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Contributions of the hippocampus and the striatum to simple association and frequency-based learning

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Using fMRI and a learning paradigm, this study examined the independent contributions of the hippocampus and striatum to simple association and frequency-based learning. We scanned 10 right-handed young adult subjects using a spiral in/out sequence on a GE 3.0 T scanner during performance of the learning paradigm. The paradigm consisted of 2 cues that predicted each of 3 targets with varying probabilities. Simultaneously, we varied the frequency with which each target was presented throughout the task, independent of cue associations. Subjects had shorter response latencies to frequently occurring and highly associated target stimuli and longer response latencies to infrequent target stimuli, indicating learning. Imaging results showed increased caudate activity to infrequent relative to frequent targets and increased hippocampal activity to infrequent relative to frequent cue–target associations. This work provides evidence of different neural mechanisms underlying learning based on simple frequencies versus associations within a single paradigm.

Keywords: Hippocampus; Striatum; Associations; Frequency; Learning

Learning can be described as a continuous reduction in the discrepancy between the predicted and actual outcome of an event (Shultz et al., 1997). This process requires the capacity to detect, process, and flexibly integrate new information into an existing framework as it becomes available. Knowing what to expect and in which context to expect it is critical to planning and maintaining appropriate thoughts and actions in different contexts over time. Adjusting behavior when these expectations are violated is an essential element of cognitive control, aspects of which are present early in life. Simple learning about events in the environment can result from how often an event is encountered or how often it is presented in a particular context or paired with other events. Understanding the neural bases of these types of learning is the objective of this study.

A common measure of learning, used in both human infant and nonhuman animal research, is response to novelty. The theoretical framework (Sokolov, 1963) underlying these novelty-preference paradigms is that attention is oriented more toward novel, relative to familiar, stimuli. A stimulus becomes familiar or learned through repeated exposures, as in the classic habituation paradigm used with infants (Bornstein, 1985). In the current study, we adapted this approach (i.e., response to novelty as an index of learning) to examine cognitive and neural processes underlying simple frequency- and association-based learning. The detection of unpredicted, salient, or novel (infrequent) events has been linked to striatal functioning in imaging and animal studies (Berns et al., 1997; Redgrave et al., 1999; Shultz et al., 1997), whereas the hippocampus has been implicated in the process of learning new associations (Gabrieli et al., 1994; Myers et al., 2003a,b; Poldrack and Packard, 2003; Poldrack et al., 2001; Squire, 1992), contextual learning (Davachi et al., 2003; Matus-Amat et al., 2004), memory for event sequences (e.g., Fortin et al., 2002), and novelty-related processing (Habib et al., 2003; Strange and Dolan, 2001). Of particular interest are studies that show that the hippocampus plays a role in the detection of a novel stimulus when presented in an established context (Halgren et al., 1980; Knight, 1996). Therefore, we hypothesized that novel or infrequently presented stimuli would recruit striatal regions, specifically the caudate nucleus, while infrequently paired associations would recruit the hippocampus.

An assumption of this study is that frequency- and association-based learning can occur simultaneously. In the natural environment, events are often associated with each other, yet each has its own characteristic frequency. Therefore, our design incorporates both variables into the learning structure, careful to ensure that the role of each variable can be independently investigated. Novel events and associations between events are based on relative frequency (i.e., frequent versus infrequent) as opposed to all-or-

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none exposures. This allows us to validly investigate systems supporting the *process* of learning as subjects are repeatedly exposed to frequency and association parameters.

Methods

Participants

Ten healthy right-handed adults were scanned (*M* age = 25 years, 5 females). Three subjects were excluded from the final data set: 1 for excessive motion and 2 for technical problems with behavioral response collection. All subjects were screened for a history of neurological or psychiatric problems and for any contraindications for MRI before participating. Written consent was obtained prior to scanning and subjects were paid for their participation.

