Prospective hippocampus and putamen activations support conditional memory-guided behavior

Running Head: Prospective activations and memory-guided behavior

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38 **SUMMARY**

39 Memory of past events, in addition to contextual cues, influence conditional behavior.

40 The hippocampus (HPC), medial prefrontal cortex (mPFC), and striatum are important

41 contributors to this process. The mechanisms by which these regions facilitate conditional

42 memory-guided behavior remains unclear. We developed a conditional-associative task in

43 which the correct conditional choice was dependent on the preceding stimulus. We examined

44 activations related to successful conditional behavior and the timing of their contributions. Two

45 distinct networks emerged: (1) a prospective system consisting of the HPC, putamen, mPFC,

46 and other cortical regions, which exhibited increased activation preceding successful

47 conditional decisions; and (2) a concurrent system supported by the caudate, dlPFC, and

48 additional cortical structures that engaged during execution of correct conditional choices. Our

49 findings demonstrate two distinct neurobiological circuits through which memory prospectively

50 biases conditional memory-guided decisions, as well as influence the execution of current

51 choices.

52 INTRODUCTION

53 Successful decision-making often requires drawing upon the past. The influence of
54 memory on decision-making has been documented across a diverse array of tasks (Weber et
55 al., 1993; Jadhav et al., 2012; Wimmer and Shohamy, 2012; Zeithamova et al., 2012; Pfeifer
56 and Foster, 2013; Gluth et al., 2015; Shohamy and Daw, 2015; Murty et al., 2016; Bornstein et
57 al., 2017; O'Doherty et al., 2017). Memory-guided behavior is dependent on mechanisms
58 wherein past events bias decisions and relevant actions are selected.

59 Memory can bias decisions through both retrospective and prospective processes
60 (Shohamy and Daw, 2015). Functional neuroimaging studies have shown that the
61 hippocampus (HPC), medial prefrontal cortex (mPFC), and striatum are associated with the
62 success of retrospective memory-guided behaviors (Wimmer and Shohamy, 2012; Zeithamova
63 and Preston, 2010; Zeithamova et al., 2012a; 2012b; Gluth et al., 2015; Shohamy and Daw,
64 2015; Murty et al., 2016). Rodent studies, on the other hand, have illustrated the importance of
65 the HPC and mPFC for prospective integration (Benchenane et al, 2010; Wang and Morris,
66 2010; Jadhav et al., 2012; 2016; Pfeifer and Foster, 2013; Euston et al., 2015; Shin and
67 Jadhav, 2015; Yu and Frank, 2015).

68 The striatum has also been shown to be important for decision-making, especially its
69 role in action-selection (Balleine et al., 2007). Neuronal activity in anterior portions of the
70 caudate, putamen, and ventral striatum exhibited both transient and sustained responses
71 (Tremblay et al., 1998). The observed neural responses across the different regions of the
72 striatum are consistent with motor preparatory, reward expectation, and prediction error signals
73 (Schultz et al., 2003). Taken together, these findings suggest the striatum likely plays a dual
74 role in mechanisms related to biasing memory and the execution of decisions.

75 The extent to which the HPC, mPFC, and regions of the striatum contribute to
76 prospective memory-guided conditional behavior in humans, as well as the timing of each, has
77 not been demonstrated. Evidence from statistical learning studies have shown predictive
78 activations in the HPC (Schapiro et al., 2012; Bornstein and Daw, 2012), while the mPFC is
79 engaged during events that share temporal associations (Schapiro et al., 2013). Striatum
80 activation, specifically in the putamen, is associated with response preparation and prediction
81 error (Bornstein and Daw, 2012).

82 We utilized a modified visuomotor associative learning paradigm (Petrides, 1997; Law
83 et al., 2005) to investigate the neurobiological mechanisms of conditional memory-guided
84 behavior, as well as differences in activations before and during decision-making. Participants
85 learned, through trial and error across multiple presentations, to associate three stimuli with a
86 specific response. Two images were known as *fixed* trials, whose associations were consistent
87 or fixed across all presentations. For the third image, the correct associated response was
88 dependent on the identity of the stimulus from the preceding trial. In other words, the correct
89 association for the third image was *conditional* on the *fixed* association of the previous trial. We
90 observed greater activations in the HPC and putamen, but not the mPFC or anterior dorsal
91 caudate, during fixed trials preceding correct compared to incorrect conditional trials. Further,
92 prospective functional interactions between the HPC and mPFC during periods of learning
93 were enhanced. In contrast, activation in the anterior dorsal caudate was elevated during the
94 execution of correct conditional relative to fixed trials. We believe these results highlight two
95 distinct neurobiological circuits through which memory prospectively biases conditional
96 memory-guided decisions, as well as influence the execution of current choices.

97

RESULTS

To examine how the HPC, mPFC, and subregions of the striatum (dorsal anterior caudate and putamen) contribute to memory-guided behavior, we collected blood oxygen level dependent (BOLD) functional magnetic resonance imaging (fMRI) while participants engaged in a memory-guided conditional associative learning task. Anatomical region of interest (ROI) and exploratory whole-brain analyses tested: 1) differences in prospective activation during fixed trials immediately preceding correct compared to incorrect conditional trials, to evaluate neurobiological mechanisms of memory's influence on conditional decisions; 2) correlation between first trial regional activation and second trial performance for sequential fixed trial pairs when the stimulus either changed or remained the same, to further validate whether prospective activations bias subsequent behavior; 3) prospective functional coupling between anatomically-connected regions of interest during periods of learning compared to periods of no-learning, to corroborate a recent study in rodents that found enhanced functional coupling during learning (Tang et al., 2017); and 4) activation differences between correct conditional and correct fixed association trials, to examine differences in brain activations for conditional trials above and beyond that observed during fixed trials at the time of correct decisions.

