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Contributions of the Amygdala to Reward Expectancy and Choice Signals in Human Prefrontal Cortex

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SUMMARY

The prefrontal cortex (PFC) receives substantial anatomical input from the amygdala, and these two structures have long been implicated in reward-related learning and decision making. Yet little is known about how these regions interact, especially in humans. We investigated the contribution of the amygdala to reward-related signals in PFC by scanning two rare subjects with focal bilateral amygdala lesions using fMRI. The subjects performed a reversal learning task in which they first had to learn which of two choices was the more rewarding, and then flexibly switch their choices when contingencies changed. Compared with healthy controls, both amygdala lesion subjects showed a profound change in ventromedial prefrontal cortex (vmPFC) activity associated with reward expectation and behavioral choice. These findings support a critical role for the human amygdala in establishing expected reward representations in PFC, which in turn may be used to guide behavioral choice.

INTRODUCTION

Research on the neural substrates of reward-related learning and decision making has highlighted the important contributions of the ventromedial prefrontal cortex (vmPFC, encompassing the orbital and medial surfaces of the frontal lobes) and the amygdala. A large number of electrophysiology, lesion, and neuroimaging studies in humans and animals have examined the functions of these two structures (Baxter and Murray, 2002; Holland and Gallagher, 2004; O'Doherty et al., 2001; Rolls, 2000). Lesion studies in rats and nonhuman primates suggest that both structures play an important role in (1) learning associations between stimuli and subsequent reward or punishment, and (2) the adaptive control of behavior following changes in such reinforcement contingencies or the value of the reinforcer (Baxter et al., 2000; Hatfield et al., 1996; Iversen and Mishkin, 1970; Izquierdo and Murray, 2004; Malkova et al., 1997). Single-unit studies have found that neurons in both structures respond to stimulus cues predictive of future rewarding or punishing outcomes, or respond in anticipation of an impending outcome (Paton et al., 2006; Schoenbaum et al., 1998, 2003; Thorpe et al., 1983; Tremblay and Schultz, 1999). Moreover, firing rates of these neurons track changes in reward contingencies over time, suggesting an important role for these regions in computing and rapidly updating reward expectations. Furthermore, lesion and neuroimaging studies in humans have also implicated amygdala and vmPFC in guiding behavioral choice under uncertainty, and have found evidence of neural activity related to expected reward and behavioral choice in both of these areas (Bechara et al., 1994, 2000; Hampton et al., 2006; O'Doherty et al., 2003a; Rolls et al., 1994).

While much is now known about the involvement of amygdala and PFC individually, these structures do not function in isolation, but as components of a network of brain structures important for reinforcement learning (RL). The two structures are known to be bidirectionally connected anatomically (Amaral and Price, 1984; Cavada et al., 2000), but very little is known about the functional significance of these connections. A small number of studies in animals have made use of the crossed-unilateral lesion technique to show that interactions between the two regions may be critical for certain reward-related functions, such as the ability to modify behavior following a change in the value of an associated reinforcer (Baxter et al., 2000). Electrophysiological studies in the vmPFC of rats (Schoenbaum et al., 2003) have found that amygdala lesions substantially reduced the population of neurons in PFC encoding expected outcomes, thus rendering these representations inflexible and stimulus-driven. The same study also found a reduced number of neurons that were subsequently encoding the expected reward of choices made. These findings suggest that signals

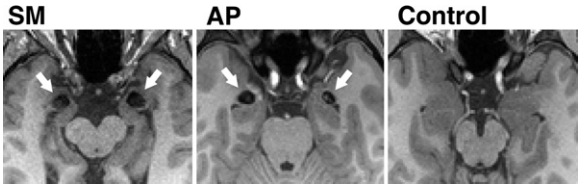

Figure 1. Axial T1-Weighted Structural MR Images from the Two Amygdala Lesion Subjects

Selective bilateral calcification of the amygdala (arrows) due to Urbach-Wiethe disease (Hofer, 1973) is evident as loss of signal on these T1-weighted structural MR scans of the brains of S.M. (left) and A.P. (middle). An image from a typical healthy control subject with intact amygdalae is also shown for comparison (right). Multiple axial slices for both amygdala lesion subjects are shown in Figure S3.

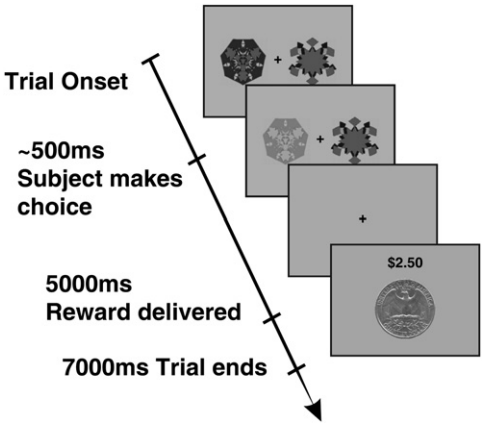

Figure 2. Probabilistic Reversal Task

At the beginning of each trial (upper left), subjects chose one of two fractals (which on each trial were randomly located to the left or right of a fixation cross). Once a stimulus was selected by the subject (~500 ms), the chosen stimulus increased in brightness and remained on the screen for a total of 2 s, after which both choices were covered up with a blank screen. Five seconds after the trial started, a reward (winning 25 cents, depicted by a quarter dollar coin) or punishment (losing 25 cents, depicted by a quarter dollar coin covered by a red cross) was shown for 1 s, with the total money earned displayed at the top ($2.50 in this figure), before being covered again by a blank screen. After 7 s, the trial ended, and was then repeated a total of 110 times. One stimulus was designated as the "correct" stimulus and resulted in a monetary reward on 70% of occasions, and a monetary loss 30% of the time, with an overall accumulation of monetary gain in the task. The other, "incorrect" stimulus resulted in a reward 40% of the time and a punishment 60% of the time, with a cumulative monetary loss. After subjects chose the correct stimulus on four consecutive occasions, the contingencies reversed with a probability of 0.25 on each successive trial. Subjects had to infer that the reversal took place and switch their choice, at which point the process was repeated.

from the amygdala play an important role in facilitating neural representations of reward expectancy in vmPFC (Holland and Gallagher, 2004).

