Parallel contributions of distinct human memory systems during probabilistic learning

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Regions within the medial temporal lobe and basal ganglia are thought to subserve distinct memory systems underlying declarative and nondeclarative processes, respectively. One question of interest is how these

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in the VTA fire in response to this novel information, releasing

extent of 7 voxels for the observation maps and 8 voxels for the feedback maps (correcting to a cluster level false positive rate of 5%). Last, standard ser the

Bonferroni correction), but no differences were observed for observation performance ($t_{(15)} = 1.04$; $p > 0.05$). As expected, participants' performance in the novel condition did not differ over time ($t_{(15)} = 1.01$; $p > 0.05$).

During the individual test phases, no differences between feedback and observation trials or between easy and hard cues were observed. In the immediate test phase, for example, a 2 (learning type: observation vs. feedback) × 2 (cue difficulty: easy vs. hard) repeated measures ANOVA was performed to examine differences in accuracy between learning types and the level of cue difficulty (excluding the

The same 2 × 2 × 2 repeated measures ANOVA was conducted on the mean BOLD signal from the hippocampus ROI and revealed a trend towards a main effect of learning type ($F_{(1,15)} = 3.36$; ; $p = 0.09$), a main effect of cue difficulty ($F_{(1,15)} = 20.69$; $p < 0.01$), a main effect of time ($F_{(1,15)} = 5.35$; ; $p < 0.05$), and a trend towards a significant interaction between learning type and time ($F_{(1,15)} = 3.76$; ; $p < 0.07$). Post hoc comparisons revealed a nearly significant increase for the feedback hard cues in the hippocampus as learning progressed ($t_{(15)} = 2.38$; $p = 0.03$; trend after sequential Bonferroni correction; Supplementary Fig. 1B).

Learning phase: Main effect of learning type

From the same learning type × cue difficulty ANOVA, a main effect of learning type was examined (Supplementary Table 2). This analysis revealed activation in different regions of the basal ganglia, specifically the right ventral portion of the head of the caudate nucleus (x, y, z = 6, 3, 4) and the left ventral caudate nucleus extending into the globus pallidus (x, y, z = −12, 2, 4; Supplementary Fig. 2). No differences with respect to cue difficulty were observed in these ROIs. At the threshold of $p < 0.005$, no voxels within the hippocampus were observed.

Learning phase: interaction of cue difficulty and learning type

An investigation of the interaction between learning type and cue difficulty from the ANOVA revealed activation in an area of the left medial prefrontal cortex. Post hoc t tests conducted on the mean parameter estimates extracted from this region indicated greater activity for observation easy compared to hard trials ($t_{(15)} = 4.63$; $p < 0.025$); but no differences in difficulty for the feedback trials ($t_{(15)} = 1.26$; $p > 0.05$). The interaction is driven by a greater BOLD response to observation compared to feedback easy cues ($t_{(15)} = 2.72$; $p < 0.025$) and a trend towards a greater response to feedback than observation hard cues ($t_{(15)} = 1.94$; $p = 0.07$).

Test phase

In the test phase, contrasting studied (observation and feedback cues) versus non-studied (novel cues) information was used to identify ROIs involved in memory processes triggered by cue presentation (Supplementary Table 3). This contrast produced one active region within the medial temporal lobe—the parahippocampal gyrus (x, y, z = −21, −40, −8; Supplementary Fig. 3A and B). Post hoc t tests on the mean parameter estimates extracted from the parahippocampal ROI revealed no significant difference between observation and feedback cues ($t_{(15)} = 0.37$; $p > 0.05$). Regions of interest just outside the hippocampus (x, y, z = −24, −22, −5), and the right caudate nucleus (x, y, z = 6, 5, 16) were also observed in this contrast, but did not survive correction at the cluster level.

Correlations within the neuroimaging data

We performed a series of Pearson's correlations to explore the relationship between the caudate nucleus and hippocampus during the learning phase. We observed a significant positive correlation between mean parameter estimates from the caudate nucleus and hippocampus ROIs extracted from the main effect of cue difficulty analysis during the observation learning session ($r = 0.498$, $p = 0.05$) (Supplementary Fig. 4A). While a similar result was not apparent during the feedback session, a trend towards a positive correlation between the caudate nucleus and hippocampus was observed during later stages of feedback learning, specifically during easy cue trials when participants' expectations were violated by the delivery of incorrect feedback ($r = 0.530$, $p = 0.08$) (Supplementary Fig. 4B).