Behavioral Performance

We found that while participants performed better and faster on fixed compared to conditional trials, both were performed better than would be expected by chance. For distributions that violated the assumptions of parametric methods, non-parametric tests were performed. To determine whether participants performed better than chance, mean accuracy was calculated across stimulus sets for each participant. Participants demonstrated significantly better than chance performance for the fixed-right (Fix_R : $0.935 \pm .009$; Fix_R vs. chance:

121 $Z = -3.920, p < .0001$), fixed-left (Fix_L : 0.928, IQR = 0.91 - 0.9; Fix_L vs. chance: $Z = -3.920, p$
122 $< .0001$), and conditional images (Conditional: $0.761 \pm .018$; Conditional vs. chance: $Z = -3.920, p$
123 $< .0001$). When comparing performance across trial types (Fix_R vs. Fix_L vs. Conditional), we
124 observed a significant difference for accuracy (Friedman test: $\chi^2(2) = 31.013, p < .0001$). To
125 determine whether unexpected mnemonic differences exist between fixed- left and right trials,
126 we compared accuracy for each. No significant difference in accuracy between fixed-left and
127 fixed-right trials was observed ($Z = -1.248, p = .212$). Given the consistent association between
128 stimulus and response for fixed trials, we expected fixed trials to be more accurate than
129 conditional trials. Thus, performance was compared between fixed and conditional trials.
130 Participants performed significantly better for both fixed-left ($Z = -3.920, p < .01$) and fixed-right
131 ($Z = -3.920, p < .01$) compared to conditional trials. Similar to accuracy, a statistically
132 significant difference was observed for reaction time between the three trial types, ($F(1,19) =$
133 $29.22, p < .0001$, partial $\eta^2 = .61$). Fixed-left ($0.580 \text{ s} \pm 0.008$) and fixed-right ($0.588 \text{ s} \pm 0.011$)
134 trials were not significantly different from one another ($t(19) = -1.086, p = .291$). However,
135 participants were significantly slower for conditional (0.632 ± 0.009) compared to either fixed-
136 left ($t(19) = -9.429, p < .001$) or fixed-right ($t(19) = -5.006, p < .001$) trials.

137 Next, we found the onset of learning for conditional trials was slower compared to fixed
138 association trials. To evaluate differences in learning between the three stimulus types, we
139 calculated learning curves using a logistic regression algorithm designed to assess learning as
140 a dynamic process across trials (Figure 1C; Smith and Brown, 2003; Smith et al., 2004, Wirth
141 et al., 2003). We examined differences in the onset of learning between fixed and conditional
142 trials. The onset of learning was defined as the trial in which the lower-bound 95% confidence
143 interval exceeded chance performance. There was a statistically significant difference in the

onset of learning between the three trial types (Friedman test: $\chi^2(2) = 22.354$, $p < .001$). The onset of learning for the fixed-left (median = 3.84, IQR = 2 - 7) and fixed-right (median = 3.83, IQR = 1 - 7) trials was not significantly different ($Z = -.081$, $p = 0.936$). In contrast, the onset of learning was delayed for conditional trials (median = 11.5, IQR = 6 - 26) compared to fixed-left ($Z = -3.267$, $p < .01$). Likewise, the onset of learning occurred later for conditional than for fixed-right trials ($Z = -3.435$, $p < .01$).

In summary, no statistically significant differences were observed for accuracy, reaction time, or learning onset between fixed left and fixed right trials. Participants, however, were slower to respond, less accurate, and exhibited a delay in the onset of learning for conditional trials compared to fixed trials. All trial types were performed significantly better than chance.

Prospective activations of the HPC and putamen, but not mPFC and caudate, differentiate conditional trial performance

Success on conditional trials required participants to remember which of the two fixed stimuli has been presented on the preceding trial. We anatomically defined regions of interest bilaterally (HPC, mPFC, anterior dorsal caudate, and putamen; see Methods) and contrasted level of activation on fixed trials immediately preceding correct and incorrect conditional trials. We predicted that the HPC, mPFC, and anterior dorsal caudate would exhibit greater prospective activations preceding correct compared to incorrect conditional trials. In contrast, we expected the putamen to play less of a role prospectively.

The HPC and putamen, but not the mPFC and anterior dorsal caudate, prospectively differentiated successful conditional memory-guided behavior. Increased HPC activation was observed during fixed trials immediately preceding correct, compared to incorrect, conditional trials (Figure 2A; $t(19) = 4.055$, $p = .0007$, $d = .81$). No significant difference in mPFC (Figure

167 2B, $t(19) = 0.879$, $p = .39$) or anterior dorsal caudate (Figure 2C, center; $t(19) = -1.507$, $p = .15$)
 168 activation was observed for fixed trials before correct and incorrect conditional trials.
 169 Interestingly, and contrary to our hypothesis, greater putamen activation was observed during
 170 fixed trials before correct relative to incorrect conditional trials (Figure 2D; $t(19) = 3.484$, p
 171 $= .002$, $d = .74$).