Much less is known about the functional significance of interactions between amygdala and vmPFC in the human brain. While some neuroimaging studies have begun to use connectivity analyses to model functional interactions between these regions, albeit not in the context of reward-learning (Heinz et al., 2005; Iidaka et al., 2001; Kilpatrick and Cahill, 2003), the use of imaging techniques alone can provide only limited data about the causal effect of neural activity in one area on neural computations in another.

Here, we studied two rare human subjects with focal bilateral amygdala lesions due to Urbach-Wiethe disease (Hofer, 1973) (Figure 1). The two subjects were scanned with fMRI while they participated in a task designed to probe reward-related learning and behavioral decision making: monetary probabilistic reversal learning (Figure 2). Previous studies have reported blood oxygenation level-dependent (BOLD) signal changes in both the amygdala and vmPFC that are related to processing rewarding and punishing outcomes in this task and encoding signals related to *subsequent* behavioral decisions (O'Doherty et al., 2003a). Moreover, activity in both of these regions tracks expected reward value during performance of this task, and these expectation signals are updated flexibly following changes in reinforcement contingencies (Hampton et al., 2006).

We investigated the effects of amygdala lesions on reward representations in vmPFC by comparing the BOLD responses measured in the subjects with amygdala lesions to those measured in healthy control subjects. We looked for the effects of the amygdala lesions on BOLD signals correlated with behavioral choice (whether to maintain current choices or switch choices in the task), computation of expected reward value (how much money they expected to earn or lose following their choices), and value of the outcomes (the actual monetary gain or loss at the end of each trial). We hypothesized that the amygdala contributes to computations of expected reward value in vmPFC, which in turn should affect signals of behavioral choice.

RESULTS

Subjects

Both amygdala lesion subjects had focal bilateral lesions in the amygdala due to Urbach-Wiethe disease (Figure 1). One of the subjects, S.M., has been extensively studied before: she is a 41-year-old woman with a high-school education, IQ in the normal range, and normal basic visuoperception, language, and memory; her lesions encompass the entire amygdalae, as well as subjacent white matter and very anterior entorhinal cortex. The second subject, A.P., is a 21-year-old woman in college with likewise normal IQ, perception, language, and memory; lesions are entirely confined to the amygdala, occupying roughly 50% of each amygdala's volume. Both subjects are fully right-handed, live independently, and show no evidence of psychopathology on tests of personality assessment. Both subjects also perform normally on standard neuropsychological tests of response switching, such as the Wisconsin Card Sorting Task and the Trailmaking task.

Behavioral Performance on Reversal Learning

Principal Component Analysis of Behavioral Measures

Behavioral performance of the amygdala lesion subjects on the probabilistic reversal task was compared with that of 41 healthy controls, 25 of similar age to A.P. (A.P.-comparisons), and 16 similar in age to S.M. (S.M.-comparisons). Subjects' performance was assessed using ten distinct behavioral measures on this task, including the number of response switches, the number of reversals attained, and the number of trials after reversal for subjects to reach the next criterion (see Experimental Procedures for a full list). As many of these measures likely overlap in the underlying cognitive functions being assessed, we first coalesced all behavioral measures using principal component analysis (PCA) in order to gain an overall assessment of the degree of impairment of the patients compared with the controls. Both amygdala patients showed significant differences on the principal component of the behavioral measures compared with controls ($p < 0.05$; Figure 3A) after adjusting for the effects of age (See Figure S4 in the Supplemental Data available with this article online for age effects on the task, and Experimental Procedures for more details). We also tested both patients and controls on a simpler deterministic version of the reversal task in which the correct stimulus was rewarded 100% of the time and the incorrect stimulus was punished 100% of the time, thus removing probabilistic contingencies as a component. Even in this task, both patients were significantly impaired compared to their controls (also plotted in Figure 3A), indicating that patients' impairment on the task is not specifically related to the probabilistic component of the reversal task. Next, we analyzed in more detail subjects' performance on specific behavioral measures.

Switching Behavior

Out of the ten measures used, the ones most consistently showing a difference between the amygdala lesion subjects and controls concerned the frequency with which subjects switched their choice of stimulus. In the probabilistic task, S.M. was significantly more likely to switch stimulus choice than controls (at $p < 0.05$). Although A.P. did not show an overall increased tendency to switch, she was significantly more likely to switch choices following receipt of a reward than her controls (at $p < 0.05$), and S.M. was trending in the same direction (at $p < 0.1$). This effect was even more marked in the deterministic task, where both A.P. and S.M. were significantly more likely to switch following a reward than controls (at $p < 0.05$ and $p < 0.01$, respectively). We also tested whether the amygdala lesion subjects were switching their choices at random by comparing the choice patterns of all subjects on the task to that of a random Monte Carlo process (averaged over 10,000 simulations). Both amygdala lesion subjects were significantly different from random performance (at $p < 0.01$), suggesting that amygdala lesions did not simply lead to random behavior, but rather resulted in a specific insensitivity in how reward value guides choice behavior.

