Published in final edited form as:
Neuroimage. 2012 January 2; 59(1): 695–707. doi:10.1016/j.neuroimage.2011.07.027.

Fear-relevant outcomes modulate the neural correlates of probabilistic classification learning

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Abstract

Although much work has implicated the contributions of frontostriatal and medial temporal lobe (MTL) systems during probabilistic classification learning, the impact of emotion on these learning circuits is unknown. We used a modified version of the weather prediction task in which two participant groups were scanned with identical neutral cue cards probabilistically linked to either emotional (snake/spider) or neutral (mushroom/flower) outcomes. Owing to the differences in visual information shown as outcomes, analyses were restricted to the cue phase of the trials. Learning rates did not differ between the two groups, although the Emotional group was more likely to use complex strategies and to respond more slowly during initial learning. The Emotional group had reduced frontostriatal and MTL activation relative to the Neutral group, especially for participants who scored higher on snake/spider phobia questionnaires. Accurate performance was more tied to medial prefrontal activity in the Emotional group early in training, and to MTL activity in the Neutral group later in training. Trial-by-trial fluctuations in functional connectivity between the caudate and MTL were also reduced in the Emotional group compared to the Neutral group. Across groups, reaction time indexed a switch in learning systems, with faster trials mediated by the caudate and slower trials mediated by the MTL and frontal lobe. The extent to which the caudate was activated early in training predicted later performance improvements. These results reveal insights into how emotional outcomes modulate procedural learning systems, and the dynamics of MTL-striatal engagement across training trials.

Keywords

functional magnetic resonance imaging; emotion; fear; procedural memory; probabilistic learning; striatum; medial temporal lobe

1. Introduction

Recent advances in the neuroscience of emotional memory have been made by investigating how emotional stimuli modulate declarative memory systems and by revealing the mechanisms of conditioned emotional learning (for a review see LaBar and Cabeza, 2006). However, much less is known about the impact of emotion on the neural systems supporting procedural or habit learning, in which cognitive or motor task performance improves gradually with feedback and practice. One influential paradigm for investigating cognitive

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aspects of procedural learning is probabilistic classification learning (PCL). In a typical PCL task, subjects predict potential outcomes based on the information provided by cues shown on a given trial. For instance, in the weather prediction task (Knowlton et al., 1996; Knowlton et al., 1994), subjects are shown combinations of 1 to 3 cue cards (out of 4 total) that are probabilistically associated with a binary outcome (rain/shine), and they learn what the classifications are through performance feedback on a trial-by-trial basis. In these tasks, performance improvement from chance levels is dependent on the integrity of the striatum, as evidenced by impaired performance in Parkinson's disease patients (Knowlton et al., 1996). Functional magnetic resonance imaging (fMRI) studies have consistently associated striatal regions, in particular the caudate nucleus, with feedback-based learning in PCL and related tasks (Aron et al., 2004; Poldrack et al., 2001; Shohamy et al., 2004; Tricomi et al., 2006; Tricomi et al., 2004).

Although the caudate is likely to mediate important aspects of learning, neuroimaging studies have suggested interactions between MTL and/or frontal regions and the striatum during the learning process (Moody et al., 2004; Poldrack et al., 2001). Task performance in Parkinson’s disease patients may be improved by recruiting these additional learning circuits. Indeed, an fMRI study of mild Parkinson’s patients showed that successful performance recruited prefrontal and medial temporal lobe (MTL) activation while left caudate activation was reduced (Moody et al., 2004). Although the MTL is implicated in fMRI studies of PCL learning (Foerde et al., 2006; Poldrack et al., 2001), evidence from amnesic patients performing PCL tasks is equivocal. One study reports no deficits relative to controls (Reber et al., 1996) with another study reporting deficits only later in learning (Knowlton et al., 1994) and a third study reporting deficits throughout the course of learning (Hopkins et al., 2004). Differences in task difficulty, patient age, and etiology of amnesia may account for these disparate findings. These studies suggest that the MTL is likely to contribute to the PCL task itself (perhaps without an impact on performance) but may provide additional benefits in later learning or in the transfer of learned contingencies to new situations.

A mechanism proposed in several studies is that the MTL facilitates flexible or conceptual knowledge about the learned task that is expressed in transfer tasks (Bayley et al., 2005; Foerde et al., 2006; Kumaran et al., 2009; Reber et al., 1996). For example, Bayley et al. found that amnesics could successfully learn (over several weeks) a specific object discrimination task. Despite similar performance on the original learned task, only control subjects could apply their knowledge to a modified version of the task. They conclude that without the function of the MTL, a slower acquisition of knowledge, mediated by the basal ganglia in the form of habit memory can support task performance, but the information acquired is rigidly organized. Together, the existing findings suggest that while the striatum provides a critical contribution to the rigid learning aspects of feedback-based tasks, other regions, including the MTL, facilitate flexible learning that can be applied in other contexts.

Emotional stimuli have the capacity to alter both attention and memory (Anderson, 2005; LaBar and Cabeza, 2006) and typically enhance declarative memory and MTL activation (Dolcos et al., 2004, 2005; Kensinger and Corkin, 2004). Survival is likely to benefit from both enhanced memory for emotional information as well as prediction of emotional outcomes based on environmental contingencies, to the extent that these effects can guide future behavior. In other cases, however, the presence of emotional stimuli can be a potent distraction and interfere with brain regions subserving ongoing tasks (Dolcos and McCarthy, 2006; Morey et al., 2009; Wang et al., 2008). In the context of nondeclarative memory, task-irrelevant emotional stimuli interspersed within an ongoing PCL task have been found to interfere with immediate task performance (Steidl et al., 2006). In a behavioral PCL study with emotional and neutral outcomes (Thomas and LaBar, 2008), we found a deficit in early

learning in fearful subjects (those with high scores on phobia questionnaires) who were shown fear-relevant outcomes, but not in fearful subjects shown neutral outcomes. Control subjects showed no such impairment with fear-relevant outcomes. Fear-relevant outcomes also promoted the use of complex strategies on the task.

The present study was designed to investigate brain activation during a PCL task with fear-relevant (snakes or spiders) or neutral (mushrooms or flowers) outcomes. Fear-relevant stimuli were used because they may provide a model for understanding habit learning in anxiety disorders. Prediction of outcomes in PCL tasks has been linked to nondeclarative as well as declarative memory processes (Poldrack et al., 2001). Based on the prior literature, *a priori* regions of interest (ROIs) included the striatum (bilateral caudate and putamen) and MTL (bilateral amygdala, hippocampus, parahippocampal gyrus including the entorhinal and perirhinal cortex). The modulation hypothesis (McGaugh, 2004) predicts that emotionally arousing experiences modulate memory. In human studies, performance on declarative tasks has been shown to benefit memory for emotional information (Dolcos et al., 2004, 2005). Performance benefits on nondeclarative tasks might not be reflected in terms of overall accuracy. Indeed, we predicted equivalent accuracy levels for subjects assigned to emotional and neutral outcome conditions, based on results from our prior behavioral study using the same design (Thomas and LaBar, 2008). Nonetheless, the neural mechanisms underlying learning are hypothesized to be modulated by the presence of emotional outcomes. Furthermore, individual differences in fear-relevancy are hypothesized to modulate MTL and striatal learning-related activity.

Because previous classification learning studies have suggested that cognitive and neural mechanisms differ between early and late learning (Knowlton et al., 1994; Poldrack et al., 2001), we were particularly interested in investigating group activation differences as a function of learning stage and changes in brain activation over time. Prior research has suggested that the contribution of striatal and MTL mechanisms change over the course of learning, with hippocampal activity emerging early and dissipating over time whereas the striatum shows the opposite pattern, perhaps reflecting the relative degrees of declarative and procedural learning processes engaged through competitive interactions (Poldrack et al., 2001; Poldrack and Packard, 2003). We were interested in tackling this issue from another angle by using RT as a proxy for the relative amount of deliberative processing engaged on a trial-by-trial basis. Thus we predicted that MTL activity would be stronger on long RT trials whereas striatal activity would be stronger on short RT trials, reflecting the relative weighting of these regions in extracting underlying contingencies versus more automatic expression of learned relationships. Finally, we used activation in these ROIs during early learning to predict the magnitude of performance improvement later in learning. It would be reasonable to speculate that both the MTL and striatum may set the stage for improved learning over time. However, a previous fMRI study that analyzed the cue portion of probabilistic classification trials reported high levels of caudate activation early in learning that were reduced later, once learning had occurred (Delgado et al., 2005). We therefore speculated that caudate nucleus activation early in learning may predict improvement later in learning.