172 To ensure these findings were not an artifact of performance on the preceding fixed
 173 trial, we conducted the same analysis limiting the scope to only correct fixed trials preceding
 174 correct and incorrect conditionals. We again observed that both the HPC (Supp. Figure 1A;
 175 $t(19) = 4.213$, $p = .0005$, $d = .98$) and putamen (Supp. Figure 1D; $t(19) = 2.547$, $p = .019$, d
 176 $= .65$) exhibited significantly greater activation during fixed trials preceding correct, compared
 177 to incorrect, conditional trials. No significant differences in mPFC (Supp. Figure 1B; $t(19) =$
 178 1.97 , $p = .063$) or dorsal anterior caudate (Supp. Figure 1C; $t(19) = -0.011$, $p = .99$) activations
 179 were observed.

180 The results of our *a priori* anatomical ROIs support the conclusion that prospective HPC
 181 and putamen, but not mPFC and dorsal anterior caudate, activations are related to successful
 182 conditional memory.

183 **Prospective cortical and subcortical activations for successful memory-guided** 184 **conditional behavior**

185 We found memory-guided behavior during conditional associative learning prospectively
 186 employs a broad network of cortical and subcortical regions to guide our choices. We
 187 performed an exploratory whole-brain analysis to evaluate the potential contributions of other
 188 cortical and subcortical regions to successful conditional memory-guided behavior. We
 189 searched for voxel-wise differences in activation during fixed trials preceding correct and

190 incorrect conditional trials. We performed a one-sample t-test using FSL *Randomise* with the
 191 threshold-free cluster enhancement (tfce) correction with a threshold of $p < 0.05$. Consistent
 192 with our *a priori* anatomical ROI analysis, clusters in the HPC and putamen survived
 193 corrections for multiple comparisons when contrasting greater activation for fixed trials
 194 preceding correct conditional trials against fixed trials preceding incorrect conditional trials.
 195 Additional clusters were observed (Figure 3) for the same contrast in the mPFC – anterior to
 196 our anatomically defined ROI, posterior cingulate cortex (PCC) – including the retrosplenial
 197 cortex, motor cortex, paracentral lobule, superior temporal cortex, ventral visual cortex, and the
 198 cerebellum (Suppl. Figure 2). No regions survived corrections for multiple comparisons when
 199 contrasting greater activation for fixed trials preceding incorrect conditional trials relative to
 200 fixed trials preceding correct conditional trials. Our exploratory results suggest a widespread
 201 cortical and subcortical network prospectively biases conditional memory-guided decisions.
 202 **Prospective putamen activation during fixed trials is related to behavioral performance**
 203 **on subsequent trials when stimulus is repeated**

204 In addition to influencing decisions on conditional trials, prospective activations should
 205 also bias behavioral performance on subsequent fixed trials, especially when those trials
 206 repeat. To evaluate the relationship between prospective fMRI activation and subsequent
 207 performance for fixed trials, temporally adjacent fixed trial pairs were selected and sorted
 208 according to whether the stimulus changed (fixed-left --> fixed-right) or remained the same
 209 (fixed-left --> fixed-left). Using the same four *a priori* anatomical ROIs, Pearson's correlation
 210 coefficients were calculated between regional activation during the first and performance on
 211 the second trial. Performance was defined as the mean proportion of correct responses for
 212 trials that either remained the same (fixed-same) or changed (fixed-change). We expected

fixed trial activations should be related to performance on upcoming fixed trials. To insure our predictions were not a result of temporal adjacency, we compared activation for conditional trials to the following fixed trial performance.

We found first fixed trial activation was associated with second fixed trial behavioral performance when the stimulus remained the same, however, conditional trial activation had no bearing on subsequent fixed trial performance. No significant correlation was observed between HPC activation and performance for fixed-change trials (Figure 4A, left; $r = .211$, $p = .37$). However, a trend was observed for fixed-same trials (Figure 4A, right; $r = .411$, $p = .07$). We did not observe a significant relationship between mPFC activation and behavior for fixed-change (Figure 4B, left; $r = -.181$, $p = .45$) nor fixed-same (Figure 4B, right; $r = .233$, $p = .32$) trials. No statistically significant association between dorsal anterior caudate activation and behavior was observed for fixed-change (Figure 4C, left; $r = -.141$, $p = .55$) and fixed-same (Figure 4C, right; $r = .028$, $p = .91$) trials. The putamen, on the other hand, exhibited a significant positive correlation between activation on the first fixed trial and performance on the subsequent fixed trial when stimuli remained the same (Figure 4D, right; $r = .531$, $p = .016$), but not when they changed (Figure 4D, left; $r = .27$, $p = .25$). Correlations were calculated between activations during conditional trials and performance on the following fixed trial. No regions showed a significant relation between conditional activation and subsequent behavioral performance (Supp. Figure 3A-D; all $r < .28$, all $p > .05$).

Consistent with our hypotheses, prospective fixed trial activations were associated with subsequent fixed trial behavioral performance in the putamen and a trend in the HPC. In addition, no similar relation was identified when comparing conditional activations to upcoming fixed trial performance.

Prospective HPC-mPFC functional correlations are enhanced during learning

We examined the functional coupling between *a priori* ROIs and known anatomically connected regions. The HPC directly projects to the mPFC (Barbas and Blatt, 1995; Cavada et al., 2000). The dorsal anterior caudate and putamen receive projections from the dorsolateral prefrontal cortex (dlPFC) and the pre- and primary motor cortices, respectively (Kunzle, 1975; Selemon and Goldman-Rakic, 1985; Flaherty and Graybiel, 1994; McFarland and Haber, 2000; Haber et al., 2006; Haber, 2016).