Granger causality analysis

To more effectively assess the level of connectivity between the hippocampus and striatum during probabilistic learning, we conducted a Granger causality analysis. This analysis examined functional connectivity in the brain using the left hippocampus from the main effect of cue difficulty analysis as the principle seed region. The resulting Granger causality maps highlight correlations between the hippocampus (seed region) and regions of the striatum during both feedback and observation probabilistic learning sessions. Specifically, this analysis yielded instantaneous influence between the hippocampus and two regions of the right caudate nucleus during feedback learning (x, y, z = 14, 18, 13) and (x, y, z = 14, 12, 19; not shown), as well as nearly the identical ROIs in the caudate nucleus (x, y, z = 14, 18, 13) and (x, y, z = 14, 10, 18; not shown) and one region of the right ventral putamen during observation learning (x, y, z = 22, 3, −4; not shown) (Fig. 4). The second Granger causality analysis performed as a control using the caudate nucleus as the seed region revealed instantaneous influence between the caudate nucleus and bilateral hippocampal regions during observation learning (x, y, z = −31, −38, −3 and x, y, z = 32, −29, −12; not shown; corrected to a cluster level false positive rate of 5%; Supplementary Fig. 5A) as well as a loci near the right hippocampus during feedback learning (x, y, z = 29, −8, −15; uncorrected for multiple comparisons; Supplementary Fig. 5B).

Prediction error analysis

Midbrain dopaminergic neurons are believed to project to both the striatum and the hippocampus (Lynd-Balta and Haber, 1994; Scatton et al., 1980 interaction may potentially be explained by dopaminergic modulation during reward related learning (Lisman and Grace, 2005; Shohamy et al., 2008) as both BG and MTL ROIs were found to correlate with a prediction error signal, further corroborating the hypothesis that these distinct memory systems interact in a parallel manner while processing probabilistic information to facilitate goal directed behavior.

an uncorrected level should be regarded with caution when interpreting the results due to the increased likelihood of producing a Type I error (Poldrack et al., 2008).

The major differences between the feedback and observation versions of our task were outlined the Materials and methods section. Despite their differences, however, the two learning sessions share the common goal of learning the value of probabilistic cues. Thus, participants may engage in a variety of cognitive strategies in order to facilitate successful performance. As learning progresses over time in the feedback session, for instance, it is possible that participants employ a more declarative based cued recall strategy during the cue phase. Participants may also use verbal rehearsal strategies during the learning phase, irrespective of the task version. Research examining how participants solve another probabilistic learning task, the Weather Prediction Task (WPT), may shed some insight into possible declarative and nondeclarative components of category learning tasks as well as the knowledge that participants may have during these types of learning tasks (Gluck et al., 2002; Meeter et al., 2006). A relatively recent study by Newell et al. (2007) found that participants had comparable declarative knowledge on a feedback and observation version of the WPT. The authors argue therefore, that the feedback version of the WPT may not be an exclusively nondeclarative task. Meeter et al. (2008) have suggested that participants may solve the WPT via engagement of rule-learning, incremental learning (both of which are thought to engage the BG), memorization techniques (MTL dependent), or some combination of these three strategies. Furthermore, Shohamy et al. (2004) suggest that participants most likely recruit multiple parallel learning systems to solve probabilistic categorization tasks. It is quite possible that both observation and feedback versions of our task contain some declarative and nondeclarative components. Therefore, the use of the terms declarative and nondeclarative in this text are meant as a reference, and not meant to suggest the sole manner in which participants may solve the tasks.

The possibility that our tasks contain elements of declarative and nondeclarative learning features may contribute to the main result that the hippocampus and striatum are involved in both feedback and observation learning—primarily being modified by cue difficulty, rather than learning type. It is possible that the involvement of multiple cognitive operations (e.g., cued recall or rehearsal strategies) is facilitating the mutual engagement of these regions, irrespective of learning type. One limitation of the current study is that this possibility cannot be definitively ruled out. Future studies may be able to better parse out the possible contributions that multiple cognitive processes have on these tasks and the subsequent neural signals in the MTL and BG.

The significance of the possibly synergistic interaction between BG and MTL during learning is still unclear. One hypothesis is that these regions cooperate in certain contexts to process new information that is conflicting with previous expectations in order to promote flexible learning and behavior (Packard and McGaugh, 1996). Although our current paradigm does not allow for direct examination of this idea, there is some indirect support from our prediction error analysis. A prediction error occurs when the actual outcome to an event differs from the expected outcome. In our paradigm, both the hippocampus and the striatum were involved in processing this error signal. This corroborates the hypothesis that these regions may be operating in parallel and perhaps interacting with each other in a synergistic manner during situations when learning requires more effort or contains conflicting information. This idea is indirectly supported by a relatively recent human fMRI study examining route recognition in Huntington's disease patients (Voermans et al., 2004). In this study, increases in hippocampus activity were attributed to compensatory mechanisms due to degrading striatal function in patients, leading the authors to postulate a noncompetitive interactive relationship between the BG and MTL during route recognition.