Behavioral paradigm

Participants viewed sequentially presented cue and target stimuli. There were 2 cues (a cartoon octopus and turtle) that predicted each of 3 targets (a cartoon orange, yellow, and blue fish) with varying probabilities (see Fig. 1). Participants were required to simply respond to the identity of the presented target by pressing one of three buttons that corresponded to the target identity using their index, middle, and pointer finger of the right hand (e.g., press the index finger for the orange fish). No feedback was given. The stimulus–response correspondence was counterbalanced. Stimulus duration was 1000 ms and the interstimulus interval (ISI) was 3000 ms. Each trial (cue plus target) was 8 s in duration. Cue 1 predicted target 1 75% of the time and predicted targets 2 and 3 25% of the time (approximately 12% each). Cue 2 predicted target 1 and target 2 25% of the time, and target 3 50% of the time. Simultaneously, we varied the frequency with which each target was presented throughout the task, independent of cue–target associations. Frequencies for targets 1, 2, and 3 were 50%, 20%, and 30% across the entire experiment.

Targets 1 and 2 and their associations with cues 1 and 2 provided the opportunity to test behavioral and neural responses to frequent versus infrequent targets (50% and 20%) and frequent versus infrequent cue–target associations (75% and 25%) (see Fig. 2). The frequency manipulation was designed so that frequent and infrequent target stimuli were preceded by and equally associated with the same cue, effectively eliminating the effects of context in the comparison. The association manipulation was such that the target itself was identical in the infrequent and frequent association conditions. Here, the manipulation rested solely on a target's probability of association with the preceding cue, thereby controlling for frequency of the target. Target 3 was included in the paradigm to make numerically possible the probabilities of occurrence and association. Pilot work indicated that behavioral evidence of learning required more exposure to the parameters than could be collected during fMRI acquisition. Therefore, four blocks (40 trials per block) of behavioral data were collected outside the scanner. Five successive blocks were collected in the scanner as fMRI data were acquired.

Image acquisition

Images were acquired using a spiral in/out sequence (Glover and Thomason, 2004) on a G.E. 3.0 T scanner (TR = 2000, TE = 30 ms, flip angle = 90°). A total of twenty-nine coronal slices of 5 mm slice thickness and 0 gap (3.125 × 3.125 mm in-plane resolution) were collected for 168 repetitions (including 8 discarded acquisitions at the onset of each of five runs). Anatomical T2-weighted images (TR = 2000, TE = 68 ms, 5 mm whole brain) were acquired at locations identical to the functional images for localization purposes. One set of high resolution SPGR images (TR = 25, TE = minimum, 1.4 mm slice thickness, 124 slice locations) was collected for 3D localization and morphometric analyses.

We used a rapid mixed trial design (Boynton et al., 1996; Dale and Buckner, 1997). For each trial of interest, two image repetitions were selected, at 4–6 and 6–8 s following stimulus onset. As the events of interest occurred every 8 s, we were unable to examine the temporal dynamics of the hemodynamic response but were able to

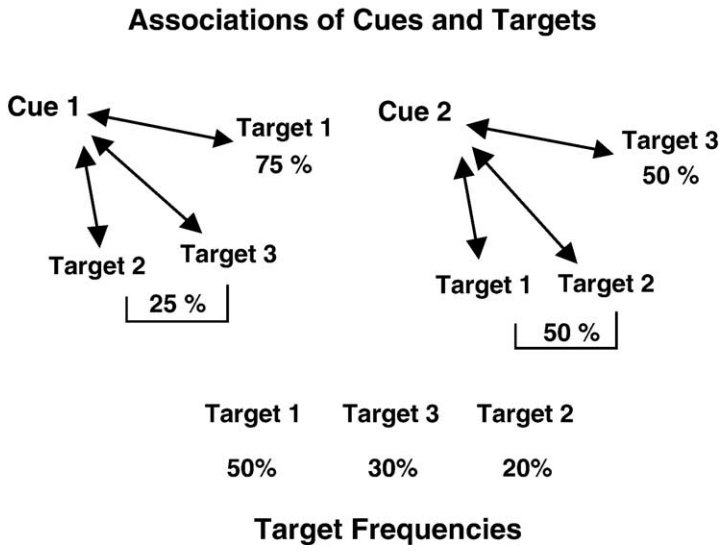

Fig. 1. Illustrates task learning parameters, frequency of target occurrences and frequency of associations between cues and targets.