To investigate how functional interactions between these regions support conditional memory-guided behavior, we performed a task-based beta-series correlation analysis (Rissman et al., 2004). A recent study in rodents using an analogous task found increased coherence between the HPC and mPFC during learning relative to steady state behavior (Tang et al., 2017). Thus, we examined the functional coupling between the three regional pairs for fixed trials preceding periods of learning and non-learning during conditional trials. To operationalize periods of *learning* and *non-learning*, the derivative of the learning curve was calculated across conditional trials. Trials with positive derivative values, representing increased rate of learning relative to preceding trials, were considered *periods of learning*. Conversely, *periods of non-learning* were defined as trials in which the derivative was either zero or a negative value, constituting decreased rate of learning. Separate beta-series were created using the fixed trials that preceded learning and non-learning conditional trials, and correlations between anatomically defined ROIs mean activation were calculated. Paired-samples t-tests were used to assess differences in the functional coupling between periods of learning versus non-learning.

Functional coupling between the HPC and mPFC was enhanced ($t(19) = 2.56, p = .019, d = .52$) during periods of learning (0.651 ± 0.041) relative to periods of non-learning (0.581 ± 0.044). Conversely, no difference in functional coupling was observed between periods of learning (0.588 ± 0.041) and non-learning (0.570 ± 0.045) for the dorsal anterior caudate and dlPFC ($t(19) = 0.453, p = .66$), nor the putamen and pre/primary motor cortex ($t(19) = 1.586, p = 0.13$) (Figure 5). Consistent with prior rodent literature (Tang et al., 2017), the present findings support the conclusion that the HPC and mPFC contribute to successful conditional memory-guided behavior through prospective functional interactions that are enhanced during learning.

Separate network supports successful execution of current conditional decision

We found the execution of conditional associations is supported by a wide network of cortical and subcortical regions distinct from the observed prospective activations. We performed a second exploratory whole-brain analysis to determine which regions contribute to successful conditional memory-guided behavior during, rather than preceding, correct conditional associative trials. We compared differences in activation during correct conditional, compared to correct fixed, association trials. We observed greater activation for correct conditional trials in the bilateral caudate, dlPFC, superior parietal lobule (SPL), anterior insular cortex, and cerebellum (Figure 6). These results reveal a separate network of brain regions important for concurrent conditional trial performance (e.g., action-selection and task execution), above and beyond those implicated in preceding fixed trials, which contribute to the execution of conditional memory-guided behavior.

DISCUSSION

Our results establish that successful conditional memory-guided behavior is differentiated by prospective activations in the HPC and putamen. In addition, a broad network of cortical and subcortical regions contribute: the mPFC, posterior cingulate cortex (including the retrosplenial cortex), superior temporal cortex, paracentral lobule, and cerebellum. Similar to the prospective influence on conditional decisions, we also identified a relationship between fixed trial activation and the subsequent fixed trial performance when the stimulus remained the same in the putamen. A trend in the HPC was observed for the same analysis. Prospective functional coupling between the HPC and mPFC was enhanced during learning compared to non-learning. Similar differences were not identified for functional coupling between either dorsal anterior caudate and dlPFC or the putamen and pre/primary motor cortex. Lastly, we observed that activations in the dorsal anterior caudate and related cortical structures (e.g., dlPFC, superior parietal lobule, anterior insula, and precuneus) were associated with successful execution of conditional memory-guided behavior when compared to correct fixed association trials. These findings demonstrate how memory-guided behavior is supported by two distinct neurobiological circuits: the first supports memory traces that prospectively bias conditional memory-guided decisions, while the second influences the execution of the current conditional choice.

Prospective neural activity constitutes an important mechanism of memory-guided behavior. Recent studies have identified relations between prospective fMRI activations and choice. For example, in a study which used a multistep reward learning task combined with regionally decodable stimuli, prospective activation of the second-stage categories was positively correlated with the degree to which participants used a model-based relative to a model-free strategy (Doll et al., 2015). In a sequential learning task where the regularity of

adjacent items was manipulated, hippocampal activation correlated with forward entropy, an estimate of the uncertainty of the upcoming stimulus conditional on the current one (Bornstein and Daw, 2012). Lastly, activations in the hippocampus during encoding have been shown to be correlated with the probability that an item was remembered during a later decision phase (Gluth et al., 2015). All together, these studies suggest that the hippocampus and other cortical regions play an important role in memory representations prospectively guiding decision-making.

Spatial navigation studies in rodents have also provided evidence for the role of prospective neural activity in decision-making. Awake sharp wave ripple (SWR) events in the hippocampus reinstate sequential patterns of 'place-cell' activity of both recent (Foster and Wilson, 2006; Diba and Buzsaki, 2007) and remote experiences (Karlsson and Frank, 2009; Gupta et al., 2010). Further, the content of SWR events are predictive of upcoming choices (Pfeiffer and Foster, 2013), indicative of whether those choices will be subsequently correct or incorrect (Singer et al., 2013), and following disruption are sufficient to impair performance in a continuous alternation task (Jadhav et al., 2012).

Our results are consistent with previous work in both humans and animals. We observed greater activation in the HPC on trials that preceded correct versus incorrect conditional memory-guided trials, similar to results observed in rodents during an analogous spatial alternation task (Frank et al., 2000; Singer et al., 2013) and statistical learning studies in humans (Bornstein and Daw, 2012). Moreover, prospective activations in the putamen (trend in the HPC) during fixed trials were related to behavioral accuracy on the next fixed trial when those trials were the same.