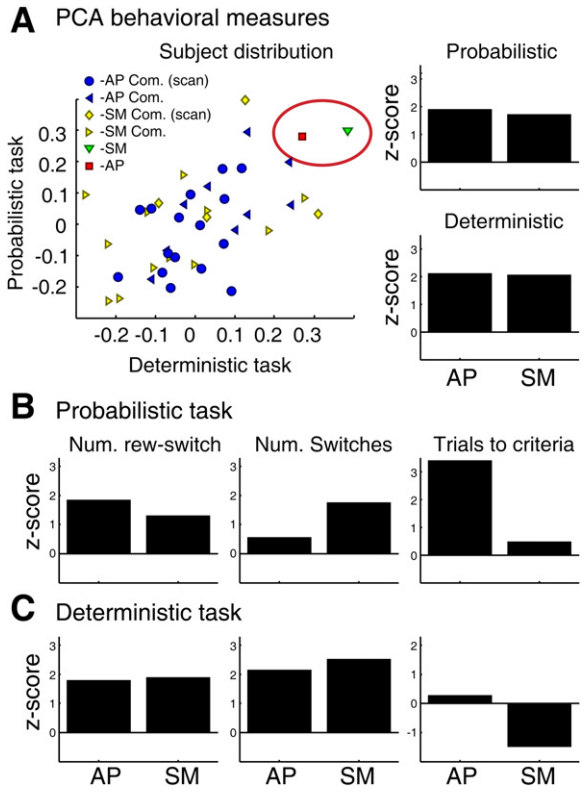

Figure 3. Behavioral Performance

(A) The first principal component across behavioral measures for the deterministic (x axis) and probabilistic (y axis) reversal tasks explained 46% and 37%, respectively, of each task's data variance. Both amygdala lesion subjects (AP = green; SM = red; both are shown circled) are significantly different in their behavior with respect to controls ($p < 0.05$, t test). Age-matched control subjects are shown in yellow (S.M.-comparisons) and blue (A.P.-comparisons). Control subjects that were also scanned are plotted separately from those who were not scanned. Equivalent z-scores of the principal component of the behavioral measures for the amygdala lesion subjects compared to their respective controls are shown on the right-hand panels. The scores for both patients are significantly different from the mean of their controls at $p < 0.05$.

(B) Specific performance measures on the probabilistic task. Both amygdala lesion subjects showed an increased tendency to switch choice behavior during task performance over their respective controls. In particular, S.M. was significantly more likely to switch behavior than controls overall (at $p < 0.05$), whereas A.P. was more likely to switch following receipt of rewarding feedback than controls were (at $p < 0.05$), while S.M. showed a tendency in the same direction (at $p < 0.1$).

(C) Specific performance measures on the deterministic task. Most notably, both patients were significantly more likely to switch their choice of stimulus following a reward than controls were (at $p < 0.05$), even though in this task obtaining a reward also implies that the current choice is correct, and it is thus always disadvantageous to switch stimulus choice following a reward.

Trials to Criterion

In the probabilistic reversal task, only A.P. took an abnormally large number of trials to reach criterion ($p < 0.001$). Neither amygdala lesion subject was impaired in the number of trials to reach criterion on the deterministic task.

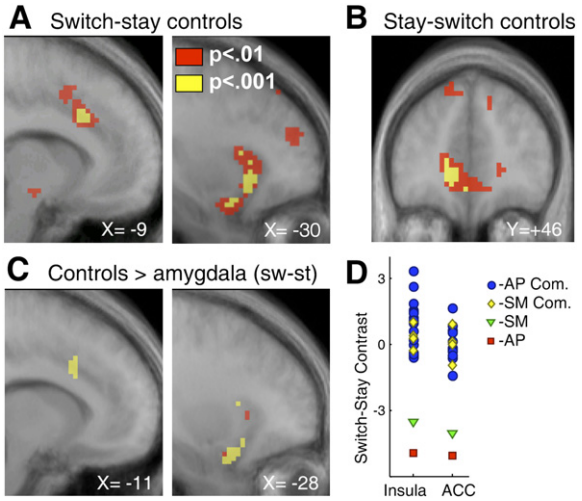

Figure 4. Behavioral Choice Signals

Contrast (aligned to the time of outcome) between trials for which subjects subsequently switch their choice of stimulus ("switch"), compared with trials for which subjects subsequently continue choosing the current stimulus ("stay").

(A) Regions showing increased BOLD signal on switch compared with stay trials in control subjects. Significant effects were observed in anterior insula/posterior lateral OFC bilaterally (−30, 21, −9 mm, z = 3.91; and 33, 21, −12 mm, z = 3.64) and ACC (−9, 21, 33 mm, z = 3.62) extending into premotor cortex (0, 18, 51 mm, z = 3.73), as shown in these sagittal slices.

(B) Regions showing increased BOLD signal on stay compared with switch trials. Significant effects were observed in mPFC (−6, 45, 21 mm, z = 3.79).

(C) Both amygdala lesion subjects had significantly less switch versus stay activity than controls in anterior insula/posterior lateral OFC bilaterally (−30, 21, −18 mm, z = 4.2; and 36, 21, −18 mm, z = 4.32) and ACC (−9, 33, 42 mm, z = 5.29).

(D) Plot of contrast estimates from switch-stay contrast in both these areas showing that responses in the amygdala lesion subjects are markedly different from responses in the control subjects (both A.P.-comparison and S.M.-comparison controls).

Perseveration

We also tested for evidence of perseveration, i.e., a propensity to continue choosing the previously rewarded stimulus once reversal has occurred. Neither patient showed evidence of perseveration on either the probabilistic or deterministic task compared with controls.

Initial Acquisition

We also tested subjects' performance during initial learning of reward contingencies, i.e., when subjects work out which stimulus pays out the most and then choose that stimulus consistently before a reversal is introduced (and before they even know a reversal will occur). Although both S.M. and A.P. showed a tendency to take more trials than their respective controls to acquire the initial contingencies, this effect did not reach statistical significance (at $p < 0.07$ and $p < 0.13$, respectively). S.M., though not A.P., was found to switch choice significantly more than controls during task performance.

fMRI Results of Probabilistic Reversal Learning

Here we report whole-brain analyses of BOLD signals showing differences between amygdala lesion subjects and controls. We restrict our analysis to those regions that show significant effects in controls in the first place (see Experimental Procedures; for a more extensive analysis of BOLD responses in normal control subjects on this same task, see Hampton et al., 2006).

Behavioral Choice Signals

In order to determine the effects of amygdala lesions on BOLD signals in orbital and medial PFC related to behavioral choice, we first conducted a simple canonical trial-based analysis of the fMRI data whereby we examined BOLD responses following receipt of the outcome on a given trial (as in O'Doherty et al., 2003a). Trials were separated according to whether on the subsequent trial following the outcome subjects changed their choice of stimulus ("switch" trials) or continued choosing the same stimulus ("stay" trials).