2. Methods

2.1 Subjects

Participants were local residents recruited through the Brain Imaging and Analysis Center at Duke University Medical Center and were reimbursed at the rate of $20/hr. The Institutional Review Board at Duke University approved the experimental protocol and human subjects procedures. A total of 43 subjects provided informed written consent to participate in this study and were randomly assigned to either the Emotional or Neutral group. A between-

groups design was necessary to employ because of strong practice effects with probabilistic classification learning and because a single, binary choice task across emotional and neutral outcomes would be uninterpretable (due to the probabilistic structure, all cue cards would be associated to some degree with both emotional and neutral outcomes) (Thomas & LaBar, 2008). All participants were screened by a self-report questionnaire for history of neurologic and psychiatric illness, substance abuse, current psychotropic medication use, and for depression by the Beck Depression Inventory (Beck et al., 1996). No subject scored within 2 *SD*'s of the phobic norms on questionnaires assessing attitudes towards snakes and spiders (Klorman et al., 1974). Following Aron et al. (2004), individuals who did not score above chance after the first 50 trials were not included in the final analyses ('non-learners', 8 from the Emotional group, 7 from the Neutral group). To ensure that the groups did not differ on other emotional characteristics, questionnaires were administered assessing emotional experience (Positive and Negative Affect Schedule; (Watson et al., 1988)), affect intensity (Affect Intensity Measure; Larsen, 1984), and current stress levels (Daily Stress Inventory; Brantley & Jones, 1993), which showed no differences between groups (all F's < 2.0). Data from 3 subjects were discarded because of MRI signal problems, leaving 12 subjects in the emotional condition (M_{age} = 22.1, 7 female) and 13 subjects in the neutral condition (M_{age} = 23.0, 3 female). Age was not significantly different between groups ($t(23) = -0.6$, $p = .55$). A chi-square test showed that the gender balance was not significantly different across groups (Fisher's exact $p = .11$). Due to the small sample size, gender was not probed further in the analyses.

2.2 Stimuli

The card cue and outcome stimuli are the same as described in our previous behavioral study (Thomas and LaBar, 2008). Briefly, each card cue contained a unique shape (square, diamond, circle, circle with arrow in center) arranged in a 5×3 grid of rows and columns. Auditory feedback (described below) and visual feedback followed the response to the cue. Visual feedback consisted of viewing one of six exemplars from each category; different exemplars were used in order to minimize habituation effects over the 100 training trials. Low-level visual properties of the pictures were equated across the exemplars. Subjects in the emotional condition saw snakes and spiders whereas subjects in the neutral condition saw mushrooms and flowers. Pictures were selected based on normative values (Lang et al., 1997) to be of lower valence for the emotional condition than the neutral condition. Valence ratings were provided following the experiment (unavailable from 1 subject in each condition) and there were no significant differences within groups between the specific stimulus categories used (snakes versus spiders, $t(10) = 1.24$, $p = .24$, or mushrooms versus flowers $t(11) = 0.99$, $p = .34$).

2.3 Study Design

The task design was modeled after that used by Aron et al. (2004) (Figure 1). Between one and three (out of four) cue cards appeared on the screen at a time, comprising 14 possible cue patterns. These patterns were associated with two outcome categories in a probabilistic manner. For example, one pattern had cue cards 2, 3, and 4 present, and appeared 4 times (4% of the total trials). The probability that outcome A occurred with this pattern was 75%, whereas the probability that outcome B occurred was 25%. Since outcome A occurred over 50% of the time, this outcome was considered 'correct'. Participants were randomly assigned to receive either the fear-relevant (snake/ spider) or neutral (flower/ mushroom) outcomes. Participants completed two runs of 50 trials each.

On each trial, one of the 14 card patterns appeared and remained on the screen for 4 sec, at which time the subject was prompted to respond with a left button press for outcome A and a right button press for outcome B. Participants then heard a high-frequency feedback tone

(duration = 1000 msec) when they predicted the trial outcome and four 100 msec bursts of white noise at 80 db when they did not predict the trial outcome (Knowlton et al., 1996; Shohamy et al., 2004; Aron et al., 2004). Similar to Thomas and LaBar (2008), the outcome photo was displayed in a dynamic fashion, first appearing small in the center of the screen for 200 msec and then appearing at full screen for 800 msec to create a looming effect toward the viewer. This was done in order to increase the emotional impact of the outcome. Following outcome presentation, there was a jittered 2–5 sec fixation screen inter-trial interval (Figure 1). The first 25 trials were pseudo-randomized such that an equal number of patterns appeared that were 'easy' (highly predictive) or 'hard' (less predictive). This procedure was conducted to reduce the number of non-learners, as indicated by pilot testing. The following 75 trials were fully randomized.

2.4 Procedure

Before scanning, subjects briefly practiced 5 random PCL trials to familiarize them with the task requirements. Instructions appeared on the screen prior to the practice trials. After the instructions, structural MRI scans were obtained. Then the two functional scans were run (50 trials each, 10.5 min duration maximum per run), with a short break between scans. Subjects used right index and middle fingers to press buttons on the MR-compatible button box.

2.5 MRI Acquisition

Scanning was performed on a General Electric 4T LX Nvi MRI scanner system equipped with 41 mT/m gradients (General Electric, Waukesha, Wisconsin, USA). Scanner noise was reduced with earplugs, and head motion was reduced with foam pads. Stimuli were presented with liquid-crystal display goggles (Resonance Technology, Northridge, CA), and behavioral responses were recorded with a four-key fiber-optic response box (Resonance Technology). A quadrature birdcage radio frequency (RF) head coil was used to transmit and receive. Sixty-eight high-resolution structural images were acquired using a 3D fast SPGR pulse sequence (TR = 500 ms; TE = 20 ms; FOV = 24 cm; image matrix = 256^2; voxel size = 1 mm × 1 mm × 1.9 mm). These structural images were acquired in the near axial plane defined by the anterior and posterior commissures. Whole brain functional images were acquired using a gradient-recalled inward spiral pulse sequence sensitive to blood oxygenation level dependent (BOLD) contrast (TR = 2000 ms; TE = 31 ms; FOV = 24 cm; image matrix = 64^2; $\alpha = 60°$; voxel size = 3.75 × 3.75 × 3.8 mm; 34 contiguous axial slices). This protocol is effective at reducing MRI-induced signal artifacts in frontolimbic regions at high field strength. These functional images were acquired in a similar orientation to the structural images. A semi-automated high-order shimming program ensured global field homogeneity. Runs consisted of the acquisition of 310 brain volumes and began with 4 discarded RF excitations to allow for steady state equilibrium.

2.6 fMRI Data Analysis

Statistical Parametric Mapping (SPM5, http://www.fil.ion.ucl.ac.uk/spm/software/) was used for preprocessing and analysis. The images were realigned and spatially smoothed using an 8-mm full-width half-maximum Gaussian kernel. Translational movement parameters never exceeded 0.5 of a voxel in any subject per run. A nonlinear high-pass filter with a 128-s cut-off was used to temporally filter the data. A twelve-step affine linear transformation procedure was used and functional images were registered to standard Montreal Neurologic Institute (MNI) space.

After preprocessing, statistical analyses were performed at the single-subject level by using the general linear model within SPM. Each cue card presentation was modeled as an impulse convolved with a canonical hemodynamic response function (HRF). Feedback was modeled

separately from the cue. The inter-trial interval, which was not explicitly modeled, served as an intrinsic baseline. Specific comparisons of interest were tested by using linear contrasts. After analysis at the individual level, the results were spatially normalized to the MNI template using SPM's registration tool for group effect analyses. Mixed-effects group analyses were performed for each contrast by using SPM random effects with factorial designs and regression with individual difference measures. Anatomical ROIs were investigated using the Wake Forest University PickAtlas (Maldjian et al., 2003; Tzourio-Mazoyer et al., 2002). These included the amygdala, hippocampus, parahippocampal gyrus, and putamen and which were selected from the AAL atlas and the caudate nucleus which was selected from the TD brodmann areas+ atlas because of further separation into head, body and tail of the caudate. Functional connectivity analyses used ROIs from the AAL atlas for the caudate and MTL. All analyses were conducted with particular focus on the hypothesis driven ROIs and whole-brain analyses additionally reported for exploratory purposes.

