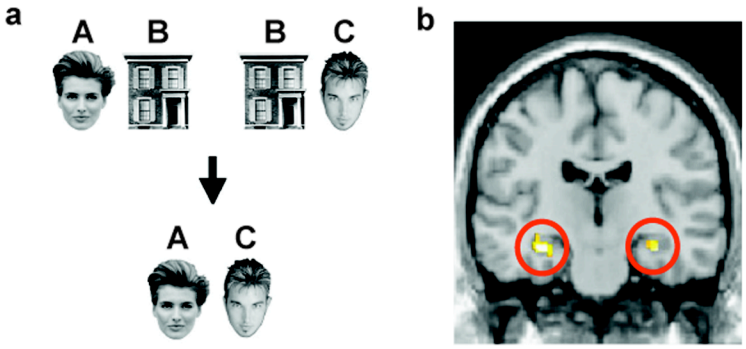
Figure 3. Recognition accuracy of controls (blue circles) and patients (red triangles) for rehearse and reorder tasks. Error bars depict the SEM across subjects, and the asterisk denotes a significant group difference for the reorder, but not rehearse task.

Figure 4. Summary of task design. At each trial, participants are asked to select via bottom press whether a short or long mouth had been presented. Figure modified with permission from Pizzagalli et al.[45]

Figure 5. Selected findings derived from the probabilistic reward task. Response bias toward the more frequently rewarded stimulus is reduced in (A) unmedicated MDD subjects;[55] (B) healthy controls receiving a single dose of a D2/3 agonist assumed to activate DA autoreceptors and thus reduce phasic DA bursts to unpredictable reward;[51] and (C) healthy controls exposed to an acute stressor.[56] Figures modified with permission.