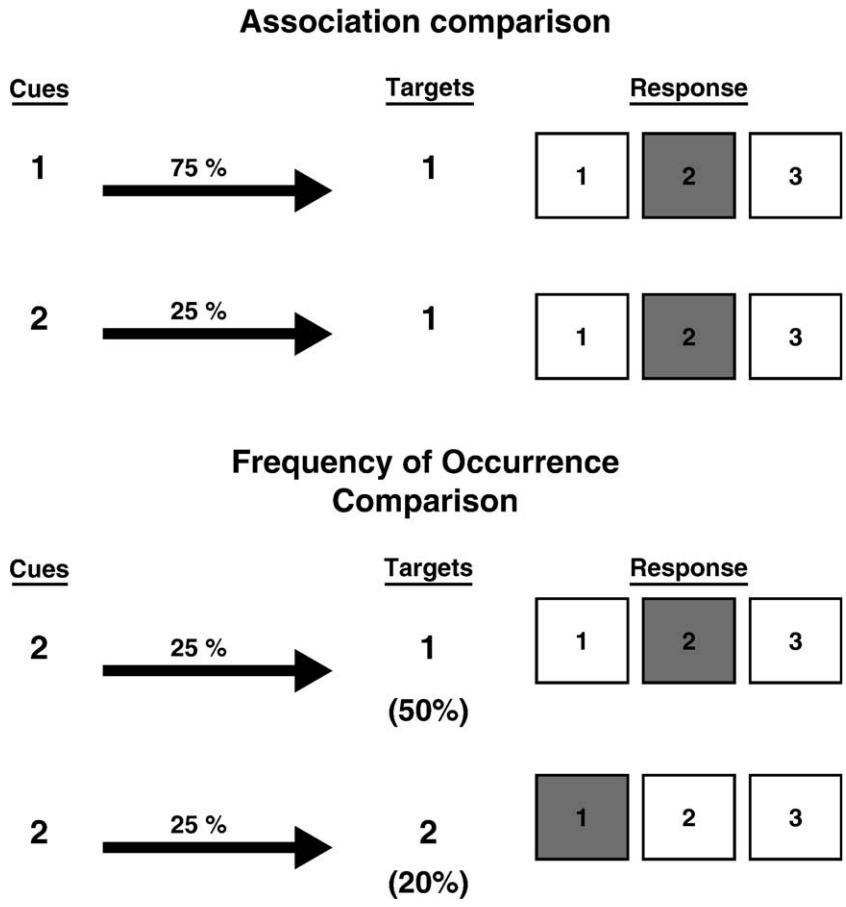

Fig. 2. The frequent target has a higher association with Cue 1 relative to Cue 2 (75% vs. 25%), providing a means of investigating response to the target based on cue–target association. The infrequent (20%) and the frequent (50%) targets are equally associated with Cue 2, allowing us to equate for context and determine regions responsive to frequency of target occurrence during learning.

examine the peak of MR signal change by analyzing the time points occurring between 4 and 8 s following stimulus onset. This estimated peak in the hemodynamic response was based on previous empirical and modeling work showing the peak in MR signal change to occur at approximately 5 to 6 s following stimulation (Boynton et al., 1996; Dale and Buckner, 1997; Davidson et al., 2004; Durston et al., 2002). Selection of these points avoided overlap in the hemodynamic response across trials of interest, given they were presented in a mixed trial rather than a blocked design. Finally, trials of interest were separated by at least 8 s and preceded by the same stimulus type (cues) to effectively equate the level of baseline noise for all comparisons, a procedure validated empirically in primary motor cortex and with modeling by Durston et al. (2002, 2003).