The contrasts reported here include: 1) overall activations and deactivations in early (first 50 trials) and late (last 50 trials) learning runs and differences between Emotional and Neutral group activations; 2) correlation with phobia questionnaire composite score in the Emotional group; 3) correct versus incorrect responses (based on the majority outcome percentage as described in Section 2.3); 4) parametric modulation of reaction time; 5) early learning correlation with performance change; and 6) correlation with average performance. For clusters in our *a priori* areas of interest (MTL, dorsal striatum), we used $p < .05$ family-wise error correction within individual lateralized structures. Whole-brain exploratory analyses were thresholded at $p < .001$ uncorrected, k = 5 voxels. Calculations for spatial extent correction for multiple comparisons were done using the REST AlphaSim utility (www.restfmri.net; toolkit V1.3), which performs simulations in the same manner as the AFNI software version. Alpha levels were computed for each contrast mask with 10000 Monte Carlo simulations, an individual voxel threshold probability of .001, a cluster connection radius of 5, and a 4 mm FWHM smoothness. In all cases, the results of these simulations yielded an $\alpha < .001$ FWE rate. The contrast of correct versus incorrect trials was additionally inclusively masked with the group effect ($p < .05$) that was presumed to be driving the interaction, which is more statistically conservative. For example, Emotional (correct > incorrect) versus Neutral (correct > incorrect) was masked with Emotional (correct > incorrect) to mitigate the potential for incorrect Neutral trials to drive group differences. The parametrically modulated RT contrasts were based on entering a regressor (normalized by SPM) for each subject, for each trial (correct and incorrect), across early and late learning. Random-effects analysis, which included group as a factor were constructed to weight the regressor in the positive direction (+1 for both groups = weighted towards increasing RTs) or negative direction (−1 for both groups = weighted towards decreasing RTs). Functional connectivity analyses were conducted using anatomical masks of the left and right caudate nucleus with MTL substructures bilaterally. Single-trial analysis time-locked to cue card onset was used to extract beta parameter estimate values and compute correlation scores between structures (one score for the first 50 and another for the second 50 trials). These scores were then Fisher-transformed and entered into separate repeated-measures ANOVAs with factors for group (Emotional, Neutral), hemisphere (right, left), learning phase (early, late), and structure (amygdala, hippocampus, parahippocampus).

3. Results

3.1 Behavioral Results

Table 1 lists reaction time, performance information, strategy percentage and performance given strategy used, for both the Emotional and Neutral groups. It also contains the phobic

score (snake, spider, and composite) for the subjects in the Emotional group. Composite phobic score is the index of individual differences in fear-relavancy in this group.

3.1.1 Reaction Time (RT)—RT data (across correct and incorrect trials) were analyzed using a mixed ANOVA with Run (1 or 2) as a within-subjects factor and group (Emotional or Neutral) as a between-subjects factor. There was a significant main effect of run, $F(1, 23) = 8.71$, $p < .01$, with subjects performing faster in Run 2 than Run 1. This was especially true for the Emotional group, $t(11) = -2.80$, $p < .05$ but not the Neutral group, $t(12) = -0.96$, $p = .36$. Correlation analysis with phobic score revealed no significant effects for Run 1, Run 2, or the difference between runs (all $p > 0.87$).

3.1.2 Learning Rate—A mixed ANOVA with run as a within-subjects factor and group as the between-subjects factor revealed no significant effects (all Fs < 1). For both groups, comparing performance to chance level yielded significant effects (all $p < 0.001$) for both Run 1 and Run 2.

3.1.3 Implicit Learning Strategy—Implicit learning strategies were evaluated in a similar manner to a previous behavioral study (Thomas and LaBar, 2008). Briefly, using mathematical models to fit each subject's data, performance was compared to the ideal use of three strategy types (simple, complex, nonidentifiable) which vary in the amount of integrative processing and number of cues used. In particular, simple strategy use encompassed both singleton and one-cue strategies whereas complex strategies included both multimatch and multimax strategies (Lagnado et al., 2006). Separate strategy analyses were conducted for each run in each group. A greater proportion of subjects in the Emotional group used complex vs. simple strategies in both early (75% vs. 25%) and late learning (91.7% vs. 8.3%). In the neutral group, complex vs. simple strategy use was more similar in early learning (54% vs. 39%, 1 subject had a nonidentifiable strategy) with a greater proportion using complex strategies in late learning (61% vs. 39%).

To test for the influence of strategy use on performance, we examined whether subjects using simple and complex strategies performed equivalently. Separate ANOVAs conducted for each run, with both group and strategy as between-subjects factors, revealed that subjects using complex strategies performed better than those using simple strategies. For Run 1, $F(1, 21) = 5.70$, $p < .03$, $M_{simple} = 60\%$, $M_{complex} = 68\%$; for Run 2, $F(1, 21) = 7.30$, $p < .02$, $M_{simple} = 54\%$, $M_{complex} = 71\%$.

3.2 fMRI Results

3.2.1 Standard Analyses—Contrasts included cue-related activity for all trials, with one contrast for early and one for late learning. Across all subjects, early learning versus the intrinsic baseline (fixation ITIs) yielded a broad set of regions in visual, frontoparietal, anterior cingulate insular cortices, posterior hippocampus, right caudate and bilateral putamen. The reverse contrast yielded default mode network regions including medial parietal, prefrontal cortices, mid-hippocampus and parahippocampal regions (see Supplemental Table 1). Within the ROIs, the Neutral group displayed greater activation within the left caudate nucleus compared to the Emotional group (see Table 2A). Repeated measures ANOVAs on beta values extracted across both early and late learning from the caudate peak revealed a significant main effect of group ($p < .05$) and no significant group × time interaction. Contrasts from late learning yielded very similar results to early learning, across all subjects (see Supplemental Table 1). However, within the MTL/striatum regions of interest, group differences (Neutral greater than Emotional) were found in the right and left amygdala (see Table 2A). Repeated measures ANOVAs on beta values extracted across both early and late learning from the amygdala peaks revealed a significant main effect of

group, and a group × time interaction in the right amygdala (both *p's* <.05) and trends for main effect of group, and a group × time interaction in the left amygdala (both *p's* < .10). In summary, analyses revealed group differences in the caudate and amygdala, with greater activation for the Neutral than the Emotional group.

3.2.2 Correlation with composite phobia score in Emotional group subjects— Simple regression contrasts (within Emotional group subjects) included the composite phobia score to assess the relationship between individual differences in fear relevancy and cue activity. During early learning (Run 1), several regions positively correlated with phobia score, including temporal and frontoparietal regions (see Table 2B). Negative correlations were found in the left caudate (see Figure 2C). During late learning (Run 2), left caudate, left amygdala and several areas in right visual cortex were negatively correlated with phobia score (see Figure 2D). No suprathreshold voxels were found for positive correlations with phobia score in late learning. Thus, reduced activation in the caudate and amygdala for the Emotional group (3.2.1) is further magnified by individual differences in fear relevancy.

3.2.3 Correct versus incorrect trials—Comparing activation on correct vs. incorrect responses provides a neural metric of learning accuracy, which in turn may be influenced by strategy use. Neural activation related to accurate performance (based on the majority outcome percentage as described in Section 2.3) was assessed for the Emotional versus Neutral group, both for early and late learning. Medial prefrontal (mPFC) activation was differentially associated with correct performance in the Emotional group in early learning (see Table 3, Figure 3). Precuneus and right anterior temporal lobe activations were differentially associated with correct performance in the Neutral group in late learning. Within the ROIs, MTL regions were differentially related to correct performance in the Neutral group (Figure 3B). In sum, accurate performance was associated with mPFC for the Emotional group in early learning and the MTL, precuneus and anterior temporal lobe for the Neutral group in late learning.

3.2.4 Functional Connectivity—Single-trial responses (beta parameter estimates) were extracted from bilateral caudate and MTL ROIs in order to test whether functional connectivity differed for the Emotional and Neutral groups. Repeated-measures ANOVAs for left caudate-MTL connectivity and right caudate-MTL connectivity both yielded a significant main effect of group (Neutral > Emotional) (both $p < 0.02$) (Figure 4). Post-hoc analyses by subregion revealed reduced connectivity between the right caudate and amygdala, relative to the hippocampus ($p < .001$) and parahippocampal gyrus ($p < .01$). To ensure that global correlations were not driving any group differences, we used the same methods to compare connectivity between the left and right putamen, which revealed no significant effect for group ($p = .88$). In order to test for a relationship between connectivity and behavioral performance, separate post-hoc correlation analyses were conducted for Emotional and Neutral groups for each learning stage. Significant correlations between connectivity and performance were only found for the Neutral group in early learning (left caudate-MTL with performance $r(11) = .58$, $p < .05$, right caudate-MTL with performance $r(11) = .56$, $p < .05$). Overall, connectivity between the caudate and MTL was reduced in the Emotional group relative to the Neutral group, and a significant relationship between caudate-MTL connectivity values and performance was only found for the Neutral group in early learning.