Figure 4A shows areas with significant responses in switch trials compared with stay trials in control subjects. This contrast revealed significantly greater activity during switch compared with stay in anterior frontal insula, extending into posterior lateral orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC). The reverse contrast revealed significant effects in medial PFC (mPFC) (Figure 4B). These results are consistent with previous studies of reversal learning in healthy control subjects (Bush et al., 2002; Cools et al., 2002; O'Doherty et al., 2003a).

Differences in Behavioral Choice Signals in Amygdala Lesion Subjects Compared with Controls

We examined regions in which the above contrast would differ between our two subjects with amygdala lesions and controls by restricting the analysis to those voxels that showed a significant effect in the controls in the first place at $p < 0.01$ (for switch-stay; Figure 4A). We found significantly greater responses in switch compared with stay trials in control subjects than in the two amygdala lesion subjects in a region of anterior insula/posterior lateral OFC bilaterally (Figure 4C). These differences were significant in each amygdala lesion subject individually compared with controls (at $p < 0.001$ for S.M. and at $p < 10^{-8}$ for A.P.). A plot of the contrast estimates for switch-stay are shown in Figure 4D. It is notable that responses in both amygdala lesion subjects are markedly different from controls. A comparison of the reverse contrast (stay-switch) between amygdala lesion subjects and controls did not reveal any significantly decreased responses in the amygdala lesion subjects.

These results indicate that bilateral damage to the amygdala results in altered responses in anterior insula/posterior lateral OFC and ACC related to behavioral choice, suggesting that in healthy individuals the amygdala makes an important contribution to the computation of behavioral control signals in those regions.

Expected Reward Signals

We next examined BOLD responses to expected reward. For this, we applied a computational model which

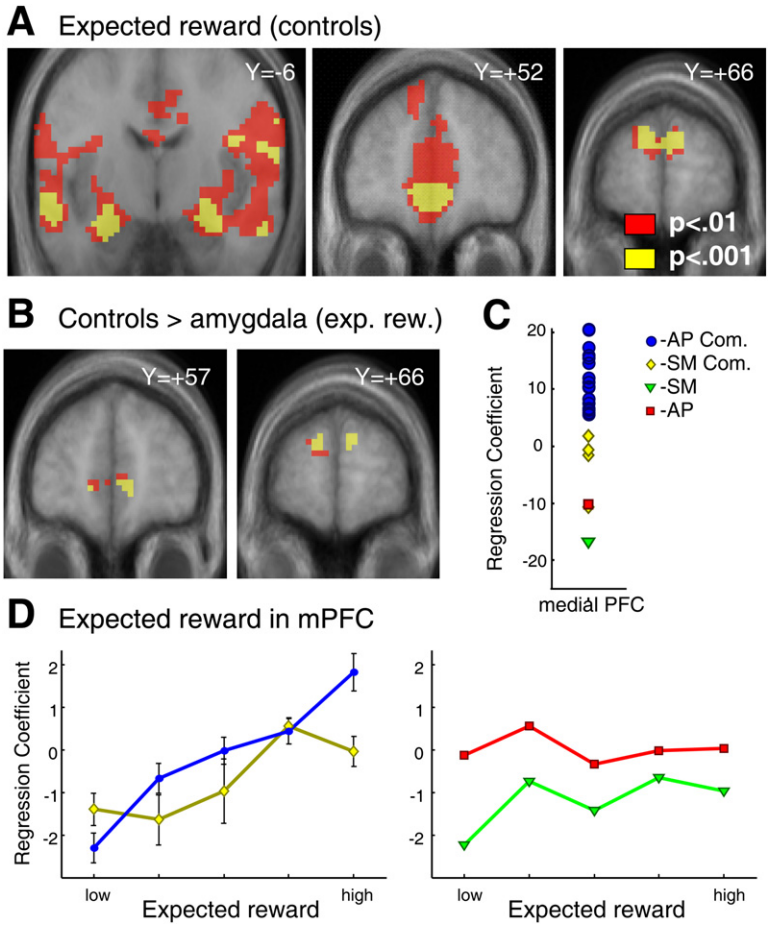

Figure 5. Expected Reward Signals in the Brain

(A) For control subjects, BOLD signals correlating with the magnitude of expected reward of a choice were found in vmPFC (6, 57, −6 mm, z = 5.13) and the amygdala bilaterally (−27, −6, −21 mm, z = 3.89) extending into hippocampus (Hampton et al., 2006).

(B) We found a significantly weaker correlation with expected reward in mPFC (6, 57, −3 mm, z = 4.12) in the two amygdala lesion subjects compared with that of controls (at $p < 0.001$).

(C) Plot of coefficients in mPFC (6, 57, −3 mm) for the expected reward regressor, indicating that both amygdala lesion subjects differ markedly from controls in their representation of expected rewards.

(D) To analyze the relationship between expected rewards and BOLD signal in mPFC, we subdivided trials into five bins depending on the expected reward value in that trial. The regression coefficients for each bin are plotted for the A.P.- and S.M.-comparison subjects (left), showing the linear relationship between expected rewards and brain BOLD activity. However, in contrast to the controls, the relationship between expected rewards and BOLD activity for both amygdala lesion subjects is nearly flat, indicating that both subjects are not computing expected rewards in mPFC in the same way as controls. Regression coefficients were extracted at the local maximum of the expected reward contrast for each subject within a 10 mm radius of the group peak (as shown in B). Error bars = SEM.

calculates expected reward signals related to subjects' choice in a trial by taking into account the history of rewards and punishments obtained, and the history of choices made (see Experimental Procedures). In our control subjects, we found significant correlations with this signal in orbital and medial PFC (Figure 5A), time-locked to the time of choice. Activity in these areas increases in a linear fashion as a function of increasing expected reward value (Hampton et al., 2006), suggesting that these areas are involved in encoding the expected reward of the currently chosen stimulus.