Image processing and analysis

All scans were reconstructed and corrected for motion using the AIR (Automatic Image Registration) version 3.8 program software

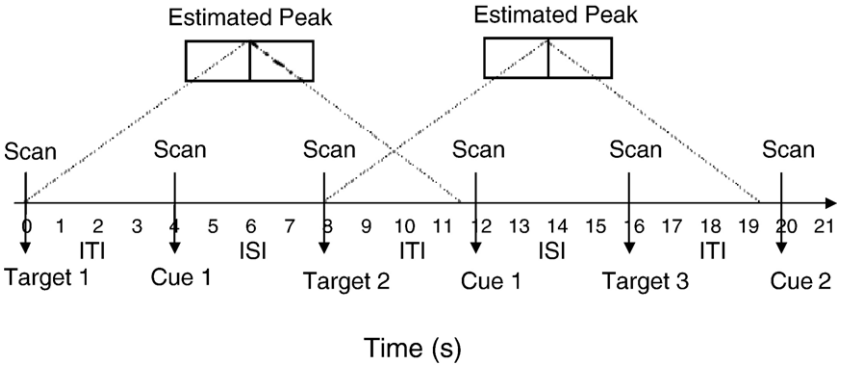

Fig. 3. Illustrates task design, an ongoing stream of alternating cue and target events separated by 3 s intervals (i.e., 8 s between target events, as well as the estimated peak of the BOLD signal every 5–6 s).

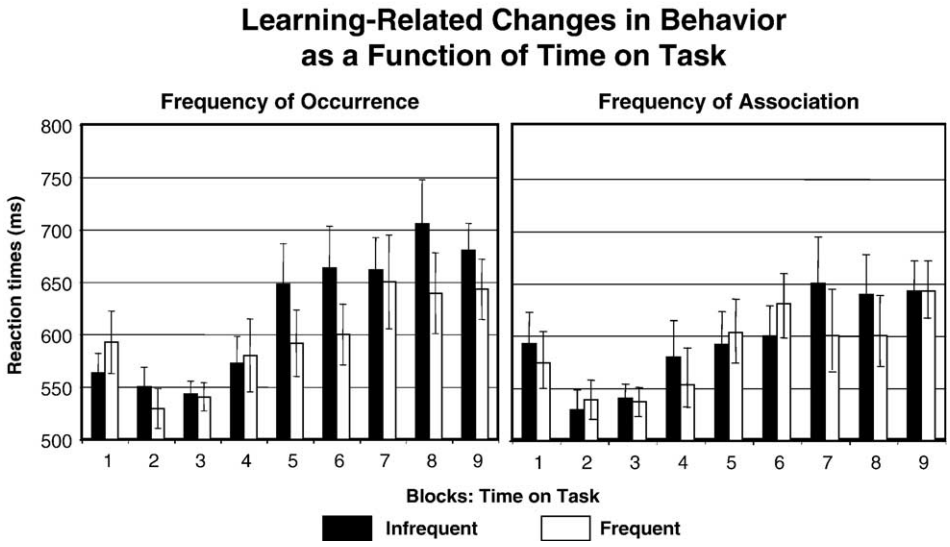

Fig. 4. Mean reaction time differences observed between the frequently and infrequently presented targets. Both the Frequency of Target Occurrence and Frequency of Cue–Target Association comparisons show continued learning as the task progresses. Response times to the infrequently presented relative to the frequently presented targets increase as probabilities of occurrence and association are learned over time on task.