Consideration for the anatomical connectivity between regions in the BG and MTL may also be helpful in determining their functional relationship during learning. One recent hypothesis about interactive communications across the striatum and the hippocampus specifically is that it may be facilitated by interconnections with midbrain dopaminergic neurons (Lisman and Grace, 2005). Dopamine neurons have been consistently linked with reward processing, particularly providing a prediction error signal during reward related learning (Schultz et al., 1997; for review see Schultz, 2002). A component of reinforcement learning models (Barto, 1995; Rescorla and Wagner, 1972), such prediction error signals typically correlate with activity in differences were also apparent. First, only regions within the basal ganglia were modified by a main effect of learning type, while no voxels were identified in the MTL showing such differentiation. Several neuroimaging papers have shown that feedback and reward processing recruit ventromedial regions of the striatum (for review see Delgado, 2007), thus, it is not surprising that this region was recruited more strongly during the feedback learning trials. It may have been expected that the MTL would be selectively modulated by the observation version given previous results (Poldrack et al., 2001); however we did not observe this. While a null result in neuroimaging is not indicative of any particular finding per se and the context and details of our paradigm differ from previous probabilistic learning studies, it is possible that MTL BOLD signals within our paradigm are recruited during both feedback and observation learning–as suggested by the main effect of difficulty analysis–to contribute to overall learning. A second difference which emerged between the hippocampus and caudate nucleus was that the hippocampus showed a main effect of time (early × late learning) during the learning session, whereas caudate nucleus responses were not significant. This effect was driven primarily by activity during feedback learning (primarily for the hard cues), which was greater during late compared to early stages of learning in the hippocampus. This result

during the gradual acquisition and expression of paired-associate memory. J. Neurosci. 25, 5720–5729.

Lee, A.S., Duman, R.S., Pittenger, C., 2008. A double dissociation revealing bidirectional competition between striatum and hippocampus during learning. Proc. Natl Acad. Sci. USA 105, 17163–17168.

Lisman, J.E., Grace, A.A., 2005. The hippocampal-VTA loop: controlling the entry of information into long-term memory. Neuron 46, 703–713.

Lynd-Balta, E., Haber, S.N., 1994. The organization of midbrain projections to the ventral striatum in the primate. Neuroscience 59, 609–623.

Mattfeld, A.T., Stark, C.E., 2010. Striatal and medial temporal lobe functional interactions during visuomotor associative learning. Cereb. Cortex.

McClure, S.M., Berns, G.S., Montague, P.R., 2003. Temporal prediction errors in a passive learning task activate human striatum. Neuron 38, 339–346.

Meeter, M., Myers, C.E., Shohamy, D., Hopkins, R.O., Gluck, M.A., 2006. Strategies in probabilistic categorization: results from a new way of analyzing performance. Learn. Mem. 13, 230–239.

Meeter, M., Radics, G., Myers, C.E., Gluck, M.A., Hopkins, R.O., 2008. Probabilistic categorization: how do normal participants and amnesic patients do it? Neurosci. Biobehav. Rev. 32, 237–248.

Middleton, F.A., Strick, P.L., 2000a. Basal ganglia and cerebellar loops: motor and cognitive circuits. Brain Res. Brain Res. Rev. 31, 236–250.

Middleton, F.A., Strick, P.L., 2000b. Basal ganglia output and cognition: evidence from anatomical, behavioral, and clinical studies. Brain Cogn. 42, 183–200.

Newell, B.R., Lagnado, D.A., Shanks, D.R., 2007. Challenging the role of implicit processes in probabilistic category learning. Psychon. Bull. Rev. 14, 505–511.

O'Doherty, J.P., Dayan, P., Friston, K., Critchley, H., Dolan, R.J., 2003. Temporal difference models and reward-related learning in the human brain. Neuron 38, 329–337.

O'Doherty, J., Dayan, P., Schultz, J., Deichmann, R., Friston, K., Dolan, R.J., 2004. Dissociable roles of ventral and dorsal striatum in instrumental conditioning. Science 304, 452–454.

Packard, M.G., Knowlton, B.J., 2002. Learning and memory functions of the Basal Ganglia. Annu. Rev. Neurosci. 25, 563–593.

Packard, M.G., McGaugh, J.L., 1996. Inactivation of hippocampus or caudate nucleus with lidocaine differentially affects expression of place and response learning. Neurobiol. Learn. Mem. 65, 65–72.

Packard, M.G., White, N.M., 1991. Dissociation of hippocampus and caudate nucleus memory systems by posttraining intracerebral injection of dopamine agonists. Behav. Neurosci. 105, 295–306.

Pagnoni, G., Zink, C.F., Montague, P.R., Berns, G.S., 2002. Activity in human ventral striatum locked to errors of reward prediction. Nat. Neurosci. 5, 97–98.

Pennartz, C.M., Berke, J.D., Graybiel, A.M., Ito, R., Lansink, C.S., van der Meer, M., Redish, A.D., Smith, K.S., Voorn, P., 2009. Corticostriatal interactions during learning, memory processing, and decision making. J. Neurosci. 29, 12831–12838.

Ploghaus, A., Tracey, I., Clare, S., Gati, J.S., Rawlins, J.N., Matthews, P.M., 2000. Learning about pain: the neural substrate of the prediction error for aversive events. Proc. Natl Acad. Sci. USA 97, 9281–9286.

Poldrack, R.A., Packard, M.G., 2003. Competition among multiple memory systems: converging evidence from animal and human brain studies. Neuropsychologia 41, 245–251.

Poldrack, R.A., Clark, J., Pare-Blagoev, E.J., Shohamy, D., Creso Moyano, J., Myers, C., Gluck, M.A., 2001. Interactive memory systems in the human brain. Nature 414, 546–550.