Prospective activations for correct versus incorrect conditional trials were observed across a wide range of cortical regions including the mPFC and the PCC/retrosplenial cortex. Prospective cortical activations may reflect cortical-hippocampal-cortical loops of information processing where cortical activations have been shown to precede and influence the content of sharp-wave ripple events in the hippocampus (Rothschild et al., 2017). These cortical-hippocampal-cortical loop dynamics have been identified during sleep and may play a similar role in awake memory-guided behavior.

We also observed prospective activation reflecting successful conditional behavior in the putamen, but not the dorsal anterior caudate. Activations in the putamen have previously been associated with model-free prediction errors (Doll et al., 2015) and conditional probability, or degree of response preparation during a sequential learning task (Bornstein et al., 2012). We believe our results are most in-line with those observed by Bornstein and colleagues (2012), especially given the strong anatomical connectivity of the putamen with the motor cortex through cortico-striato-thalamo-cortical loops (Kunzle, 1975; Alexander et al., 1986; Flaherty and Graybiel, 1994; McFarland and Haber, 2000; Haber, 2016).

The precise mechanism by which prospective neural activity influences memory-guided behavior remains unknown. The observed activations in the current study may reflect a retrieval process that is important for deliberation at the time of a choice (Carr et al., 2011). However, there is evidence prospective activations reflect imagined future options that will be important for upcoming decisions (Addis et al., 2007; Yu and Frank, 2015). Further experiments are necessary to disambiguate the relevant mechanisms, with a strong likelihood that both mechanisms contribute to successful behavior dependent on the demands of the task.

Our results establish that functional interactions between the HPC and mPFC constitute an important mechanism supporting memory-guided conditional behavior that can be modulated by learning. Functional interactions between the HPC and mPFC have been shown to play an important role during sleep (Siapas and Wilson, 1998). Increased neuronal synchrony has been observed during slow-wave sleep (Buzaki, 1996), while disruptions of this coherence significantly impair stabilization and subsequent memory performance (Ego-Stengel and Wilson, 2010). More recently, functional coupling between the HPC and mPFC in awake behaving animals has been shown to be an important mechanism in memory-guided behavior (Jones and Wilson, 2005a; 2005b; Benchenane et al., 2010; Remondes and Wilson, 2013; Brincat and Miller, 2015; Yu and Frank, 2015; Jadhav et al., 2016; Tang et al., 2017). For example, coupling of spike timing and theta coherence increases at choice points in mazes, with the degree of coherence modulated by behavioral performance (Jones et al., 2005; Benchenane et al., 2010). Sharp-wave ripple events have also been shown to couple with prefrontal cortex neuronal activity, leading to both increases and decreases of spiking activity in mPFC neurons (Jadhav et al., 2016). We observed stronger HPC-mPFC coupling during learning relative to non-learning periods, similar to a recent rodent study (Tang et al., 2017). In the rodents, this functional interaction subsequently declined over the course of the experiment. While we did not observe a similar decrease in functional correlation, this may be attributable to the single session of data collection in our study, compared to the multiple days of testing in the rat study. Previous human neuroimaging studies have shown coupling between the HPC and ventral mPFC play a central role in memory-guided-decision-making (Zeithamova et al., 2012; Gluth et al., 2015). Zeithamova and colleagues (2012) observed increased functional connectivity between the HPC and mPFC across encoding repetitions.

372 While they did not observe a change in functional correlations across runs consistent with a
 373 possible learning related effect, their task explored the influence of memory on decision-
 374 making using a transitive inference design capitalizing on “retrospective integration” (Shohamy
 375 and Daw, 2015) through retrieval mediated learning. Our current task, on the other hand, taxes
 376 prospective integration which may elicit different dynamics in functional coupling between the
 377 HPC and mPFC.

378 The dorsal anterior striatum represents currently relevant associations of goal-directed
 379 behavior. The striatum has long been suspected to support instrumental behavior (Graybiel,
 380 1995). Instrumental behavior is dissociable into goal-directed (Dickinson and Balleine, 1994)
 381 and stimulus-bound or habitual (Dickinson et al., 1994) control. The distinct forms of
 382 instrumental behavior have been mapped to different neurobiological circuits. Specifically,
 383 evidence suggests that goal-directed behavior is mediated by dorsomedial cortico-striato-
 384 thalamo-cortical circuits (Yin et al., 2005), while stimulus bound behavior is supported by
 385 dorsolateral circuits in the rodent (Yin et al., 2004). A similar functional subdivision is observed
 386 in primates along the anterior/posterior axis (Miyachi et al., 1997; 2002). Dorsal anterior
 387 caudate neurons modulate their firing as goal-directed associations are learned (Tremblay et
 388 al., 1998; Blazquez et al., 2002; Miyachi et al., 2002; Hadj-Bouziane and Boussaoud, 2003;
 389 Brasted and Wise, 2004), with responses preceding those observed in the dorsolateral
 390 prefrontal cortex (Pasupathy and Miller, 2005). Similar activations have been observed in
 391 humans during instrumental tasks (O’Doherty et al., 2004; Tricomi et al., 2004). We observed
 392 greater activation in the dorsal anterior caudate and affiliated cortical structures for correct
 393 conditional more so than for correct fixed associations. These results suggest that at the time

of action selection the dorsal anterior caudate contributes to the representation of goal-directed associations.