Figure 6. Compared to subjects failing to develop a response bias toward the more frequently rewarded stimulus in the probabilistic reward task ("no-learners"), learners showed significantly (A) lower FRN to reward feedback; (B) higher dACC activation to reward feedback at the time of the FRN; and (C) higher basal ganglia activation to gain outcomes in an unrelated task (Monetary Incentive Delay task). Figures modified with permission from Santesso et al.[57]

Figure 7, Example of a trial-sequence of the probabilistic reversal learning paradigm for fMRI.


a
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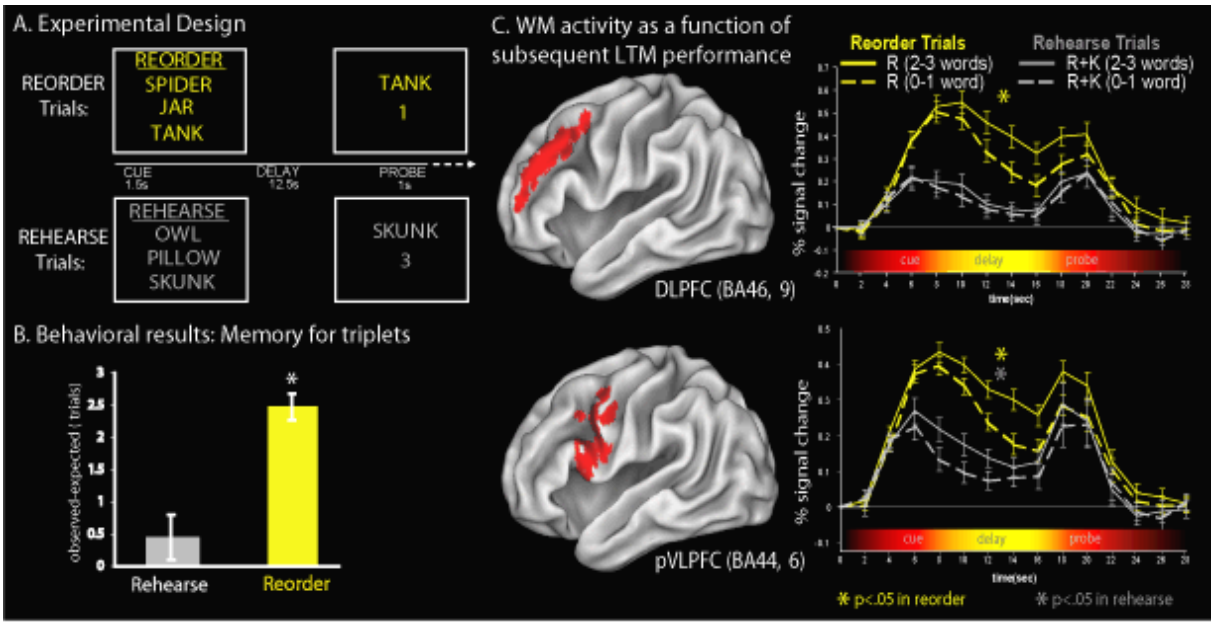
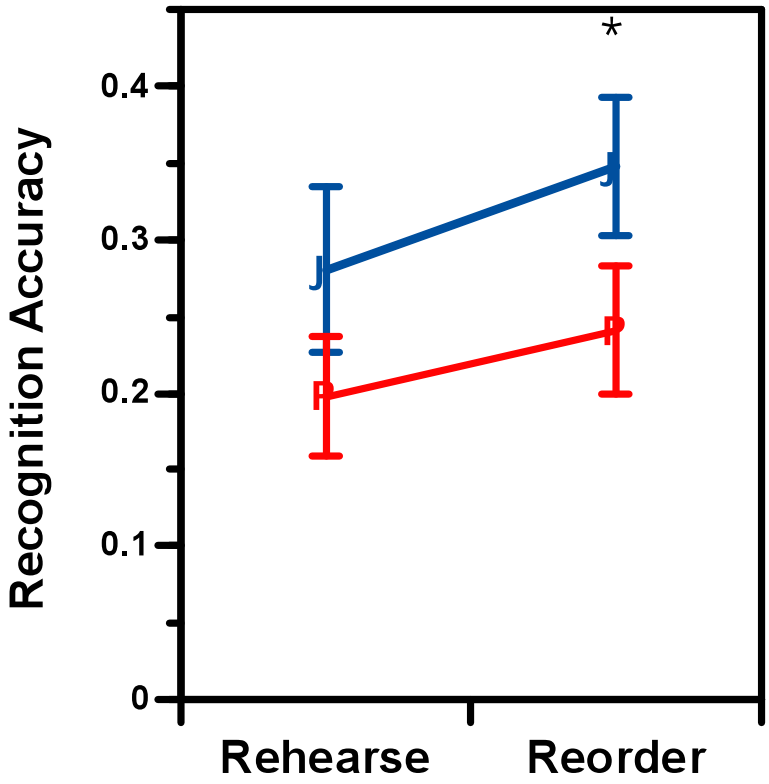
B
B
C
A
C
b