(e.g. Woods et al., 1993). A sample representative brain (male subject with average brain size and good orientation) was selected for co-registration and spatial alignment. Each subject's functional data were then normalized and spatially smoothed with a FWHM distribution of 8 mm. The representative brain and functional data sets were brought into Tailarach coordinate space by conventional landmarks using AFNI version 2.50 (e.g., Cox, 1996). Previous research indicates that the hemodynamic response peaks at 5 to 6 s post stimulus presentation. Therefore, scans acquired at 4–6 and 6–8 s following stimulus presentation were analyzed (see Fig. 3) in order to maximize measurement of MR signal change at the peak of the hemodynamic response. Only correct trials were analyzed. Approximately 50 data points per subject per condition were included in an analysis of variance (ANOVA) testing frequency of target occurrence and association conditions. The analyses were conducted with the NeuroImaging Software package version 3.5 (Laboratories for Clinical Cognitive Neuroscience and Neuroscience of Cognitive Control, University of Pittsburgh and Princeton University).

Results

Behavioral results

A repeated measures ANOVA comparing all conditions of interest (infrequent and frequent targets and associations) was significant [$F(2, 174) = 8$, $P < 0.001$]. Post hoc analyses identified significant differences in reaction time for the infrequent relative to the frequently presented targets [$t(87) = 2.411$, $P < 0.05$], but not for infrequent relative to frequent associations [$t(87) = 1.382$, $P > 0.05$] when averaged across the entire experiment. To understand learning-related changes over the duration of the task, we calculated raw difference (infrequent minus frequent) scores to measure

Table 1a
Regions of activity in the frequency of target occurrence manipulation: Novel > Frequent

Region	Cluster Size (voxels)	Average *F*	Maximum *F*	Tailarach			Broadmann Area
				x	*y*	*z*	
L Anterior Insula	10	9.05	15.7	40	12	5	44
L Inferior Parietal Lobule	39	11.11	32.19	42	−32	48	40
L Superior Parietal Lobule (LPS/LPI)	32	11.49	21.61	36	−39	54	7/40
L/R Caudate	7	7.55	10.08	0	−1	18	
L Postcentral Gyrus	31	9.69	17.67	42	−20	46	1/2
R LPS	21	11.11	19.56	−5	−61	59	7
R Premotor	23	12.07	19.99	−34	−9	60	6/4
R Superior Frontal Gyrus	14	10.05	30.34	12	−21	14	
R Inferior Frontal Gyrus	5	11.02	17.74	−34	21	6	47/45
R Middle Frontal Gyrus (GFI/GFM)	9	9.48	24.63	53	31	7	47/45
R Postcentral Gyrus	24	8.83	15.06	−71	−15	32	1/2
R Cerebellum	10	10.2	29.16	−30	−41	−34	

Table 1b
Regions of activity in the frequency of target occurrence manipulation: Frequent > Novel

Region	Cluster Size (voxels)	Average F	Maximum F	Tailarach			Broadmann Area
				x	y	z	
L Middle Temporal Gyrus (GTM)	24	11.96	26.72	63	−58	18	37
L Superior Temporal Gyrus	21	10.63	17.85	62	−45	21	22
L Insula/IFG	6	9.2	12.9	34	−9	5	44
L Lateral Sulcus	21	9.38	19.11	61	−39	22	40/22
R Fusiform Gyrus	8	9.76	16.79	−34	−23	−18	20
R Parahippocampal Gyrus (GF/GH)	5	8.1	11.18	−36	−24	−18	20/36

potential changes in behavior during learning. Separate scores were calculated for the Frequency of Target Occurrence and Frequency of Cue–Target Association manipulations per block for each subject. The behavioral data were entered into a linear regression analysis as coefficients with Time on Task as the dependent variable. The regression analysis was significant [$F(2,85) = 4.820$, $P = .01$], with learning based on *both* Frequency of Target Occurrence [$t = 3.025$, $P < 0.01$] and Cue–Target Association [$t = 2.163$, $P < 0.05$] as reliable predictors of Time on Task (see Fig. 4). The effect size for the Frequency of Target Occurrence manipulation [beta = 0.363] was larger than the Frequency of Cue–Target Association manipulation [beta = 0.260].