Conclusions

Taken together, these findings provide evidence for complementary memory processes underlying successful conditional memory-guided behavior. We posit the first of these mechanisms to represent a prospective encoding system which serves to procure and maintain multiple types of representations across past experience for future conditional decisions. In addition, we propose that a second conditional memory-guided system facilitates concurrent utilization of past knowledge during choice deliberation. Our findings illustrate successful conditional memory-guided decisions arise from the involvement of multiple learning and memory systems.

EXPERIMENTAL PROCEDURES

Participants

Twenty-seven right-handed volunteers performed a conditional visuo-motor associative learning task in the scanner. All participants provided written informed consent in accordance with local Institutional Review Board requirements. Individuals were recruited from the Florida International University community and financially compensated for their time. Six individuals were excluded from the reported analyses. Three were removed for excessive motion (greater than 20% of time points were flagged as outliers following our outlier detection procedures using 1 mm normalized frame-wise displacement and 3 standard deviations above the mean signal intensity as thresholds). Three were removed for poor task performance (lower bound of the 95% confidence interval never exceeded chance performance). Lastly, one participant was removed as a result of experimenter error – the first image set was erroneously presented for

all six runs. The final sample size was 20 participants (13 females; mean age = 20.82 years, SD = 1.78).

Materials and Procedures

The conditional memory-guided associative learning task was modified from a visuomotor associative learning task (Law et al., 2005; Kirwan et al., 2007; Mattfeld and Stark, 2010; 2015; Stark et al., 2018). The experiment was run using PsychoPy2 software (Peirce, 2009) on a Dell PC computer (Windows 8). Stimuli were back-projected and viewed using a fixed mirror mounted on the head coil. Participants were presented three unique kaleidoscopic image sets. Each set was learned across two scanning runs. Participants completed 6 total scanning runs. Each run lasted 6.6 minutes. Stimuli were presented 40 times during each run or 80 times total (across 2 runs), resulting in 240 learning stimulus trials per set. Individuals were instructed to learn through trial-and-error the associations between each image and one of two concurrently presented boxes, which flanked the stimulus. Two of the three images were associated with either the left or right box exclusively, for which the correct response remained consistent across trials. We refer to these trials as *fixed* associative learning trials. The association for the third image, however, was conditional on the identity of the image from the preceding trial and thus could change across trials. We refer to these trials as *conditional* associative learning trials (Figure 1A).

Each learning trial began with the presentation of a centrally located fixation cross for 300 ms, after which a computer-generated kaleidoscopic image (Miyashita et al., 1991) flanked by empty boxes on both the right and left was presented for 500 ms. The image was then replaced by a fixation cross for a hold period of 700 ms, followed by a white “Go!” response cue and an additional 700 ms response window for participants to make their selection.

Participants responded using their index finger to select the left box and middle finger to select the right box. Responses were recorded using a MR-compatible response box. The chosen box was highlighted to indicate selection. Deterministic feedback (green “Yes!”, red “No!”, or white “?”) was provided for 800ms after the response. In addition to the learning stimulus trials, 40 perceptual baseline (BL) trials were presented to serve as a temporal jitter between trial types, distribute cognitive demand, and provide a reference for the fMRI signal. Sequence and timing of perceptual BL trials was identical to learning trials (Figure 1B). Participants were asked to identify the “whiter” of the two boxes presented on a random static background. Perceptual difficulty changed with performance (Supplementary Materials). Trial types were pseudo-randomly presented across experimental runs; the sole caveat being conditional trials could not follow one another in trial sequence.

Perceptual Baseline Trials

To serve as a temporal jitter between trial types, distribute cognitive demand, and provide a reference for the fMRI signal, 40 perceptual baseline (BL) trials were presented randomly across each experimental run. Sequence and timing of perceptual BL trials was identical to learning trials (Figure 1B). During BL trials participants were presented with a random static pattern image created through the binarization of random values for each pixel of screen resolution (1280 x 800). Randomly generated pixel values greater than 0.85 became white, while those below that threshold became gray. Placed over this static background, a white fixation cross was presented in the center of the screen, flanked on the left and right by two white outlined boxes. In identical fashion to the larger image, the contents of each box were also random static patterns (320 x 200); however, the binarization threshold to produce a white pixel was considerably lower and, for target, vacillated as a function of performance. For

the first BL trial, binarization thresholds for target and foil were initially set at 0.55 and 0.65, respectively. Participants were tasked with identifying the “whiter” of the two boxes. If the participant responded correctly to seven out of the previous 10 trials, the white threshold for the target box would increase by 10% of that for the last trial, producing fewer white pixels and bringing the image closer to the constant foil threshold of 0.65, thereby increasing the difficulty of the task. Conversely, if response to fewer than five of the preceding 10 BL trials were correct, the threshold decreased by 10% of the previous value, leading to a “whiter” target and easier identification.

Prescan Training

All participants received prescan training of 75 total trials (60 learning stimuli and 15 BL trials) using a practice set of 3 images specific to the training session. Prescan training allowed participants the opportunity to become acquainted with the nature and timing of the task and mitigated the loss of trials due to nonresponse at the beginning of the first experimental run. Prescan training was conducted on a MacBook Pro using identical finger-response mapping to that used during scanning session.