A. Experimental Design
REORDER Trials:
REORDER
SPIDER
JAR
TANK
TANK
1
CUE
1.5s
DELAY
12.5s
PROBE
1s
REHEARSE Trials:
REHEARSE
OWL
PILLOW
SKUNK
SKUNK
3
B. Behavioral results: Memory for triplets
observed-expected (trials)
Rehearse
Reorder
C. WM activity as a function of subsequent LTM performance
DLPFC (BA46, 9)
pVLPFC (BA44, 6)
Reorder Trials
R (2-3 words)
R (0-1 word)
Rehearse Trials
R+K (2-3 words)
R+K (0-1 word)
% signal change
cue
delay
probe
time(sec)
* p<.05 in reorder
* p<.05 in rehearse


*
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0.3
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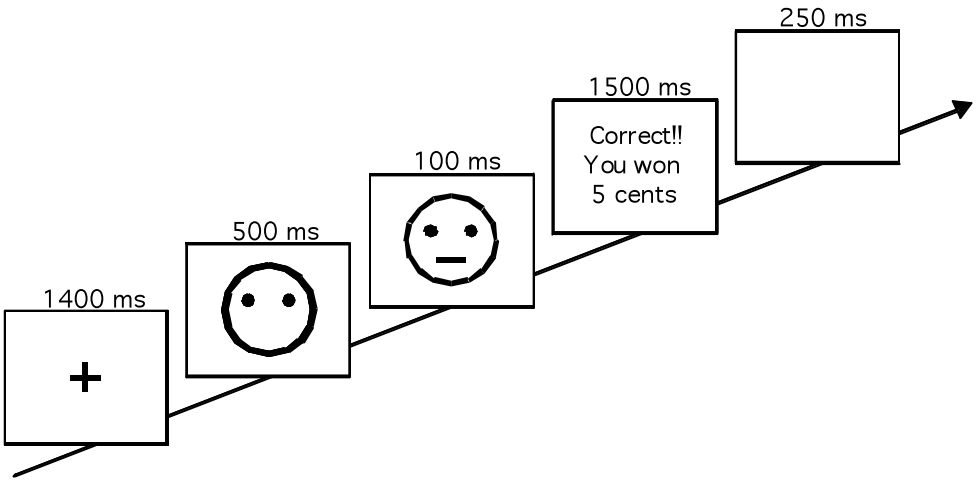
0.1
0
Recognition Accuracy
Rehearse
Reorder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+
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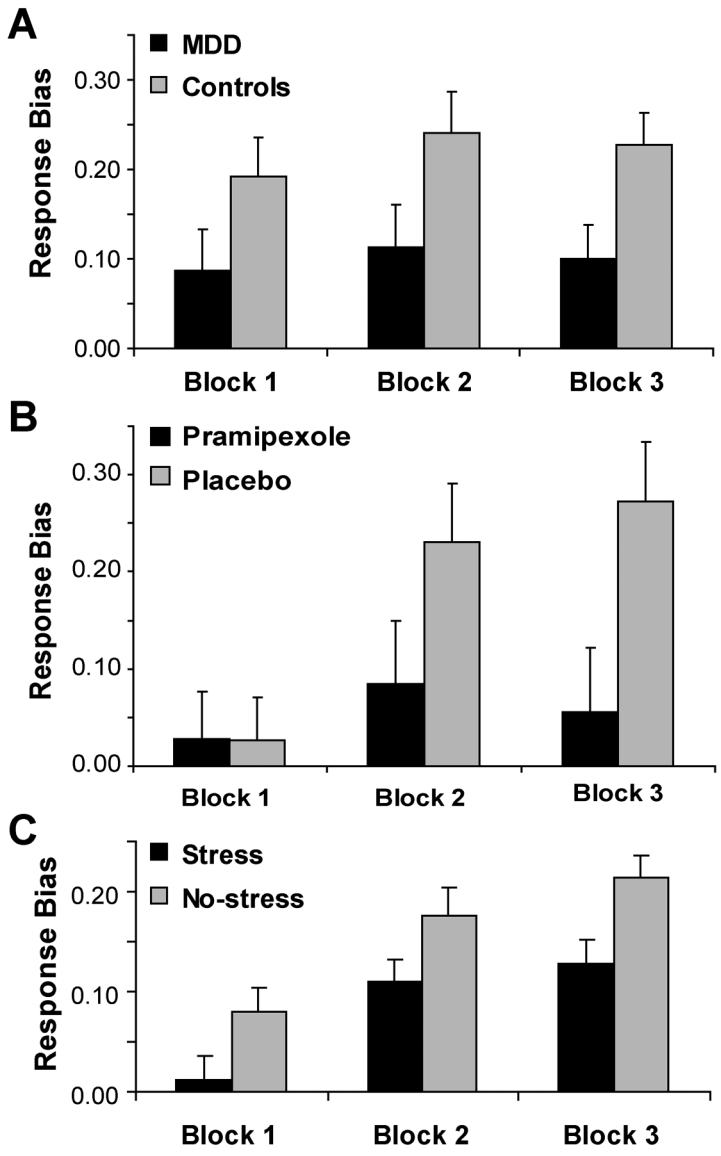
Correct!!
You won
5 cents
250 ms


