

COGNITIVE NEUROSCIENCE

Differentiable contributions of human amygdalar subregions in the computations underlying reward and avoidance learning



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Abstract

To understand how the human amygdala contributes to associative learning, it is necessary to differentiate the contributions of its subregions. However, major limitations in the techniques used for the acquisition and analysis of functional magnetic resonance imaging (fMRI) data have hitherto precluded segregation of function with the amygdala in humans. Here, we used high-resolution fMRI in combination with a region-of-interest-based normalization method to differentiate functionally the contributions of distinct subregions within the human amygdala during two different types of instrumental conditioning: reward and avoidance learning. Through the application of a computational-model-based analysis, we found evidence for a dissociation between the contributions of the basolateral and centromedial complexes in the representation of specific computational signals during learning, with the basolateral complex contributing more to reward learning, and the centromedial complex more to avoidance learning. These results provide unique insights into the computations being implemented within fine-grained amygdala circuits in the human brain.

Introduction

The amygdala is composed of distinct subregions, each having unique inputs and outputs and each playing distinct functional roles in associative learning and the motivational control of behavior (Cardinal *et al.*, 2002; LeDoux, 2007). In humans, although much is now known about the functions of the amygdala as a whole (Buchel & Dolan, 2000; Bechara *et al.*, 2003; Phelps, 2006; Adolphs, 2008; Seymour & Dolan, 2008), the precise functional contribution of its subregions remain unknown due to limitations in spatial resolution and analysis methods.

Here we focused on two distinct forms of instrumental conditioning: reward-learning, in which an animal learns to select actions to obtain rewards, and avoidance-learning, in which an animal learns to select actions to avoid aversive outcomes. We focused on the differential contribution of the basolateral and centromedial complexes to these forms of learning. These areas have been differentially implicated in a variety of motivational and learning phenomena (Killcross *et al.*, 1997; Holland *et al.*, 2002; Holland & Gallagher, 2003; Corbit & Balleine, 2005; Petrovich *et al.*, 2009). Although there is evidence for a differential contribution of these areas in the control of food consumption by appetitive and aversive learned cues, respectively (Holland *et al.*, 2002; Petrovich *et al.*, 2009), the specific contribution of these regions in instrumental reward and avoidance learning remains largely unexplored.

To address this question, we used a high-resolution functional magnetic resonance imaging (fMRI) procedure of the amygdala, together with an amygdala-specific normalization approach, to functionally resolve activity in distinct amygdalar subregions across subjects, without the need for extrinsic spatial smoothing. Previous fMRI studies have reported computational learning signals in amygdala such as expected outcomes and prediction errors during performance of similar tasks (Elliott *et al.*, 2004; Seymour *et al.*, 2005; Yacubian *et al.*, 2006; Hampton *et al.*, 2007). Consequently, we hypothesized that we would find these different signals to be present within the amygdala in the present study.

Furthermore, we hypothesized the presence of an uncertainty signal pertaining to the model-derived estimate of expected outcomes. Several pieces of evidence indirectly point toward a possible role for the amygdala in encoding such a signal. First, the amygdala has long been known to be involved in influencing the allocation of attention and orienting to conditioned stimuli, which could be driven by estimation uncertainty (Gallagher *et al.*, 1990; Dayan *et al.*, 2000; Davis & Whalen, 2001). Secondly, amygdala activation has been found when making decisions under conditions of high ambiguity (and hence uncertainty) about outcomes (Hsu *et al.*, 2005). Finally, amygdala neurons have been implicated in encoding 'associability' which is in essence a form of uncertainty about estimated outcomes (Pearce & Hall, 1980; Roesch *et al.*, 2010). Thus, we postulated that the amygdala would also be involved in encoding a representation of uncertainty in the estimation of learned outcomes during task performance.

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Going beyond previous fMRI studies, our use of high-resolution fMRI allowed us establish the extent to which these signals are localized to different subregions of the amygdala, both as a function of the type of computational signal involved and as a function of the type of learning involved (whether reward or avoidance learning).

Materials and methods

Subjects

Twenty right-handed subjects (11 females) with a mean age of 22.65 ± 3.29 years participated in the study. All subjects were free of neurological or psychiatric disorders and had normal or correct-to-normal vision. Written informed consent was obtained from all subjects, and the study was approved by the Trinity College ethics committee. Subjects were informed before performing the task that they would receive what they earned or lost during the task, added to an initial amount of 25 Euros. On average, subjects earned 31.5 ± 4.38 Euros.