3.2.4 Parametric modulation by Reaction Time—Across learning trials, changes in RT could reflect shifts in cognitive processing from more deliberate to more automatic expressions of learned relationships. We therefore combined all subjects and all trials in order to assess global activation changes related to faster or slower responses. To account

for potential differences in RT, the parametrically modulated SPM analyses were computed in a factorial design, with group (Emotional, Neutral) as the factor. Within the ROIs, the left caudate (see Table 3 and Figure 5A) was associated with faster RTs and bilateral MTL regions (see Table 3 and Figure 5B) were associated with slower RTs. Repeated measures ANOVAs on beta values extracted (from the standard analyses) across both early and late learning from the caudate peak revealed no main effect of group (p = .93) but a trend toward a group × time interaction (p < .06) whereas there were no significant effects for the MTL peaks (all $p's$ > .18). Paired t-tests revealed a trend for greater activation in late versus early learning in the caudate peak in the Emotional group (p <.09), while the Neutral group exhibited no difference (p =.86). In the whole brain analysis of parametric modulation for decreasing (faster) RT only the left caudate was significant. The reverse contrast for increasing (slower) RT revealed primarily temporal and frontal regions (see Table 3). Analysis of all learning trials across both groups revealed the caudate and MTL to be modulated by RT in opposing directions.

3.2.5 Correlation of early learning activation with performance change— Activation during early learning may set the stage for future learning and reflect individual differences in performance improvement/decline. This contrast employed regression with the magnitude of performance change (late learning percent correct minus early learning percent correct) across all subjects to assess the relationship between specific activations and the expression of task learning. Within the ROIs, left and right caudate nucleus were positively correlated with performance change (Figure 5C). In the whole-brain analysis, regions that positively correlated with performance change (see Table 5) included left visual cortex, right cingulate, and frontal cortex. No suprathreshold clusters were found for the negative correlation. In sum, across all subjects, greater activation in the caudate nucleus early in learning was related to greater improvement in task performance.

3.2.6 Correlation of activation with average performance—Individual differences in performance may affect brain activation over the entire course of learning. This contrast employed regression with the average performance for each run (for each subject) across all subjects. Within the ROIs, the left hippocampus was negatively correlated with average performance (see Figure 5D). In the whole-brain analysis, occipital cortex was positively correlated with average performance while several frontal and parietal regions and the cerebellum were negatively correlated with average performance (see Supplemental Table 2). The peak was very similar to the overall deactivations reported in the hippocampus in early and late learning (see Supplemental Table 1). Extracted beta values from the hippocampal peak of this analysis were negative (mean = −.51, Emotional= −.73, Neutral = −.31). A t-test of group values showed a trend for an effect of greater deactivation in the Emotional than Neutral group, $t(23)$= −2.1, p =.05.

4. Discussion

4.1 Emotion effects

To test the effects of emotion on neural responses during classification learning, we compared data from the cue period of an identical PCL task across groups who received either Emotional (snakes and spiders) or Neutral (mushroom, flowers) outcomes. The presence of fear relevant outcomes during the PCL task was associated with reduced recruitment of the caudate and amygdala (Fig. 2A & 2B). Notably, individual differences in fear relevancy were associated with reduced activation in similar regions. In the Emotional group, negative correlations were found between the composite phobia score and left caudate activation in early learning and left amygdala and caudate in late learning (Fig. 2C & 2D). Correct responses were associated with mPFC activation in the Emotional group in

early learning (Fig. 3A) and the MTL in the Neutral group in late learning (Fig. 3B). Furthermore, the Emotional group displayed significantly weaker connectivity between the caudate and MTL compared to the Neutral group (Fig. 4). Taken together, the results suggest that circuitry typically associated with PCL tasks is disrupted when fear relevant outcomes are integrated into the task.

4.2 Emotion and MTL/Striatum Activation Differences

The Emotional group showed decreased activation in ROIs in both early and late learning, characterized as decreased left caudate response in early learning and decreased MTL (amygdala in particular) in late learning. The caudate nucleus has been associated broadly with habit learning and value-based decision making (Daw et al., 2005; Daw et al., 2006; Delgado et al., 2008; Delgado et al., 2005; Graybiel, 2005; Shohamy et al., 2008; Tricomi et al., 2006; Tricomi et al., 2004). Although the amygdala result may seem surprising at first glance, recent studies in humans and animals have reported a role for the amygdala in the coding of upcoming feedback in response to neutral cues (Bischoff-Grethe et al., 2009; Kahn et al., 2002; Paton et al., 2006; Spiegler and Mishkin, 1981). Another study in rats using a stimulus-response habit task found a double dissociation between amygdala and striatal function (McDonald and Hong, 2004). While the dorsal striatum was required for habit learning to occur, the amygdala was required in order to develop a preference for the reinforced stimulus. In the present study, the Emotional group had a significantly lower overall amygdala response (Fig. 2B), and reduced association with correctness (Fig. 3B) during late learning. The current data support the idea that during early learning (first 50 trials), both behaviorally and neurally, the group receiving emotional outcome photographs was not engaged in habit-based learning to the same degree as the group receiving neutral outcome photographs. The fact that an aversive visual stimulus was the outcome in the Emotional group, whether the subject's response was correct or not, may have removed an incentive of feedback prediction and thus blunted the amygdala's response. For the Neutral group, it is possible that the amygdala and other associated MTL regions performed a similar function in this task as they might in the episodic domain, namely to associate trial level information during the cue with a particular outcome. In both early and late learning, despite equivalent behavioral performance, activation levels in regions strongly linked to feedback based habit learning were reduced in the Emotional group.

4.3 Emotion and Functional Connectivity Between the MTL and Striatum

Given the evidence for striatal and MTL system interactions during learning, we assessed group differences in trial-by-trial functional connectivity between the caudate nucleus and substructures of the MTL. Bilateral caudate connectivity with MTL substructures was significantly reduced for the Emotional group relative to the Neutral group. Disrupted functional connectivity could mean that the Emotional group was less able to maximize the contribution of each system. Task performance in the first 50 trials was significantly correlated with functional connectivity in the Neutral but not Emotional group, providing evidence for an influence of emotion on interactions between the striatal and MTL systems related to performance in PCL tasks. The connectivity analyses suggest that a pattern that was beneficial to the Neutral group had no relation to performance and was not expressed to the same degree by the Emotional group.

4.4 Emotion and Task Behavior

A previous behavioral study of emotional versus neutral information in a PCL task reported initial impairments that equalized with more learning (Steidl et al., 2006). Their paradigm used interspersed emotional pictures during the weather prediction task and therefore may have had a distracting influence (Anderson, 2005; Dolcos and McCarthy, 2006). In our previous behavioral study, fearful subjects shown emotional outcomes, but not neutral

outcomes, had deficits in early learning and altered strategy use (Thomas and LaBar, 2008). The emotional information in our paradigm was integrated into the flow of the task, potentially reducing any distracting influence in non-fearful subjects; however, as described above, the presence of the fear-relevant outcomes may have blunted the amygdala's response to feedback incentives. The strategy analyses in the present study suggest that the Emotional group was able to use complex strategies even early in learning despite an associated RT cost. Therefore, the neural circuitry typically employed in solving PCL tasks may have been relied on to a lesser extent, with a concomitant shift to alternate neural circuitry, as discussed further below. In other tasks, mutliple memory systems are tested after the induction of stress, with a common finding of bias towards procedural response strategies (Schwabe et al., 2010). In contrast to those findings, our fearrelevancy manipulation might bias subjects toward more complex strategies. Although the neural correlates associated with the task differ between groups, any costs of activation differences are ameliorated in terms of overall behavioral performance and in this regard, fear-relevant stimuli may provide a benefit.

Performance measures from our behavioral study (Thomas and LaBar, 2008) suggest that there may be an optimal level of fearfulness towards fear-relevant stimuli, similar to the relationship expressed by the Yerkes-Dodson law (Yerkes and Dodson, 1908). In the non-fearful subjects of the present study, only negative correlations were found within the striatal and MTL ROIs. However, at the level of the whole brain, the composite phobia score was positively correlated during early learning with regions associated with enhanced attention. These include occipital, temporal and frontal regions implicated in spatial attention and working memory (Corbetta et al., 1998; Corbetta et al., 2002; LaBar et al., 1999). Furthermore, differential mPFC recruitment by the Emotional group for correct responses in early learning may be a neural correlate of an alternate approach to the task. The mPFC has been implicated in abstract strategizing, predictability, and the emergence of conceptual knowledge in decision making tasks (Hampton et al., 2006; Koch et al., 2008; Kumaran et al., 2009; Tsuchida et al., 2010). Together, these findings suggest that emotional outcomes can enhance activation in regions associated with attention and strategic processing in early learning.