Differences in Expected Reward Signals between Amygdala Lesion Subjects and Controls

In a direct comparison between areas correlating with expected reward signals in the amygdala lesion subjects and areas in the controls, we found significant differences in mPFC at $p < 0.001$ (Figure 5B). These results were significant in each subject individually when compared with controls at $p < 0.001$ for A.P. and $p < 0.0001$ for S.M. A consistent difference between A.P. and controls, and between S.M. and S.M.-comparison subjects, can be seen when plotting the regression coefficients of mPFC in all subjects (Figure 5C), confirming that the amygdala lesion subjects process the expected reward value of each choice abnormally. These results were obtained by fitting a model to the behavior of the group of 16 A.P. controls that were scanned, and then using the model parameters as the regressor against the fMRI data from the amygdala lesion subjects and the controls. However, in order to account for the possibility that a difference in model parameters between the controls and amygdala lesion subjects could account for the above results, we also performed the same analysis using parameter fits derived individually from each of the amygdala lesion subjects. This analysis yielded the same results: a significant difference in expected reward signals in mPFC in amygdala lesion subjects compared with controls (see Figure S1A).

To further characterize how amygdala lesion subjects process expected reward representations in mPFC, we plotted the signal in mPFC measured with fMRI against the expected reward signals obtained from the model of the subjects' task performance. We sorted trials into one of five bins to capture different ranges in the expected reward values and fitted each bin separately to the fMRI data. For controls, this analysis shows a linear increasing relationship between the magnitude of the evoked fMRI signal in this region and expected reward value. By contrast, responses in mPFC in the amygdala lesion subjects

did not display a clear linear increasing relationship with expected reward (Figure 5D).

Responses to Rewarding and Punishing Outcomes

We also looked for responses relating to the receipt of rewarding or punishing feedback at the time of outcome. When comparing responses to receipt of rewarding outcomes compared with punishing ones, in our control subjects we found significant activity relating to receipt of reward in medial PFC and medial OFC (Figure 6A), consistent with previous reports (Anderson et al., 2003; Knutson et al., 2001; O'Doherty et al., 2001, 2003a; Small et al., 2001). And on the other hand, when testing for areas responding to punishing outcomes compared with rewarding ones, we found significant effects in the anterior ventrolateral PFC extending into lateral OFC, also consistent with previous results (Gottfried et al., 2004; O'Doherty et al., 2001, 2003b).

Differences in Responses to Rewarding and Punishing Outcomes in Amygdala Lesion Subjects Compared with Controls

We then compared the above contrast in amygdala lesion subjects to that in the control subjects, again restricting ourselves to those regions that showed significant effects (at $p < 0.01$) of rewarding or punishing feedback in the control subjects in the first place. We found no significant differences in BOLD responses to rewarding or punishing feedback in amygdala lesion subjects compared with controls at $p < 0.001$ uncorrected, with only a single voxel surviving in mPFC in the reward contrast at $p < 0.01$ (Figure 6B). These results suggest that processing of rewarding and punishing feedback in OFC and mPFC remains intact after amygdala lesions. Thus, amygdala lesions appear to selectively impair the generation of expected reward signals in PFC, as well as the signals for behavioral choice that would normally be based on those expected reward signals, but leave the generation of reward outcome signals essentially unaffected.

Controlling for Behavioral Differences between Amygdala Lesion Subjects and Controls

In order to control for the possibility that differences in behavior between the amygdala lesion subjects and controls could contribute to the imaging results observed, we performed a follow-up analysis in which we selected only those trials on which every subject had made a correct choice according to the underlying task contingency. That is, we selected those trials on which subjects correctly maintained their choice of stimulus (if their current choice of stimulus was correct), and those trials on which subjects correctly switched their choice of stimulus after the contingencies had reversed. All other trials were modeled separately as error trials of no interest. We then conducted the same analyses reported above for each contrast of interest. All of the above results held up (see Figures S1B and S2), indicating that the abnormal signal in PFC that we report following amygdala damage cannot be due simply to differences in the distribution of errors made between controls and amygdala lesion subjects.

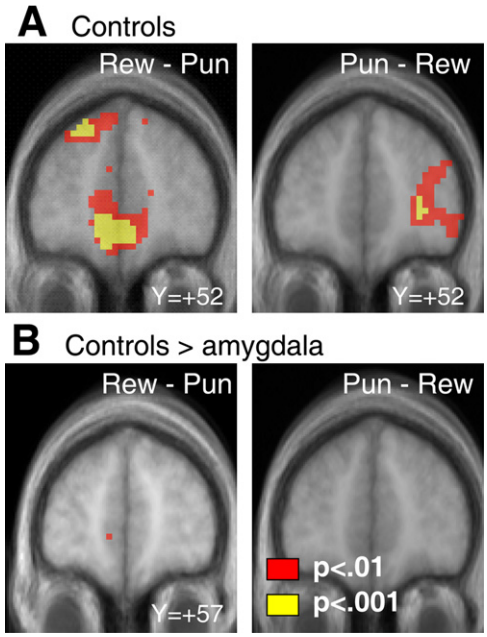

Figure 6. Responses to Receipt of Rewarding and Punishing Outcomes

(A) In a direct comparison of BOLD responses to rewarding and punishing outcomes in control subjects, we found significantly increased activity in medial OFC following receipt of rewarding outcomes compared with punishing outcomes (−3, 57, −9 mm, z = 4.23), and increased activity in anterior ventrolateral PFC extending into far lateral OFC following the receipt of punishing outcomes compared to rewarding outcomes (27, 52, 6 mm, z = 3.45).

(B) However, in a direct comparison of responses to rewarding outcomes between the amygdala lesion subjects and controls, we found no significant differences (except one voxel at $p < 0.01$ in mPFC). Similarly, no differences were found in BOLD signal responses to punishing outcomes between amygdala lesion subjects and controls. This suggests that outcome representations in orbital, medial, and lateral PFCs are unaffected by the amygdala lesions.