Task description

Subjects participated in a probabilistic reversal learning task, which was divided into three sessions lasting approximately 16.5 min each, with a 2- to 3-min break between sessions. Each session was composed of 72 trials, leading to a total of 216 trials. The task was equally divided in three conditions: a reward condition, an avoidance

condition and a neutral condition, so that each condition was presented 24 times per session. The presentation order of these conditions was randomized across sessions and subjects. To ensure that each of the three conditions was presented an equal number of times per session, each condition was presented twice every six trials. On each trial, a fractal stimulus indicating the condition was displayed on the screen for 1–6 s. Subjects were then presented with a two-armed bandit slot machine and were asked to select the left or right arm. One action (left or right) was designated the correct action in that choosing it led to a monetary reward (+50 cents) 80% of the time and no monetary reward (0 cents) 20% of the time in the reward condition or no monetary reward (0 cents) 80% of the time and a monetary loss (–50 cents) 20% of the time in the avoidance condition. Consequently, choosing the correct action led to accumulating monetary gain in the reward condition and avoiding cumulating monetary loss in the avoidance condition. Choosing the incorrect action led to no monetary reward (0 cents) 80% of the time and a monetary reward (+50 cents) 20% of the time in the reward condition or a monetary loss (–50 cents) 80% of the time in the avoidance condition. There was no correct/incorrect action in the neutral condition as all actions led to no monetary gain (0 cents). Subjects had 1 s to make their choice and subsequently waited for 1–8 s while the slot machine was spinning before the outcome was displayed for 1 s. The next trial started after a 1- to 6-s inter-trial interval (Fig. 1). If subjects chose the correct action on four consecutive occasions in a given condition, the contingencies reversed with a probability of 0.4 on each successive trial. Once reversal

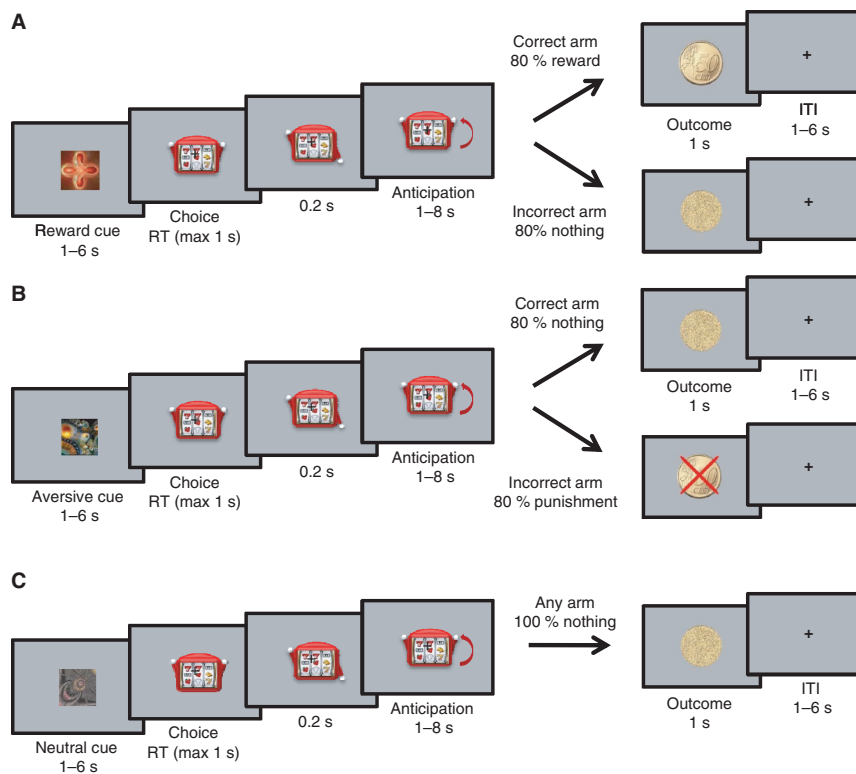


FIG. 1. Reward/avoidance instrumental learning task. Sequence and timing of events of the reward (A), avoidance (B) or neutral (C) conditions. The reward (A), avoidance (B) or neutral (C) cue was shown for 1–6 s, followed by the choice of the left or right arm of the slot machine (maximum 1 s). The chosen arm went down for 200 ms after which the slot machine spun for 1–8 s. If the correct action was chosen, a 50-cent coin/a scramble coin (0 cents) was displayed for 1 s 80% of the time in the reward/avoidance condition, respectively, whereas if the incorrect action was chosen, a scramble coin/crossed-out 50-cent coin (–50 cents) was displayed for 1 s 80% of the time in the reward/avoidance condition, respectively. All actions led to a scramble coin (0 cents) in the neutral condition. The trial ended with a 1- to 6-s interval (ITI).

occurred, subjects then needed to choose the new correct action on four consecutive occasions before reversal could occur again (with 0.4 probability). Subjects were informed that reversals occurred at random intervals throughout the experiment but were not informed of the precise details of how reversals were triggered by the computer (so as to avoid subjects using explicit strategies, such as counting the number of trials to reversal). The subject's task was to accumulate as much money as possible and thus keep track of which action was currently correct in a given condition and choose it until reversal occurs. Subjects used a button box to select their left or right action. If subjects did not make their choice in the 1 s provided, the current trial was aborted and the same trial was started again, to ensure that subjects did not avoid the trials in the avoidance condition. The assignment of the fractal images as cues in all three conditions was randomized across sessions and subjects.