It is unclear whether the altered neural correlates had any impact on the rigidity or flexibility of learning between groups. In the future, the flexibility of learning could be assessed by using transfer tests (Reber et al., 1996) to further probe for differences between Emotional versus Neutral groups. Another potential impact of altered processing could be on long-term retention of learning, as suggested by Steidl and colleagues (2006). Future studies could assess group differences after a larger delay (weeks to months). Although there were no significant differences in behavioral performance (percent correct) between groups, the Emotional group had a statistically significant speeding of their responses from early to late learning as well as a greater proportional use of complex strategies. Attenuation of regions typically associated with PCL tasks such as the striatum and MTL may be counteracted by the increased use of alternate learning mechanisms such as mPFC. Fear relevant outcomes are likely to alter both the cognitive and neural mechanisms engaged in learning.

4.5 Beyond Emotion

The differences between groups provide information about unique neural substrates. However, by investigating performance related measures, regardless of group assignment, we may be able to better delineate the role of structures involved in habit learning. Across all subjects, the left caudate was associated with faster RTs in a parametric analysis (Fig. 5A). Although caudate activation was generally related with faster RTs, ANOVAs on the extracted beta values from this peak suggest a trend whereby subjects in the Emotional group may increase activation in this region over time (late vs. early) to a greater extent than

the Neutral group.Additionally, left caudate activation magnitude during early learning correlated with degree of performance change (late minus early) (Fig. 5C). An account that ties these findings together is that the caudate is optimized to extract information that is easy to attain within the structure of the task, and that once this information is learned, the caudate is needed to a lesser extent (Delgado et al., 2005; Mattfeld and Stark, 2010). In terms of RTs, when information is readily available, RTs are likely to be reduced. In terms of performance improvement, later learning is likely to benefit from an early foundation on which more complex contingencies can be extracted. The caudate activation was consistently localized across all analyses conducted -- correlations between activation levels (parameter estimate beta values) from the unique peaks in the caudate nucleus reported in all the analyses ranged between 0.43 and 0.94 (all $p < .05$).

The striatal learning mechanism is hypothesized to provide information about outcomes across multiple trials, perhaps without conscious awareness (Knowlton et al., 1996; Knowlton et al., 1994). However, fMRI results from PCL tasks (Dickerson et al., 2010; Foerde et al., 2006; Moody et al., 2004; Poldrack et al., 2001; Poldrack et al., 1999), provide substantial evidence that the striatum and MTL both contribute to these tasks and subjects may rely on an interaction between multiple learning mechanisms.

The present study showed that, in contrast to the caudate, the MTL was associated with slower RTs across all subjects (Fig. 5B) and the left hippocampus was negatively associated with average performance (Supplemental Table 2). In patients with MTL damage, PCL studies using the weather prediction task have suggested impairments in late learning (Knowlton et al., 1994) or across the entire learning session (Hopkins et al., 2004). A role for MTL regions in response learning has been reported in animal research (Atallah et al., 2008; Packard, 1999; Packard and McGaugh, 1996). Models of striatal function posit a competitive, but interactive, relationship with the MTL memory system (Packard and Knowlton, 2002; Poldrack and Packard, 2003). However, in addition to the interactive memory model, the complementary learning systems view (Atallah et al., 2004; McClelland, 1998; McDonald and Hong, 2004; White and McDonald, 2002) posits that these systems may compete ***or*** cooperate during the independent processing of information. According to White and McDonald's theory, the hippocampus, dorsal striatum and amygdala are specialized to represent stimulus events, responses, and reinforcers, respectively. The present findings are consistent with this interactive view insofar as the MTL system may learn complex associations at the trial level (which would require more processing time) while the striatal system may facilitate responses to rapidly learnable material (which would be expressed on trials with faster responses). However, consistent with the directionality of effects reported by Poldrack et al. (2001) decreases in left hippocampal activation are associated with overall task performance. In the Neutral group, the amygdala was more responsive on correct trials (where positive feedback was more likely to be presented), which is consistent with a role in coding reinforcement. Finally, functional connectivity between the caudate and MTL was correlated with early learning, but only in the neutral group. These separate systems complement each other by extracting unique information about the task at hand, with several accounts arguing for rigid (striatal) versus flexible (MTL) applications of knowledge gained (Bayley et al., 2005; Foerde et al., 2006; Kumaran et al., 2009). The present findings added a unique perspective to the prevailing interacting systems view by linking striatal-MTL connectivity to early learning, which suggests a cooperative relationship between these systems across trials in traditional PCL tasks. However, the results also link faster RTs to the caudate and slower RTs to the MTL on a trial-by-trial basis, consistent with a temporary biasing of one system over the other. Together, the results suggest that the MTL and striatal systems interact both cooperatively and competitively across different timescales.

5. Conclusions

PCL tasks are thought to mimic procedural learning in real-world scenarios where events can cue emotional outcomes probabilistically. However, the standard weather prediction task does not contain a strongly affective outcome so the generalization of probabilistic learning mechanisms to emotionally arousing scenarios is unknown. A modification to the standard weather prediction task involving the presentation of fear-relevant outcomes resulted in reduced recruitment of the caudate nucleus and several MTL substructures. This finding was bolstered by the fact that the left caudate nucleus and bilateral amygdala were found in both the group comparison analysis (Neutral vs. Emotional) and the within-group correlation of phobia score (Emotional group). Thus, the reductions in activation are potentially related to individual differences in fear relevancy. In early learning, emotional outcomes were also associated with greater activation in regions associated with attentional and strategic processing, including the mPFC. This finding suggests the use of an alternate learning mechanism, especially early in the course of learning. In addition to group differences in BOLD response, functional connectivity analyses revealed a reduction in striatal-MTL connectivity for the Emotional group. Furthermore, the connectivity measure was significantly correlated with performance in the Neutral but not the Emotional group. Together, the results suggest that emotional outcomes in category learning alter the cognitive and neural learning mechanisms employed, with a shift in the connectivity and regions supporting accurate task performance.

Additional analyses that took behavioral measures such as RT and future performance improvement into account corroborated the role of the caudate nucleus and MTL in category learning. Interestingly, however, the RT analysis indicated that MTL regions were recruited on slow response trials whereas the caudate was recruited during rapid trials, suggesting an alternative view to competitive models (Poldrack and Packard, 2003). Instead, the results suggest that these learning systems may be complementary (Atallah et al., 2004; McClelland, 1998; White and McDonald, 2002), with the caudate nucleus setting the stage for enhanced learning by extracting readily available information (Delgado et al., 2005). As this information accumulates over learning trials, more complex relationships can be extracted based on slower learning associated with individual trials. Together, the results of this study demonstrate how emotion modulates procedural learning and further delineates striatal and MTL contributions to specific aspects of procedural learning.

Research Highlights YNIMG 8504

- fMRI study of Emotional vs. Neutral groups using a modified weather prediction task
- Caudate and MTL activation were modulated by fear-relevant outcomes
- Functional connectivity between caudate-MTL was reduced by fear-relevant outcomes
- Reaction time and performance analyses found unique caudate and MTL contributions
- Data provide evidence for temporary switching between complementary memory systems

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank Matt Fecteau and Steven Green for their assistance with data collection and analysis. This work was supported in part by NSF grant 0745919, and NIH grants R01 DA027802 and 2 P01 NS041328.