A
MDD
Controls
Response Bias
0.30
0.20
0.10
0.00
Block 1
Block 2
Block 3
B
Pramipexole
Placebo
Response Bias
0.30
0.20
0.10
0.00
Block 1
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Block 3
C
Stress
No-stress
Response Bias
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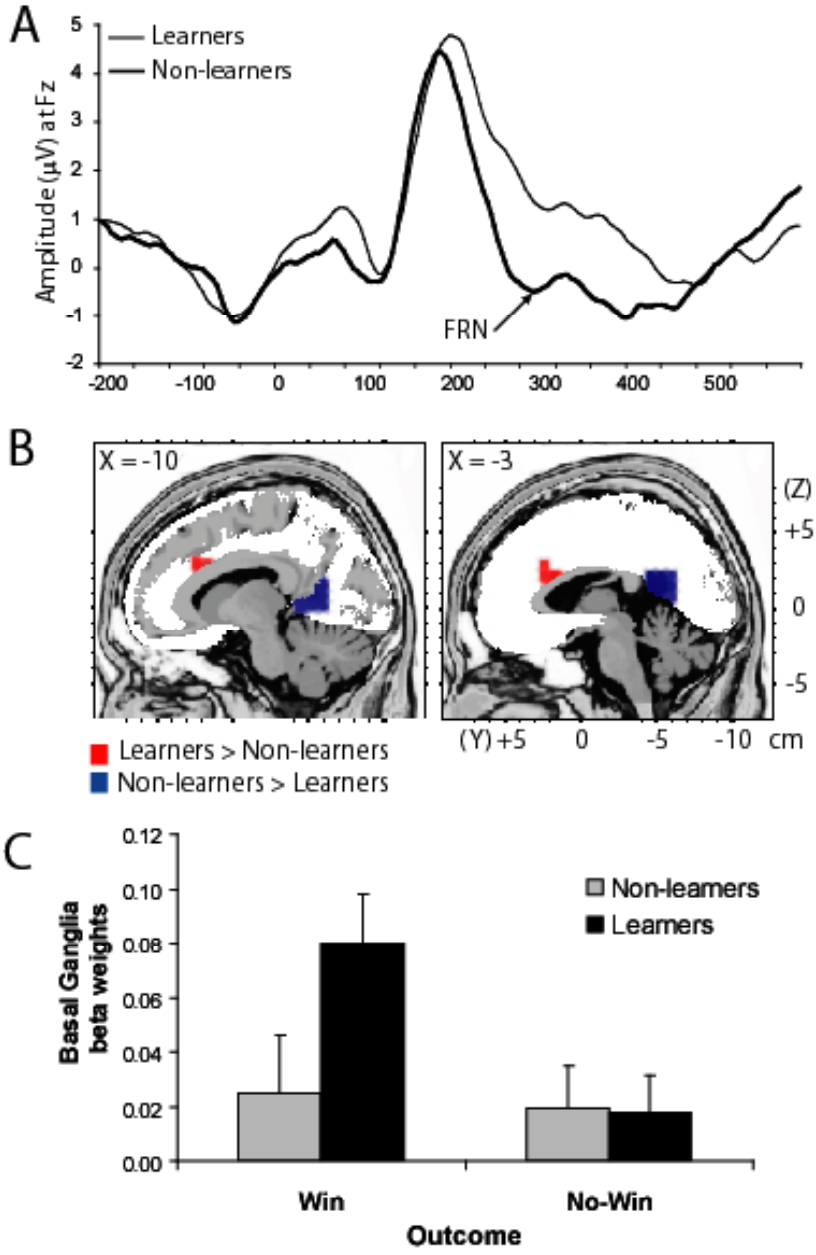
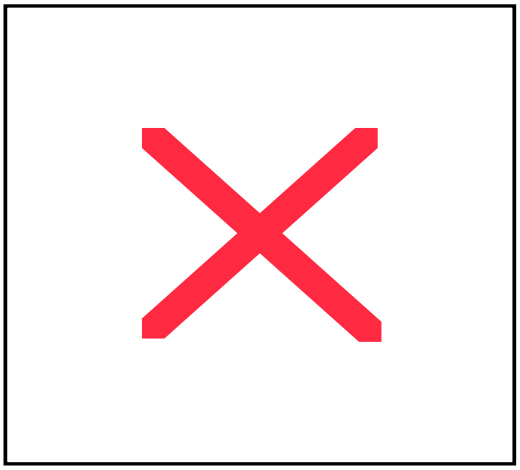
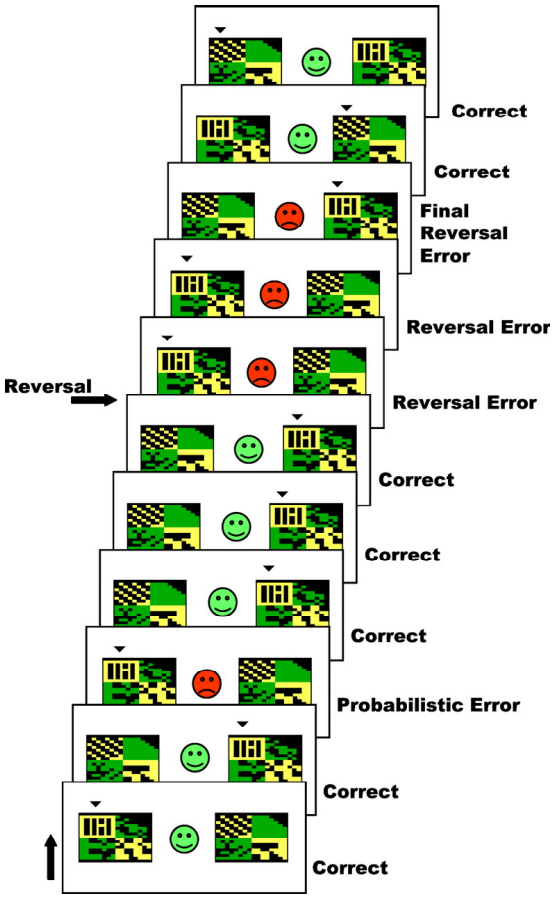
0.10
0.00
Block 1
Block 2
Block 3


A
Learners
Non-learners
Amplitude (μV) at Fz
FRN
B
X = -10
X = -3
(Z)
+5
0
-5
(Y) +5
0
-5
-10
cm
Learners > Non-learners
Non-learners > Learners
C
Basal Ganglia beta weights
Non-learners
Learners
Win
No-Win
Outcome




Correct
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Correct
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