Neuroimaging Data Acquisition

Imaging data were acquired on a General Electric Discovery MR750 3T scanner (Waukesha, WI, USA) with a 32-channel head coil at the University of Miami Neuroimaging Facility (Miami, FL). Functional images were obtained using a T2*-sensitive gradient echo pulse sequence (42 interleaved axial slices, acquisition matrix = 96 x 96 mm, TR = 2000 ms, TE = 25 ms, flip angle = 75°, in-plane acquisition resolution = 2.5 x 2.5 mm, FOV = 240 mm, slice thickness = 3 mm). For each experimental run, 200 whole brain volumes were acquired. Acquisition of imaging data began after the fourth volume to permit stabilization of the

magnetic resonance signal. A high-resolution, three-dimensional magnetization-prepared rapid gradient echo sequence (MP-RAGE) was collected for the purposes of coregistration and normalization (186 axial slices, voxel resolution = 1 mm isotropic, acquisition matrix = 256 x 256 mm, TR = 9.184 ms, TE = 3.68 ms, flip angle = 12°, FOV = 256 mm).

Neuroimaging Preprocessing

Data were preprocessed and analyzed using the following software packages: Analysis of Functional Neuroimages (AFNI version 16.3.18; Cox, 1996), FMRIB Software Library (FSL version 5.0.8; Jenkinson et al., 2012), FreeSurfer (FS version 6.0.0; Fischl, 2012), Advanced Normalization Tools (ANTs version 2.1.0; Avants et al., 2008), and Neuroimaging in Python (NiPy version 0.4.0. dev0, Gorgolewski et al., 2016) using a Nipype (version 1.0.0.dev0) pipeline. T1-weighted structural scans underwent cortical surface reconstruction and cortical/subcortical segmentation. Surface reconstruction was visually inspected and errors were manually edited and resubmitted. Functional data were first ‘despiked’ removing and replacing intensity outliers in the functional time series. We then performed simultaneous slice timing and motion correction (Roche, 2011), aligning all functional volumes to the middle volume of the first run. An affine transformation was calculated to co-register functional data to their structural scan. Motion and intensity outlier timepoints (>1 mm frame-wise-displacement; >3 SD mean intensity) were identified. Functional data were spatially filtered with a 5 mm kernel using the *SUSAN* algorithm (FSL), which preserves the underlying structure by only averaging local voxels with similar intensities. The last three volumes of each run were removed to eliminate scanner artifact observed during preprocessing.

Normalization

Anatomical images were skull-stripped and then registered to the MNI-152 template via a rigid body transformation (FSL FLIRT; DOF = 6). This step was used to minimize large differences in position across participants and generate a template close to a commonly used reference. Advanced Normalization Tools (ANTs; Avants et al., 2008) software was used to create a study-specific template to minimize normalization error for any given participant. Each participant's skull-stripped brain was normalized using the non-linear symmetric diffeomorphic mapping implemented by ANTS. The resulting warps were applied to contrast parameter estimates following fixed-effects modeling for subsequent group-level tests.

Task-based fMRI Data Analysis

fMRI data were analyzed using FSL (www.fmrib.ox.ac.uk/fsl) based on principles of the general linear model. We used two separate univariate models at the first-level to evaluate memory-guided conditional behavior. All models included regressors of no interest which consisted of: motion parameters (x, y, z translations; pitch, roll, yaw rotations), the first and second derivatives of the motion parameters, the normalized motion, first, second, and third order Lagrange polynomials, as well as each outlier time-point that exceeded the artifact detection thresholds. In the first model, the regressors of interest consisted of fixed trials that immediately preceded both correct and incorrect conditional trials. All other trial types (e.g., conditional, fixed trials that preceded fixed trials, and fixed trials that preceded baseline trials) were modeled in a single regressor. Contrasts examined differences in activation between fixed trials that preceded correct versus incorrect conditional trials. The second model included regressors of interest for correct and incorrect fixed and conditional trials. The contrast of interest for the second model was differences in activation for correct conditional versus correct fixed trials. Event regressors were convolved with FSL's double gamma hemodynamic

response function with an onset coinciding with the presentation of the stimulus and a duration of 3 seconds. Following the first-level analyses fixed effects analyses across experimental runs were performed for each participant for the respective contrasts of interest. Contrast parameter estimates from the fixed effects analysis were normalized to the study specific template and group-level analyses were performed using the FSL's *randomise* threshold-free cluster enhancement (tfce) one sample t-test ($p < 0.01$).

Task-based Functional Connectivity Analysis

A beta-series correlation method (Rissman et al., 2004) was used for our task-based functional connectivity analysis. We employed a least-squares single (LSS) approach (Mumford et al., 2012) given our fast event-related design. Briefly, a separate general linear model was run for each trial of interest. All first level models included a regressor for the single relevant trial and all remaining task and nuisance regressors with the relevant trial removed from its respective task regressor. Trials of interest were defined by whether they preceded periods of learning or non-learning for conditional trials. The learning state was defined by taking the first derivative of each conditional stimulus learning curve, if the value was positive, indicating an increase in the probability of being correct relative to the previous trial, then that trial was labeled a learning trial. If the value was less than or equal to zero, representing a decrease or no change in performance, then the trial was labeled as a non-learning trial. The fixed trials preceding learning and non-learning conditional trials were separately modeled and constructed into beta-series. *A priori* regions of interest were defined and the average beta-series from each region were correlated with one another. The functional coupling during learning versus non-learning periods was quantified by the degree to which the respective beta-series correlated.