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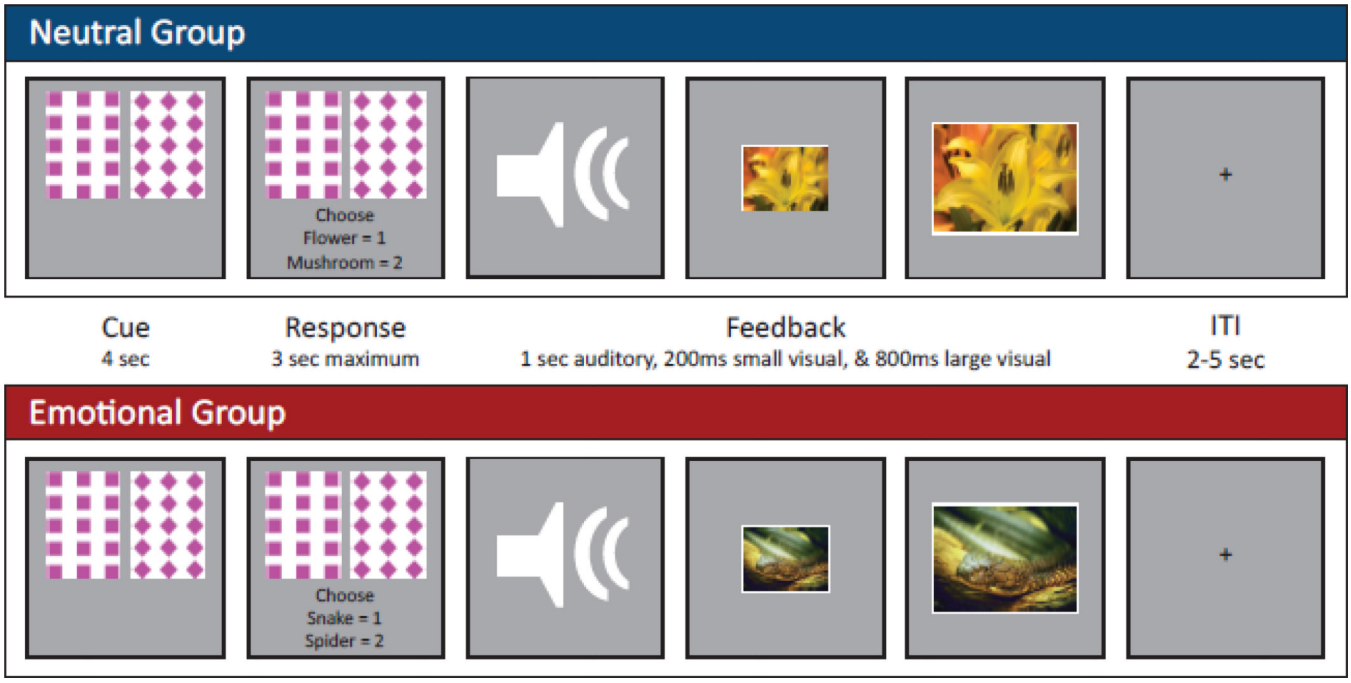

Figure 1.

An example trial for the Neutral and Emotional groups. Subjects were assigned to either the Neutral group (flower/mushroom outcome photographs) or the Emotional group (snake/spider outcome photographs). The flower and snake images shown are from the public domain and are for illustration purposes only. The duration of the response phase was determined by the subject, with a maximum of 3000 msec. Feedback consisted of 1000 msec auditory (tone for correct, white noise bursts for incorrect) and 1 second visual display in a looming manner (200 msec small, 800 msec large). Trials were separated by an inter-trial interval (ITI) of 2000–5000 msec with a fixation cross in the center of the screen.

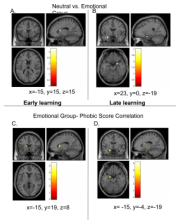

Figure 2.

Activation in early (2A and 2C) and late (2B and 2D) learning, which correspond to fMRI runs comprising the first 50 and second 50 trials, respectively. All contrasts are shown for purposes of display at $p < 0.01$, extent threshold of 3 voxels, within region of interest masks consisting of bilateral amygdala, hippocampus, parahippocampal gyrus, caudate, and putamen. A) Group comparison, Neutral > Emotional in early learning, focused on a region of the left caudate nucleus. B) Group comparison, Neutral > Emotional in late learning, focused on bilateral amygdala. C) Within-group (Emotional) negative correlation with phobia score in early learning, showing a region of the left caudate nucleus. D) Within-group (Emotional) negative correlation with phobia score in late learning, showing a region of the left caudate nucleus and left amygdala.

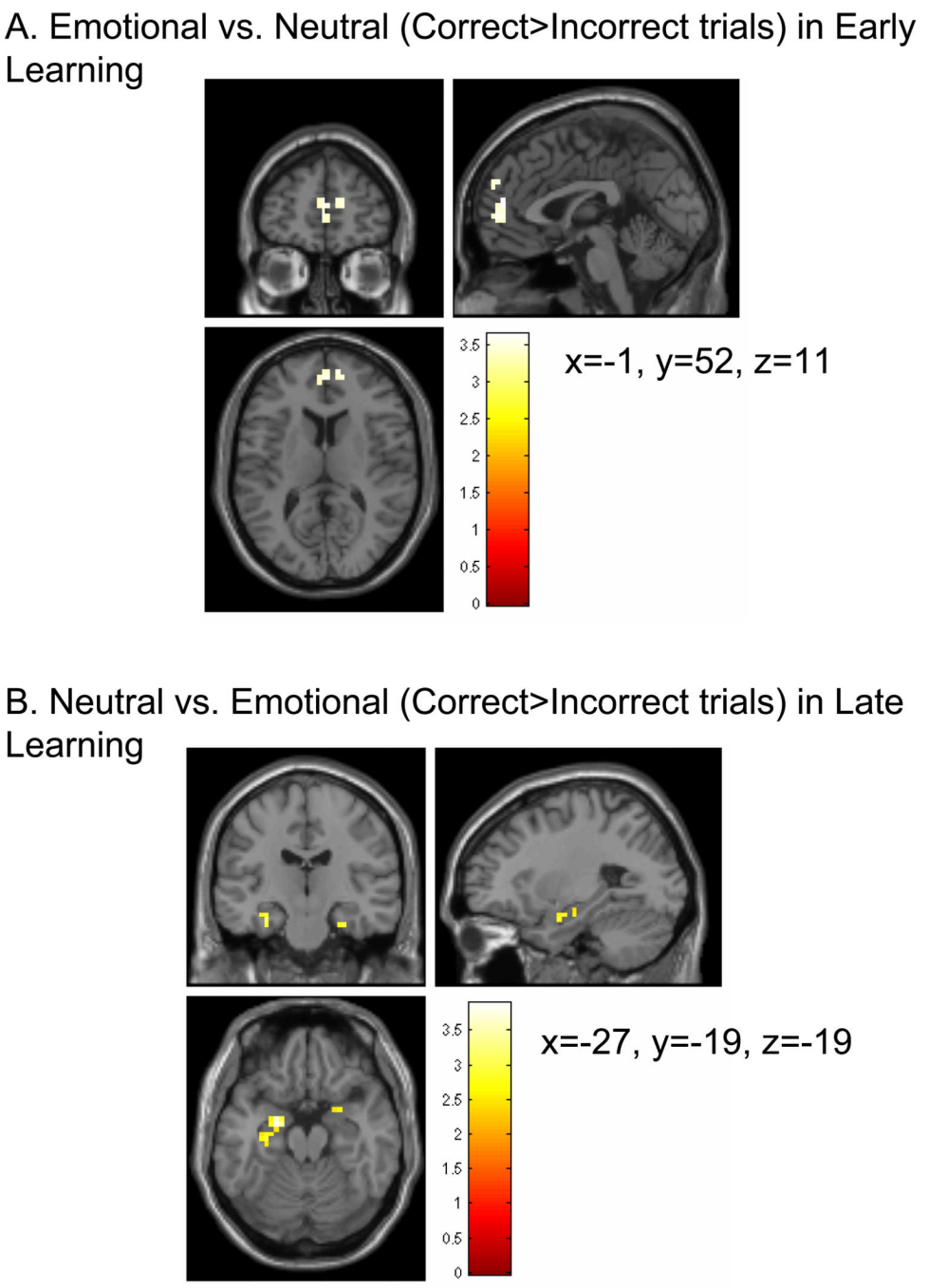

Figure 3.

Interaction between group (Emotional, Neutral) and correctness (correct, incorrect). A) Emotional vs. Neutral group for correct > incorrect trials in early learning, showing two regions in medial PFC (mPFC). Image shown at $p < 0.001$, extent threshold of 5 voxels. B) Neutral vs. Emotional group for correct > incorrect trials in late learning, showing bilateral MTL regions. Contrast shown for purposes of display at $p < 0.01$, extent threshold of 3 voxels, within a region of interest mask consisting of bilateral amygdala, hippocampus, parahippocampal gyrus, caudate, and putamen.