Imaging results

A voxelwise 10 (Subject) × 2 (Infrequent vs. Frequent Target) ANOVA comparing the infrequent and frequent target conditions was performed to determine regions of activity pertaining to the frequency of target occurrence manipulation. The main effects of Condition are shown in Table 1 ($P < 0.05$ with at least 5 contiguous voxels). Of specific interest is the caudate activity. Subsequent time-series analyses showed that this region was more engaged in the detection of infrequent relative to frequent target events [$t(9) = 2.90$, $P < 0.05$]. In order to test for the effects of cue–target association, we ran a separate voxelwise 10 (Subject) by 2 (Infrequent vs. Frequent Association) ANOVA. We found significant left hippocampal activity in this comparison, but no caudate activity (see Table 2). A subsequent time-series analysis showed greater hippocampal activity to the infrequent relative to frequent associations [$t(9) = 3.651$, $P < 0.01$]. To test for changes in MR signal intensity in the hippocampal and striatal regions as a function of learning, we conducted a linear regression analysis with Time on Task as the independent variable. The regression analysis was significant [$F(2,47) = 3.189$, $P = .05$], with hippocampal [$t = -2.392$, $P < 0.05$] but not striatal signal change values [$t = -0.705$, $P > 0.05$] obtaining as reliable predictors of Time on Task (see Fig. 5). Hippocampal activity decreased as function of Time on Task. Finally, we tested the association between behavioral and MR signal change across learning. For each time-series comparison, both a percent difference in fMRI signal change and percent difference in reaction time between frequent and infrequent events were calculated. This analysis showed a significant negative correlation with behavior [$r = -0.916$, $P < 0.05$] for the left hippocampus but no significant correlations for the caudate, perhaps due to significant learning prior to scanning.

General discussion

We examined neural mechanisms underlying simple frequency- and association-based learning. We provided evidence that the hippocampus, specifically the left hippocampus, was recruited for infrequent relative to frequent cue–target associations, while the caudate nucleus was recruited for infrequent relative to frequent target occurrences. Using response to novelty as an index of learning, we investigated the behavioral and neural systems underlying learning of sequential information. Our behavioral data suggest, perhaps not surprisingly, that simple frequency learning takes place earlier than does learning associations, with associations learned more slowly. Over time, reaction times to frequently occurring stimuli and frequently associated stimuli decreased relative to infrequent stimuli and associations. The reaction time differences observed between the frequent and infrequent stimuli were driven mainly by slower responses to the infrequent as opposed to faster responses to frequent targets. Thus, the response to novelty (longer responses torelatively infrequent stimuli) served as an index of the extent of learning.

In the current study, decisions or reaction times were biased in favor of faster responses to frequently occurring events and longer responses to rare ones. This bias was shown both behaviorally and neurally within the striatum. The most frequently occurring target was directly compared with the least frequent target, with both preceded by and equally associated with the same cue. The unexpected target resulted in striatal recruitment, specifically caudate, supporting the hypothesis that this region may signal a prediction error between expected and actual events (e.g.,

Table 2a
Regions of activity in the frequency of association manipulation: Novel > Frequent

Region	Cluster Size (voxels)	Average F	Maximum F	Tailarach			Broadmann Area
				x	y	z	
L Cerebellum	22	9.05	17.76	24	−49	−20	
L Inferior Temporal Gyrus	32	8.33	17.91	33	−71	1	37/19
Left Hippocampus	6	8.27	14.96	30	−6	22	
L Insula/GFI	7	8.4	11.34	22	11	−1	44
R Inferior Frontal Gyrus	18	10.31	24.06	−22	17	−27	4

Table 2b
Regions of activity in the frequency of association manipulation: Frequent > Novel