DISCUSSION

Amygdala and vmPFC are known to play an important role in reward-related learning and decision making, yet little is known about how these structures interact to support such functions in the human brain. In the present study, we provide evidence that neural representations in orbital, medial, and lateral PFC related to the computation of expected reward and the computation of behavioral choice based on such reward, depend on input from the amygdala. Moreover, our results indicate that reward outcome representations in vmPFC are not as dependant on amygdala input.

Consistent with previous reports (Cools et al., 2002; O'Doherty et al., 2003a), we found robust signals related to behavioral choice in posterolateral OFC, anterior insula, and ACC in healthy individuals. By contrast, these signals were significantly reduced in both subjects with amygdala lesions. Moreover, this effect is unlikely to be driven by

differences in behavioral performance between the amygdala lesion subjects and their controls, as these results held up even when behavioral differences between the patients and controls were taken into account in the fMRI analysis by restricting analysis to only those trials in which both amygdala lesion subjects and controls made the correct choices. Thus, differences in neural signals in this area are unlikely to be merely a consequence of the degree of behavioral impairment on the task, but are likely to be a direct consequence of the amygdala lesions. These results support the hypothesis that the production of signals related to behavioral choice in OFC and ACC relies directly on input from the amygdala.

This conclusion leaves open the question of what precisely the amygdala contributes to behavioral choice signals in PFC. Computational models of decision making, such as those grounded in RL approaches, conceive of behavioral decision making as being driven by an underlying computation of expected rewards or utilities for different available actions or stimuli. Decisions are then weighted according to the relative value of the different actions, so that over the course of learning, choices associated with higher value become favored (with the caveat that actions believed to be suboptimal nonetheless may sometimes be selected for the purposes of exploration [Daw et al., 2006]). The decision process is likely therefore to involve an explicit comparison between expected reward values available for different actions. In the case of reversal learning, there are only two possible actions: either maintaining current behavioral choice when the chosen stimulus is believed to be correct, or switching stimulus choice once a change in contingencies has been detected. Here we used a computational model of decision making, which is essentially a modified RL algorithm that additionally takes into account the reversal structure of the task. This model computes expected reward signals based on the history of prior outcomes. Previously we have shown that BOLD signals in vmPFC reflect computations of expected reward according to this model (Hampton et al., 2006). We hypothesize that these expected reward signals are then used as input to the decision-making process in order to determine whether to maintain current stimulus choice or switch stimulus choice in the task.

In the present study we found that expected reward signals in mPFC were markedly abnormal in the amygdala lesion subjects. Whereas control subjects showed a linear increase in activity in this region as a function of increased expected reward value, no such relationship was found in the subjects with amygdala lesions. The absence of normal expected reward signals in the mPFC of subjects with amygdala lesions implies that these signals can no longer be used appropriately to generate behavioral decisions. The lack of these expected reward signals could therefore also account for the difference in observed behavioral choice signals. Thus, we suggest that the primary contribution of amygdala-vmPFC interactions is computing expected reward values, which, once established, are then used to generate behavioral decisions.

While we found significant effects of amygdala lesions on prefrontal signals of expected reward and behavioral choice, we found no such effects on signals of receipt of the outcome. In control subjects, receipt of monetary reward elicited robust signal in mPFC extending down to the medial orbital surface, consistent with many previous findings (O'Doherty et al., 2001, 2003b; Small et al., 2001). However, when comparing BOLD signals in controls to those in amygdala lesion subjects, we found no significant differences, except for a single voxel at $p < 0.01$, suggesting that differential processing of reward feedback in this area is unaffected by the lesions. Similarly, BOLD signal to punishing feedback was found in lateral areas of PFC (on the lateral surface and extending down to lateral OFC) in controls, again consistent with prior observations. However, once again there were no differences in these responses between activity in amygdala lesion subjects and controls. Thus, our findings indicate that amygdala lesions selectively impair some, but not all, aspects of reward-related processing in vmPFC, ruling out a nonspecific effect of amygdala lesions on vmPFC function or on the BOLD signal in general.

Although the present results largely support findings from the animal literature of a role for the amygdala in facilitating computations of expected outcomes in PFC (Schoenbaum et al., 2003), there are also interesting differences. Most notably, typically in the animal literature, selective lesions of amygdala have generally failed to produce impairments on reversal learning (Izquierdo and Murray, 2007; Schoenbaum et al., 2003) or have even been shown to abolish impairments induced by orbitofrontal lesions (Stalnaker et al., 2007). Yet here we report that our amygdala lesion subjects were consistently impaired in the degree to which they tended to switch their choice following receipt of rewarding feedback. Besides the obvious interspecies differences, there are a number of other possible differences between the present study and prior animal studies that could account for such results. First, no prior animal studies have specifically addressed the effects of amygdala lesions on choice switching behavior (to our knowledge). Moreover, our human subjects with amygdala lesions developed these lesions at some point during their development, whereas amygdala studies of reversal learning in animals typically involve relatively acute effects. Furthermore, while many animal studies target specific amygdala nuclei such as the basolateral nucleus, here, we believe that essentially all of the amygdala is compromised functionally in both patients, although we cannot exactly quantify the extent of damage because we do not have the resolution (with MRI) to make conclusions about specific nuclei, and because of the nature of the lesions (although MRI shows the regions that are calcified, it is likely that immediately surrounding regions are also compromised functionally). It should also be noted that the present results pertain to the effects of amygdala lesions on acquisition of new

learning, but leave open the question of whether such lesions might also affect behavior based on associations that were acquired before the lesions.

The results of the present study highlight an important contribution of amygdala-vmPFC interactions toward the computation of expected reward value in humans, and support a model of decision making whereby these expected reward signals, once computed, are integrated in vmPFC and then subsequently used to guide behavioral decision making. More generally, these results highlight the utility of combining studies of human subjects who have discrete lesions with neuroimaging in order to address computationally driven hypotheses about the functional significance of neural interactions between brain areas. While the present study has addressed the role of amygdala lesions on vmPFC function, a fruitful avenue for future research will be to investigate the converse effects of vmPFC lesions on amygdala function, and to explore interactions with additional structures involved in reward processing, such as the ventral striatum.