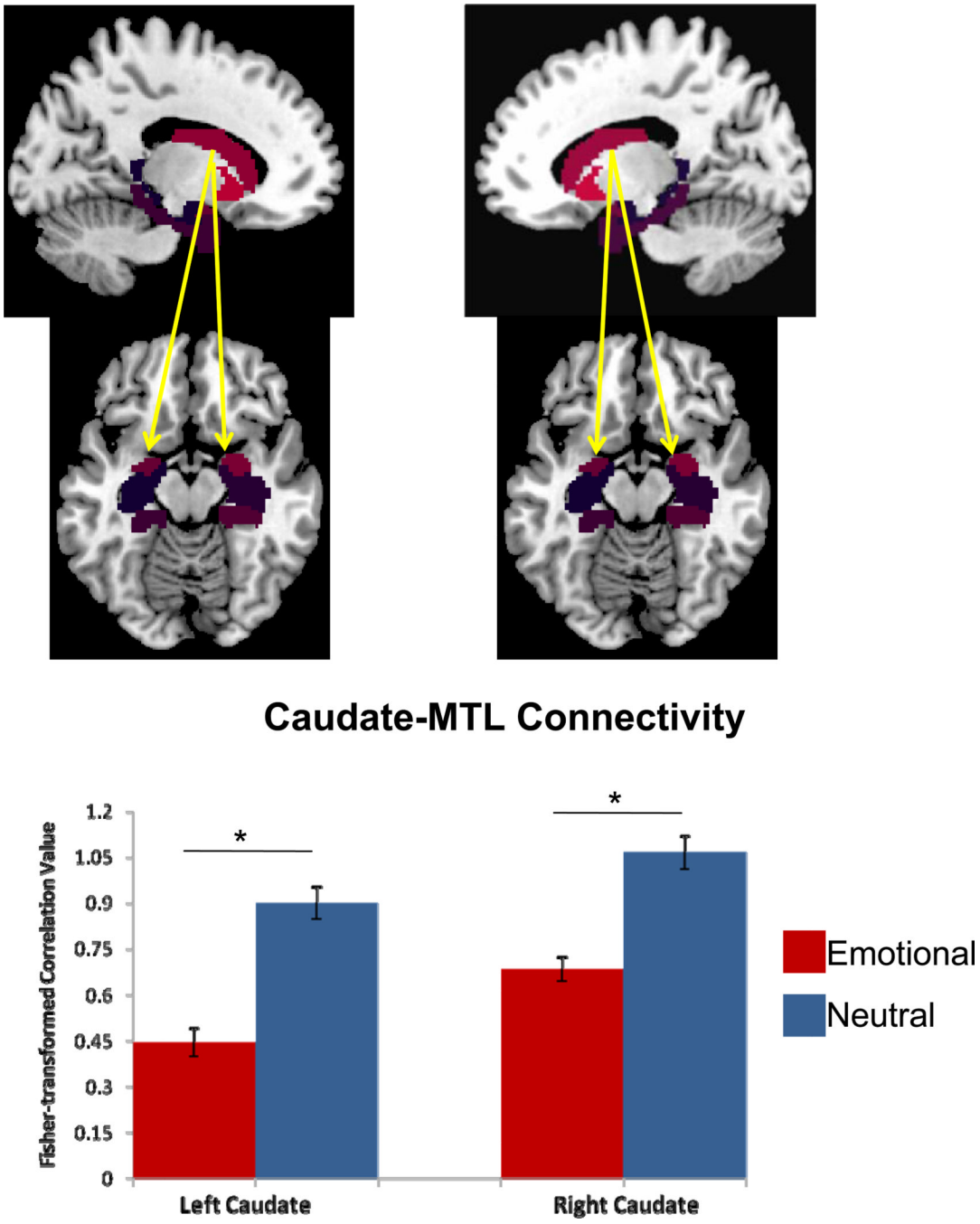

Figure 4.

Functional connectivity between left caudate nucleus (anatomical mask) and MTL regions and right caudate nucleus and MTL regions, as a function of group. Separate ANOVAs were run for the left and right caudate, with factors for hemisphere (left MTL, right MTL), learning phase (early, late), structure (amygdala, hippocampus, and parahippocampal gyrus), and group (Emotional, Neutral). No significant main effects were found for hemisphere or learning phase. A significant effect of structure for the right caudate is detailed in the text. However, no significant interactions were found for either the left or right caudate. For simplicity, group main effects are shown averaged across hemisphere, learning phase and structure.

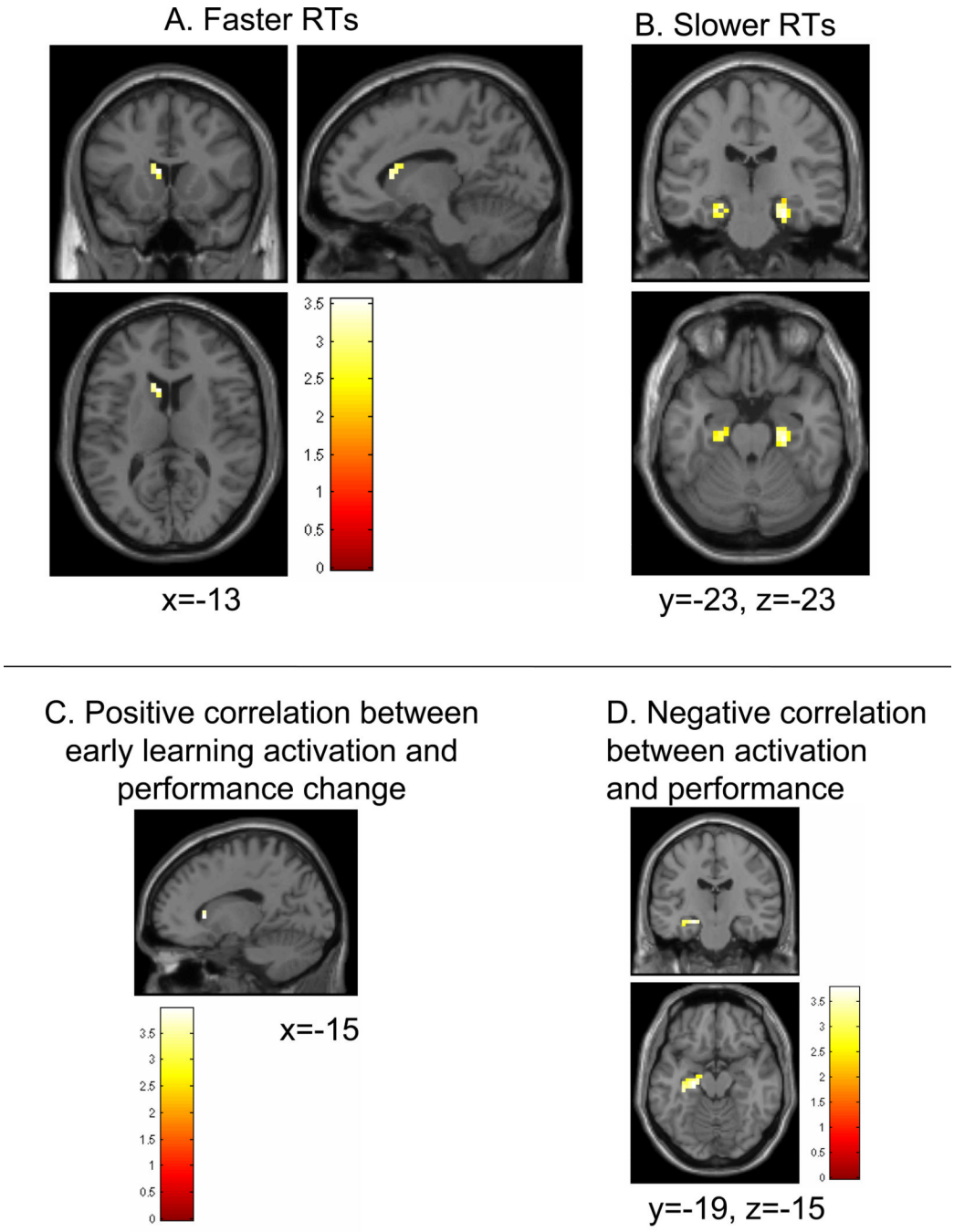

Figure 5.

Additional activations as a function of behavioral metrics. Top panel: Analysis of all subjects with parametric modulation by reaction time (RT). Bottom panel: Regression analysis of early learning activation with behavioral performance change. Contrasts are shown for purposes of display at $p < 0.01$, extent threshold of 3 voxels, within a region of interest mask consisting of bilateral amygdala, hippocampus, parahippocampal gyrus, caudate, and putamen. A) Contrast weighted toward faster RTs, showing a region of the left caudate nucleus. B) Contrast weighted toward slower RTs, showing bilateral medial temporal lobe (MTL) regions. C) Positive correlation shown from contrast of early learning activation (first 50 trials) correlated with change in behavioral performance (late percent

correct minus early percent correct). D) Negative correlation shown from contrast of all activation (100 trials) correlated with behavioral performance.