Anatomical Region of Interest

Anatomical regions of interest (ROIs) were defined using each participant's structural scan. The hippocampus, putamen, and pre/primary motor cortex (precentral, paracentral, caudal middle frontal, and opercularis labels) were bilaterally defined by binarizing the segmentations from the FreeSurfer aparc+aseg.mgz files. The medial prefrontal cortex was also bilaterally defined using FreeSurfer segmentation (rostral and caudal anterior cingulate labels). We chose to limit our definition of the mPFC to the anterior-most portion of the anterior cingulate cortex; admittedly, while the ventral medial prefrontal cortex also receives input from the hippocampal formation, this region was not included due to substantial MRI signal drop-out. The dorsolateral prefrontal cortex was defined using the Lausanne Atlas. The dorsal anterior caudate was manually segmented in accordance with anatomical landmarks outlined in the Atlas of the Human Brain (Mai et al., 1997): the appearance and secession of the anterior commissure defined the rostral boundary, while the lateral ventricle served as the medial edge and the internal capsule formed the lateral surface. All masks were back-projected to functional space for analysis.

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Figure 1. Schematic diagram of experiment and behavioral results. (A) Each subject completed a total of 960 trials – comprised of three unique stimulus image sets of 320 trials each. Sets were further divided into two runs of 160 trials: 40 presentations of each trial type per set. (B) Task and baseline trials were identical in structure: participants fixated on a central crosshair for 300 ms. The stimulus was subsequently shown for 500 ms followed by removal and a 700 ms delay, before a “Go!” signal (300 ms) indicated the onset of a 700 ms response window. Feedback was immediately provided for 800 ms. Total trial duration was 3000 ms. (C) Performance curves were calculated for each participant across all image sets, producing a total of 60 unique curves. Performance is defined as the probability of a correct response on the respective trial. Dark red lines represent the average curve for each stimulus type, while the surrounding pink expanse indicate the upper and lower bound 95% confidence intervals. Blue dashed line indicates chance performance of 50%.

Figure 2. Activations preceding correct and incorrect conditional trials. Anatomical regions of interest included the: (A) hippocampus, (B) medial prefrontal cortex (mPFC), (C) dorsal caudate, and (D) putamen. Boxplots with overlaid swarm plots represent the activations for fixed trials preceding correct (corr cond) and incorrect (incorr cond) conditional trials. We observed significantly greater activation in the (A) hippocampus and (D) putamen during fixed trials that preceded correct compared to incorrect conditional trials.

Figure 3. Prospective cortical activations for successful memory-guided conditional behavior. Cortical regions exhibiting greater activation for fixed trials before correct conditional (cond) trials > fixed trials before incorrect conditional (cond) trials following whole-brain exploratory analysis (FWE tfce correct $p < 0.05$). Regions of activation included medial prefrontal cortex (mPFC), posterior cingulate cortex, superior temporal, motor cortex, ventromedial occipital, and the paracentral lobule.

Figure 4. Prospective fixed trial activation correlations with subsequent fixed trial performance. Correlations between preceding fixed trial activation and subsequent fixed trial performance for same (e.g. fixed left → fixed left) and change (e.g. fixed left → fixed right) trial pairs. A trend was observed between activation in the hippocampus and fixed same pairs (A, right), while no significant relationship was observed in the same region for fixed-change pairs (A, left). No significant correlation between prior fixed activation and subsequent fixed

830 performance was found for the (B) medial prefrontal cortex, or (C) dorsal caudate in either
831 change or same pairs. A statistically significant positive correlation was found for the putamen
832 on fixed same pairs (D, right), but not for fixed change pairs (D, left).
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Figure 5. Hippocampus-mPFC functional correlations enhanced during learning.

Boxplots with overlaid swarm-plots represent distributions of correlations for periods of learning and non-learning between anatomically connected regions of interest. Paired-sample t-tests revealed only the hippocampus and medial prefrontal cortex (mPFC) exhibited enhanced correlations as a function of learning. Dorsal lateral prefrontal cortex = dlPFC.

Figure 6. Activations for correct conditional trials compared to correct fixed trials.

Cortical and subcortical regions exhibiting greater activation for correct conditional trials compared to correct fixed trials following a whole-brain exploratory analysis (FWE tfce correct $p < 0.05$). Regions of activation included the bilateral caudate, dorsolateral prefrontal cortex, presupplementary motor area, anterior insula, superior parietal cortex, precuneus, and cerebellum.

Supplementary Figure 1. Fixed trial activations preceding correct and incorrect conditional trials for only correct fixed trials. Anatomical regions of interest included the: (A) hippocampus, (B) medial prefrontal cortex (mPFC), (C) dorsal caudate, and (D) putamen. Boxplots with overlaid swarm plots represent the activations for only correct fixed trials preceding correct (corr cond) and incorrect (incorr cond) conditional trials. Similar to our original analysis we observed significantly greater activation in the (A) hippocampus and (D) putamen during correct fixed trials that preceded correct compared to incorrect conditional trials.

Supplementary Figure 2. Prospective cerebellar

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872 **activations for successful memory-guided conditional behavior.** Regions of the
 873 cerebellum exhibiting greater activation for fixed trials before correct conditional trials > fixed
 874 trials before incorrect conditional trials following whole-brain exploratory analysis (FWE tfce
 875 correct $p < 0.05$).
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 877

Supplementary Figure 3. Prospective conditional

879 **trial activation correlations with subsequent fixed trial performance.** Correlations
 880 between preceding conditional trial activation and subsequent fixed trial performance trial
 881 pairs. No significant correlation between prior conditional activation and subsequent fixed
 882 performance was found for the (A) hippocampus, (B) medial prefrontal cortex, (C) dorsal
 883 caudate, or (D) putamen.
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