EXPERIMENTAL PROCEDURES

Subjects

Two subjects with bilateral amygdala lesions (A.P.: age 20, Full-Scale IQ 98, VIQ 92, PIQ 106; and S.M.: age 42, Full-Scale IQ 88, VIQ 86, PIQ 95) participated in this study (Buchanan et al., 2007). Forty-one healthy, normal subjects also participated in the experiment, twenty-five similar in age to A.P. (seventeen female; mean age 22 ± 3 years) and sixteen similar in age to S.M. (all female; mean age 44 ± 8 years). Sixteen of the subjects similar to A.P. (eight female) and four subjects similar to S.M. (all female), also participated in the fMRI experiment. Control subjects excluded those with a prior history of neurological or psychiatric illness. All subjects gave informed consent and the study was approved by the Institutional Review Board at Caltech. Before executing the task, subjects were informed that they would receive what they earned (or lost) in the task, added to an initial amount of $25. It was not possible for subjects to produce a net monetary loss in the study.

Training

Subjects were trained on three different versions of the task. The first was a simple version of the reversal task, in which one of the two fractals presented yielded monetary rewards 100% of the time and the other yielded monetary losses 100% of the time. These then reversed according to the same criteria as in the imaging experiment proper (cf. Figure 2). This training phase ended after subjects successfully completed three sequential reversals. The second training phase consisted of the presentation of two stimuli that delivered probabilistic rewards and punishments as in the experiment (see Figure 2), but where the contingencies did not reverse. The training ended after the subject consecutively chose the "correct" stimulus ten times in a row, or after 100 trials, whichever came first. The final training phase consisted of the same task parameters as in the actual imaging experiment (stochastic rewards and punishments as described in the main text, and stochastic reversals). This phase ended after the subject successfully completed two sequential reversals. Different fractal stimuli were used in the training session from those used in the scanner. Subjects were informed that they would not receive renumeration for their performance during the training session.

Task Description

Subjects participated in a probabilistic reversal learning task, as described in Figure 2. In addition to the reversal trials, we also included null event trials, which were 33% of the total number of trials, randomly intermixed with the reversal trials. These trials consisted of the presentation of a fixation cross for 7 s. In addition, subjects also participated in a second deterministic reversal task (the order of presentation of the tasks was counterbalanced), which was identical to the probabilistic task except that reward contingencies were deterministic (i.e., the correct stimulus was associated with reward 100% of the time, while the incorrect stimulus was always associated with punishing feedback). This latter task also consisted of 110 choice trials and an additional 55 randomly intermixed null event trials.

fMRI Study Procedure

The amygdala lesion subjects and the subset of control subjects who participated in the fMRI experiment underwent exactly the same training procedure outside the scanner as described above, and in addition underwent both the probabilistic and deterministic task in the scanner (in counterbalanced order). fMRI data from the deterministic task was lost for one of the amygdala lesion subjects (A.P.) due to that subject moving out of the field of view during that session. For this reason, we restrict our reporting of the fMRI results to the probabilistic version of the task for which good data was obtained from both amygdala lesion subjects. However, we report the behavioral results from both the probabilistic and deterministic versions.

Data Acquisition and Preprocessing

BOLD fMRI was conducted using a Siemens 3.0 Tesla Trio MRI scanner to acquire gradient echo T2* weighted echo-planar images (EPI) with an eight-channel phased array head coil. Visual stimuli were presented using Restech (Resonance Technologies, Northridge, CA) goggles, and subject responses were recorded with a button box. Oblique axial-coronal slices were acquired at 30° to the Anterior Commissure-Posterior Commissure (AC-PC) line for a neutral head position to minimize signal loss and geometric distortion in the OFC. A total of 580 volumes (19 min) were collected during the experiment in an interleaved-ascending slice order. The imaging parameters were: echo time (TE), 30 ms; field-of-view (FOV), 192 mm; in-plane resolution and slice thickness, 3 mm; repetition time (TR), 2 s. Whole-brain, high-resolution T1-weighted structural scans (1 × 1 × 1 mm) were also acquired from the control subjects, coregistered with their mean EPI images, and averaged to permit anatomical localization of the functional activations at the group level. Image analysis was performed using SPM2 (Wellcome Department of Imaging Neuroscience, Institute of Neurology, London, UK). Temporal normalization was applied to the scans, with each slice centered to the middle of the scan (TR/2). To correct for subject motion, all EPI volumes were realigned to the first volume, spatially normalized to a standard T2* template with a resampled voxel size of 3 mm, and spatially smoothed using a Gaussian kernel with a full width at half-maximum (FWHM) of 8 mm. Intensity normalization and high-pass temporal filtering (using a filter width of 128 s) were also applied to the data (Friston et al., 1995). The same process was applied to the amygdala lesion subjects, and no qualitative spatial distortion effects due to the normalization process could be seen near the lesioned area in either the functional EPI or structural T1-weighted scans.

Data Analysis

Behavioral Data Analysis

To compare the behavior of the amygdala lesion subjects with that of controls in both reversal tasks, we used ten different behavioral measures: (1) response timing (how many ms after the trial start did subjects take to respond); (2) choice timeouts (defined as those that took longer than 1 s) after receiving a punishment in the previous trial; (3) total number of choice switches; (4) number of choice switches after receiving a reward; (5) number of choice switches after receiving a punishment; (6) number of double switches (i.e., number of switches that occurred twice in a row); (7) number of task reversals; (8) number of trials after task reversal it took for subjects to switch choice; (9) number

of trials after task reversal it took for subjects to reach the task criterion; and, for the probabilistic reversal task only, (10) number of consecutive punishments leading to a switch in choice. Many of these behavioral measures were correlated across subjects. Measurements (3) to (10) can be considered to have a binomial distribution and are modeled as a beta distribution across subjects (the beta distribution being a conjugate prior distribution of the binomial distribution—Rice, 1995). Once fitted to a beta distribution, they were converted to an equivalent normal Gaussian distribution. All other measures were assumed to have a Gaussian distribution, and were normalized to unit variance and zero mean. Age effects were removed from each behavioral measure by regressing subjects' age and using the regression residuals as age-corrected data. These were renormalized for the analysis reported in Figure 3. p values were calculated to compare each amygdala lesion subject to control subjects (using t tests between two sampled means) and converted to equivalent z-scores for plotting in Figure 3.