Table 1

	Emotional	**Neutral**
Subjects	12	13
Performance (% correct)		
Early Learning	64.4 (10.5)	65.1 (9.7)
Late Learning	68.4 (12.5)	65.6 (13.5)
Difference	3.9 (10.1)	0.05 (13.8)
Reaction Time (milliseconds)		
Early Learning	765 (159)	621 (78)
Late Learning	637 (185)	593 (108)
Difference	128 (156)	28 (105)
Strategy (% complex/%simple/%unknown)		
Early Learning	75/25/0	53.8/38.5/7.7
Performance Early	65.7 (11.1)/60.7(9.2)	72(4.4)/58.8(7)/48
Late Learning	91.7/8.3/0	61.5/38.5/0
Performance Late	69.9(12)/52	72.5(12.3)/54.6(5.6)
Phobic Score		
Snake (out of 30)	4.25 (4.3)	n/a
Spider (out of 31)	6.17 (7.2)	n/a
Composite (out of 61)	10.42 (9.5)	n/a

Table 2

A. Cue-related Activity			***Early Learning***				***Late Learning***			
Emotional vs. Neutral	**H**	**BA**	**x**	**y**	**z**	**Z value**	**x**	**y**	**z**	**Z value**
ROI			no suprathreshold clusters				no suprathreshold clusters			
Whole Brain			no suprathreshold clusters				no suprathreshold clusters			
			Early Learning				***Late Learning***			
Neutral vs. Emotional	H	BA	x	y	z	Z value	x	y	z	Z value
ROI										
Caudate body	L	--	−15	15	15	2.96*	--	--	--	--
Amygdala	R	--	--	--	--	--	23	0	−19	2.74*
Amygdala	L	--	--	--	--	--	−30	0	−23	2.58*
Whole Brain										
Dorsal PFC	L	9	−15	53	38	3.65	no suprathreshold clusters			
Temporal	R	39	53	−75	19	3.45				
Temporal	R	22	49	−56	19	3.37				
B. Phobia Composite Score Regression (Emotional Group only)										
			Early Learning				***Late Learning***			
Correlation	H	BA	x	y	z	Z value	x	y	z	Z value
Positive- ROI			no suprathreshold clusters				no suprathreshold clusters			
Positive- Whole Brain										
Occipital	R	19	38	−64	4	4.55	no suprathreshold clusters			
Parietotemporal	L	40	−53	−53	27	4.05				
Temporal	R	39	38	−49	8	3.62				
Dorsal frontal	R	6	19	15	61	3.58				
Temporal	R	21	45	−34	−11	3.51				
Negative- ROI										
Caudate body	L	--	−15	19	8	3.64*	−15	11	19	2.98*
Caudate head	L		−15	23	4	3.26*				
Amygdala	L	--	--	--	--	--	−19	−4	−19	3.55*

A. Cue-related Activity			*Early Learning*				*Late Learning*			
Emotional vs. Neutral	**H**	**BA**	**x**	**y**	**z**	**Z value**	**x**	**y**	**z**	**Z value**
Negative- Whole Brain										
Caudate	L	--	−15	19	8	3.64	--	--	--	--
Occipital	R	18	--	--	--	--	19	−90	15	3.51
Occipital	R	17	--	--	--	--	15	−90	−4	3.43
Occipital	R	19	--	--	--	--	41	−83	−15	3.29

H= hemisphere, BA= Brodmann area (nearest grey matter), PFC= prefrontal cortex, *x*,*y*,*z* coordinates in MNI space,

* FWE < .05.

Table 3

Correct vs. Incorrect Trials			***Early Learning***				***Late Learning***			
Emotional vs. Neutral	**H**	**BA**	**x**	**y**	**z**	**Z value**	**x**	**y**	**z**	**Z value**
ROI			no suprathreshold clusters				no suprathreshold clusters			
Whole Brain										
Medial PFC	M	10	4	56	4	3.40		no suprathreshold clusters		
Dorsomedial PFC	M	9\10	0	56	30	3.26				
			Early Learning				***Late Learning***			
Neutral vs. Emotional	H	BA	x	y	z	Z value	x	y	z	Z value
ROI										
Hippocampus	L	--	--	--	--	--	−23	−8	−19	3.60*
Amygdala	L	--	--	--	--	--	−23	−4	−19	3.32*
Parahippocampus	R	--	--	--	--	--	26	−23	−27	3.20*
Whole Brain										
Anterior temporal lobe	R	21	--	--	--	--	45	8	−38	4.24
Precuneus	M	31	--	--	--	--	−4	−68	27	3.68
Anterior cingulate	L	32	--	--	--	--	−15	38	11	3.67
Precuneus	R	31	--	--	--	--	11	−56	30	3.61
Dorsomedial PFC	M	9\10	--	--	--	--	4	56	34	3.36

H = hemisphere, M= midline (x value between ±8), BA= Brodmann area (nearest grey matter), PFC= prefrontal cortex, x,y,z coordinates in MNI space,

*FWE < .05.

Table 4

Parametric modulation by Reaction Time						
Faster	**H**	**BA**	**x**	**y**	**z**	**Z value**
ROI						
Caudate body	L	--	−8	15	11	3.14*
Caudate body	L	--	−11	19	8	2.93*
Whole Brain						
Caudate	L	--	−11	23	8	3.45
Slower	H	BA	x	y	z	Z value
ROI						
Parahippocampus	R	--	26	−23	−23	3.54*
Parahippocampus	L	--	−26	−23	−19	3.14*
Hippocampus	L	--	−23	−19	−19	3.13*
Whole Brain						
Lateral parietal	L	39\40	−60	−53	30	4.71
Lateral temporal	L	39	−53	−71	15	3.98
Ventrolateral PFC	L	47	−41	30	−19	3.81
Dorsal PFC	L	9	−11	56	30	3.77
Cuneus	R	18	11	−71	0	3.66
Ventrolateral PFC	L	44\45\47	−45	23	8	3.63
Parahippocampus	R	35	26	−23	−23	3.54
Ventrolateral PFC	R	47	38	26	−23	3.51
Orbitofrontal	M	11	−8	49	−11	3.51

H = hemisphere, M= midline (x value between ±8), BA= Brodmann area (nearest grey matter), PFC= prefrontal cortex, x,y,z coordinates in MNI space,

* FWE < .05

Table 5

Correlation of early learning activation with performance change						
Positive	**H**	**BA**	**x**	**y**	**z**	**Z value**
ROI						
Caudate head	L	--	−15	23	4	3.42*
Caudate head	L	--	−4	4	4	2.52*
Whole Brain						
Cuneus	L	19	−23	−86	34	3.88
Anterior cingulate	R	32	26	30	30	3.81
Inferior PFC	R	45	30	30	15	3.65
Negative	H	BA	x	y	z	Z value
ROI			no suprathreshold clusters			
Whole Brain			no suprathreshold clusters			

H= hemisphere, BA= Brodmann area (nearest grey matter), PFC= prefrontal cortex, x,y,z coordinates in MNI space,

*FWE < .05

Table 6

Correlation with average performance values						
Positive	**H**	**BA**	**x**	**y**	**z**	**Z value**
ROI		no suprathreshold clusters				
Whole Brain						
Occipital	M	17	4	−94	−4	3.29
Negative	H	BA	x	y	z	Z value
ROI						
Hippocampus	L	--	−23	−19	−15	3.50
Whole Brain						
Posterior cingulate	R	31	11	−45	23	4.75*
Anterior PFC	L	10	−26	53	15	4.55
Ventromedial PFC	M	10\11	8	41	−11	4.40
Precentral gyrus	R	4\6	11	−30	65	4.22
Dorsal frontal	L	6	−19	15	61	4.09
Cerebellum	L	--	−19	−49	−27	3.85
Ventral parietal	R	40	45	−26	27	3.67
Anterior PFC	R	10	11	60	15	3.65
Posterior cingulate	M	31	4	−34	38	3.61
Dorsal frontal	R	6	15	11	61	3.56
Hippocampus	L	--	−23	−19	−15	3.50
Precentral gyrus	R	6	23	−23	61	3.44
Precentral gyrus	R	6	41	−11	49	3.43
Precentral gyrus	L	4	−11	−38	72	3.38
Dorsolateral PFC	L	9\46	−34	26	30	3.30
Anterior cingulate	L	32	−11	19	46	3.28

H= hemisphere, M= midline (x values between ±8), BA= Brodmann area (nearest grey matter), PFC= prefrontal cortex, x,y,z coordinates in MNI space,

*FWE < .05.