Region	Cluster Size (voxels)	Average *F*	Maximum *F*	Tailarach			Broadmann Area
				x	*y*	*z*	
L Superior Frontal Gyrus	10	8.08	11.39	2	25	2	6/8
L Middle Frontal Gyrus	11	9.75	15.56	24	8	46	6
L Lateral Sulcus	16	11.29	19.42	63	−52	22	40/22
R Pretcentral Gyrus	12	9.46	17.9	−30	−20	62	4
R Putamen	13	7.87	16.12	−25	−28	11	
L/R Cingulate Gyrus	53	16.18	76.35	−5	−36	29	40
R Superior Frontal Gyrus	8	11.45	16.91	−29	−17	61	4
R Central Sulcus	14	8.2	13.22	−22	−25	45	3/4

Montague et al., 1996; Shultz et al., 1997) or perhaps is generally responsive to salient events (e.g., Horvitz, 2000; Redgrave et al., 1999). These data are consistent with detection of violations of expectancy paradigms (Casey et al., 2000; Davidson et al., 2004), where an increase in striatal activity accompanied the presentation of an unexpected stimulus (Casey et al., 2000) and a decrease in activity accompanied the omission of an expected stimulus (Davidson et al., 2004). Taken together, these results suggest a role for the striatum in learning by detecting violations in the frequency of event occurrence, potentially providing signals for adaptive modifications in behavior. This finding is consistent with previous work (Casey et al., 2000; Mink, 1996) showing that the striatum is involved in slowing the execution of motor and cognitive commands by suppressing those responses that are in competition with the most salient response. The pattern of striatal activity to the frequency manipulation was specific to the caudate nucleus rather than the putamen. Specifically, caudate activity coincided with inferior frontal activity for the infrequent target condition, while putamen activity coincided with motor cortex activity for the cue-association condition. The recruitment of the putamen (motor cortex projection) appears to reflect motor preparation as the subject learned to associate a particular response with a cue, as evidenced by faster reaction times for these trials.