PCA

PCA was performed on all behavioral measures of a task to characterize behavior with a single explanatory variable. The first principle component in the deterministic task accounted for 46% of behavioral variance in that task (second principal component—19%), and the first principle component in the probabilistic task accounted for 37% of behavioral variance in that task (second principal component—also 19%), whereas each behavioral measure on its own accounts for 10% of behavioral variance for each task by definition.

Computational Model-Based Analysis: Generating Expected Reward Signals

In order to generate signals related to subjects' expected reward value on each trial, we used an approximation to the Hidden Markov Model formulation used previously (Hampton et al., 2006), whereby in order to choose optimally, it is necessary to compute expected reward signals not only by taking into account the history of rewards and punishments received on a given choice, but also the structure of the task: namely, that when one choice is correct, the other is not. Rewards and punishments received on each trial were used to update both the selected and unselected choices. Thus, after making choice A and receiving a reward, the update of the value of both choices becomes:

$$\begin{aligned} V_A^{t+1} &= V_A^t + \eta\left(R^t - V_A^t\right) \\ V_B^{t+1} &= V_B^t + \eta\left(-R^t - V_B^t\right) \end{aligned} \tag{1}$$

where $R^t - V^t{}_A$ is the prediction error between the reward R^t subjects obtained at time t, and the expected reward $V^t{}_A$ of their choice. This model is therefore a variant of standard RL, except for the additional updating of the action not taken (action B), similar to fictive updating in RL (Coricelli et al., 2005; Montague et al., 2006). This model states that subjects assume that the reward they would have received for the choice not taken is exactly opposite to the reward they receive for their current choice. Although reward outcomes are probabilistic, this update correctly captures the anticorrelation between choice values in this task.

To choose which action to make (A or B), the model compares their expected rewards to select which will give the most reward in the future. The probability of choosing action A is:

$$P(A) = \sigma(\beta(V_B - V_A) - \alpha) \tag{2}$$

where $\sigma(z) = 1/(1 + \exp(z))$ is the Luce choice rule (Luce, 2003) or logistic sigmoid, α indicates the indecision point (when it's equiprobable to make either choice), and β reflects the degree of stochasticity in making the choice (i.e., the exploration/exploitation parameter).

In order to estimate the free parameters in the model, we fit the model predictions to subjects' actual behavioral data, and selected those parameters which minimized the error in the fit of the model to the behavioral data (using logistic log-likelihood errors). We used the multivariate constrained minimization function (fmincon) of the Optimization Toolbox 2.2 in Matlab 6.5 (www.mathworks.com) for this fitting procedure. We tested for data overfitting by comparing out-of-sample log-likelihoods to training log-likelihoods, and did not find significant differences (Figure S5).

FMRI Data Analysis

Behavioral Choice

For the analysis of behavioral choice signals, we conducted an analysis similar to that reported in O'Doherty et al. (2003a). For this, we categorized trials according to subjects' reward outcomes and *subsequent* behavioral choices. We modeled event-related responses at the time of receipt of the outcome, and differentiated between trials in which subjects subsequently switched their choice of stimulus (switch trials), and trials in which subjects maintained their current choice of stimulus (stay trials). These two types of trials were further differentiated by whether subjects received a punishment or a reward as a consequence of their choice in the *current* trial. Separate regressors were entered for reward-stay, reward-switch, punish-stay, and punish-switch trials, by constructing sets of delta (stick) functions at the time of the outcome for each trial type. A common regressor across all trial types was also modeled at the time of choice. These regressors were then convolved with a canonical hemodynamic response function. In addition, the six scan-to-scan motion parameters produced during realignment were included to account for residual motion effects. These regressors were fitted to each subject's fMRI data individually, and the regression parameters were then taken to the random effects level, to generate group random effects statistics. The regression parameters for both amygdala lesion subjects were modeled separately at the random effects level from the regression parameters for the control subjects. A linear contrast was then computed between the amygdala lesion subjects and controls to identify areas showing significant differences between the two groups. For the results reported in the present study, we tested for areas showing significantly decreased responses in the amygdala lesion subjects as compared with those in the controls (at $p < 0.001$ uncorrected) in our regions of interest, restricted to those areas showing significant effects for the switch-stay contrast in the control subjects (at $p < 0.01$ or lower). The results were also masked to show only those voxels in *each of the two* amygdala lesion subjects that are significantly different from controls (at $p < 0.05$ or lower).

Expected Reward Signals

We conducted an additional analysis to detect brain regions correlating with expected reward. For this, regressors were constructed using the trial-by-trial expected reward signals as predicted by the computational model described above, given the trial history of each individual subject. These were then entered as parametric regressors set at the time of choice. We also modeled the outcome received on each trial (whether a reward or a punishment was obtained). As before, these regressors were convolved with a hemodynamic response function, and motion regressors were included as effects of no interest.

These regression fits were then taken to the random effects level separately for the contrasts of expected reward at the time of choice, and for the contrast of rewards received versus punishments received at the time of outcome. A comparison was then computed between the amygdala lesion subjects and controls separately for each contrast. Statistical significance was reported at $p < 0.001$ uncorrected in our regions of interest. As before, we restricted our analysis to those voxels showing significant effects in the relevant contrast in the controls (at $p < 0.01$ or below), and show only those voxels that survive a comparison between each individual amygdala lesion subject and controls (significant at $p < 0.05$).

Supplemental Data

The Supplemental Data for this article can be found online at http://www.neuron.org/cgi/content/full/55/4/545/DC1/.

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