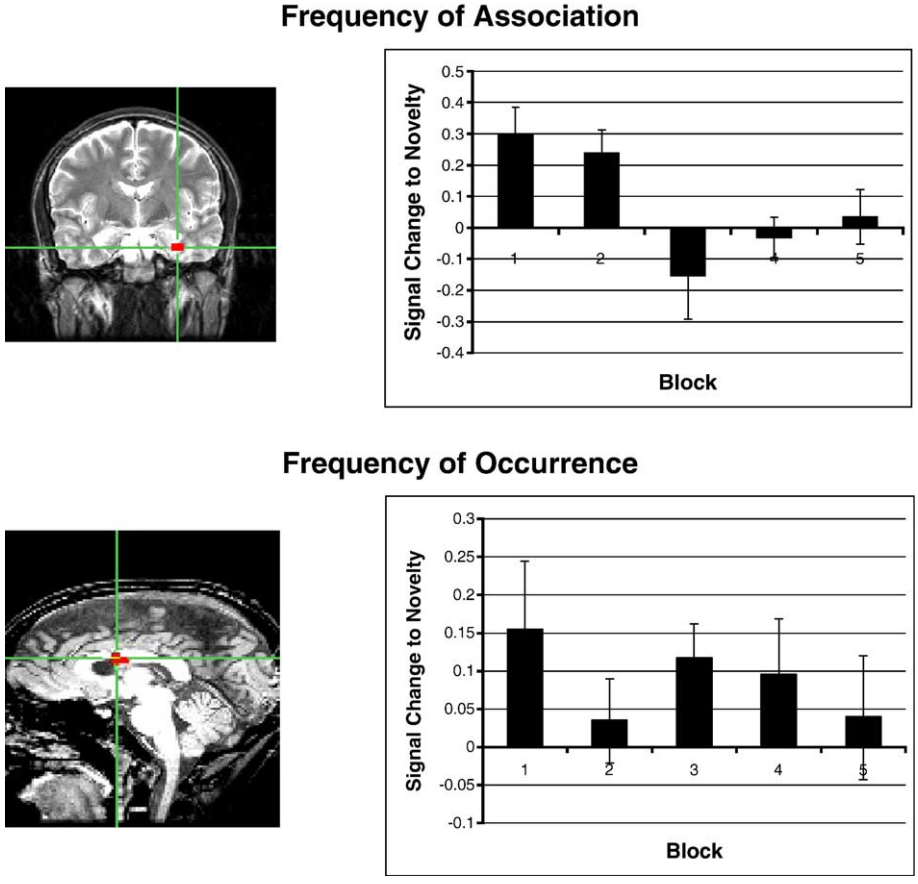

Fig. 5. Illustrates significant ROIs for each comparison as well as signal changes to novelty during learning.

Hippocampal activity during the learning of cue–target associations supports models that stress the role of the hippocampus in relational or configural processing, i.e., binding together into one memory, multiple features of an experience (Cohen et al., 1997; Eichenbaum, 2000; O'Reilly and Rudy, 2001). The same target was preceded by two different cues, one with which it was highly associated and one with which it had a more novel or less frequent association. The hippocampus was preferentially active to the infrequent association, suggesting involvement in learning of new associations or linking a cue with a novel target.

The hippocampal activity in the frequency of cue–target association manipulation showed an adaptive habituating response that correlated negatively with behavior. Specifically, there was less hippocampal recruitment as the association became less novel with continued repetition over the length of the task. Behaviorally, reaction times to infrequent cue–target associations showed an increased cost (longer response latencies), providing evidence of learning about cue–target associations. This habituating response to novelty replicates previous work on the hippocampus (Clark et al., 2000; Strange and Dolan, 2001). It has even been suggested (Yamaguchi et al., 2004) that hippocampal, together with prefrontal, activity is critical for the orienting response (Sokolov, 1963). We were able to extend this work by investigating the change in hippocampal activity to more novel presentations over the course of learning a true environmental structure. There was no evidence of habituation in the caudate nucleus over this task, consistent with recent imaging studies (e.g., Yamaguchi et al., 2004).

The current work suggests that, when learning about simultaneous but independent frequency and associations of events (i.e, each target had its own frequency and a separate association with a cue), the striatum and hippocampus play independent roles. There was no reliable hippocampal activity in the frequency of occurrence manipulation and no striatal activity for the cue–target association comparison. This finding is consistent with previous empirical and theoretical work (Atallah et al., 2004; Casey et al., 2002) showing independent contributions of these regions in different aspects of learning. Our findings are also consistent with neuropsychological and imaging results suggesting that medial temporal and basal ganglia structures play complementary or independent roles during learning (e.g., Myers et al., 2003a,b), but not competitive roles as there was no evidence of deactivation of these regions or an inverse correlation in the pattern of activity of these regions (Poldrack and Packard, 2003; Poldrack et al., 2001).

The current behavioral and imaging findings are interesting in light of the developmental work using novelty preferences and looking time measures as evidence of learning. Infants must be able to sort environmental input into some representation that mirrors environmental structure. Adaptively, this would allow them to maneuver through the environment, represent objects in their absence, etc. In fact, there is evidence that much of learning in infancy is based on detection of environmental structure. Studies of language development (Saffran et al., 1996), auditory sequence learning (Saffran et al., 1999), and visual sequence learning (Kirkham et al., 2002) all suggest that infants can learn simple statistics and probabilities from environmental inputs. This learning necessarily involves the detection and flexible integration of novel information as it becomes available. Frequency of occurrence of an event strengthens its representation, leading to learned expectations and predictions about that event. Associations between events establish predictions regarding contexts in which to expect an event. These are parameters that are often simultaneously learned in the natural environment. We suggest that systems that are intact early in development may support such learning.

Acknowledgments

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