Prescan training

Before scanning, the 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 actions yielded monetary rewards/no monetary reward 100% of the time, and the other action yielded no monetary reward/monetary losses 100% of the time in the reward/avoidance conditions, respectively. These then reversed according to the same criteria as in the imaging experiment proper, in which a reversal was triggered with a probability of 0.4 after four consecutive choices of the correct action. This training phase was ended after the subject successfully completed two sequential reversals. The second training phase was identical to the first part except that no reversal occurred and that the outcome was probabilistic, as in the experiment. The training ended after the subject consecutively chose the correct action eight times in a row. The final training phase consisted of the same task parameters as in the actual imaging experiment (stochastic outcomes, and stochastic reversals as described above). 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 remuneration for their performance during the training session.

Data acquisition

Functional imaging was performed on a 3-T Philips scanner equipped with an eight-channel SENSE (sensitivity encoding) head coil. As the focus of our study was on the amygdala, we only acquired partial T2*-weighted images centered to include the amygdala while subjects were performing the task. These images also encompassed the ventral part of the prefrontal cortex, the ventral striatum, the insula, the hippocampus, the ventral part of the occipital lobe and the upper part of the cerebellum (amongst other regions). Nineteen contiguous sequential ascending slices of echo-planar T2*-weighted images were acquired in each volume, with an in-plane resolution of 1.58×1.63 mm, and a slice thickness of 2.2 mm and a 0.3-mm gap between slices [repetition time (TR): 2000 ms; echo time (TE): 30 ms; field of view: $196 \times 196 \times 47.2$ mm; matrix: 128×128]. A whole-brain high-resolution T1-weighted structural scan (voxel size: $0.9 \times 0.9 \times 0.9$ mm) and three whole-brain T2*-weighted images were also acquired for each subject. To address the problem of spatial echo-planar imaging (EPI) distortions which are particularly prominent in the medial temporal lobe (MTL) and especially in the amygdala, we also acquired gradient field maps. To account for

physiological fluctuations, subjects' cardiac and respiratory signals were recorded with a pulse oximeter and a pressure sensor placed on the umbilical region and further removed from time-series images (see fMRI data analysis below). We discarded the first three volumes before data processing and statistical analysis to compensate for the T1 saturation effects.

Preprocessing

All EPI volumes (partial scans acquired while subjects were performing the task and the three whole-brain functional scans acquired prior to the experiment) were corrected for differences in slice acquisition and spatially realigned. The mean whole-brain EPI was co-registered with the T1-weighted structural image, and subsequently all the 'partial' volumes were co-registered with the registered mean whole-brain EPI image. 'Partial' volumes were then unwrapped using the gradient field maps. Due to a technical problem, gradient field maps for two of the subjects could not be obtained. After the structural scan was normalized to a standard T1 template, the same transformation was applied to all the 'partial' volumes with a resampled voxel size of $0.9 \times 0.9 \times 0.9$ mm. To maximize the spatial resolution of our data, no spatial smoothing kernel was applied to the data. These preprocessing steps were performed using the statistical parametric mapping software SPM5 (Wellcome Department of Imaging Neuroscience, London, UK).

Whole amygdalae segmentation

Amygdalae regions of interest (ROIs) were manually segmented for each subject by a single observer using a pen tablet (Wacom Intuos3 Graphics Tablet) in FSL View (FSL 4.1.2). This program allows magnification and the simultaneous viewing of volumes in coronal, sagittal and horizontal orientations. Amygdalae were manually outlined on each coronal image containing the amygdala using detailed tracing guidelines based on the Atlas of the Human Brain (Mai *et al.*, 2008). Outlines were checked in horizontal and sagittal planes when they proved more valuable for the identification of structure boundaries. The anterior limit of the amygdala was defined using the horizontal and sagittal planes. The following guidelines were used – in its rostral part, the amygdala is bordered ventromedially by the entorhinal cortex, ventrally by the temporal horn of the lateral ventricle and subamygdaloid white matter and laterally by white matter of the temporal lobe. Midrostrocaudally, the amygdala increases in size and is bordered ventromedially by a thin tract of white matter separating the amygdala and the entorhinal cortex, laterally by the white matter of the temporal lobe and medially by the semiannular sulcus. Caudally, the amygdala is bordered dorsally by the substantia innominata and fibers of the anterior commissure, laterally by the putamen, ventrally by the temporal horn of the lateral ventricle and the alveus of the hippocampus, and medially by the optic tract.

Amygdalae normalization

Because structures in the MTL exhibit significant inter-individual anatomic variability, the signal-to-noise ratio in group analyses is substantially limited in this area (Insausti *et al.*, 1998). Atlas-based approaches used to register whole-brain EPI images across subjects (such as SPM) look for a global optimum alignment which is achieved under the limitations imposed by the available degrees of freedom, and which is at the expense of regional accuracy. Consequently, blood oxygen level-dependent (BOLD) signals in

the MTL may be underestimated or possibly missed (Miller *et al.*, 2005). Alignment of the MTL is substantially improved by a ROI-alignment (ROI-AL) approach, where segmentations of ROIs are drawn on structural images and aligned directly, resulting in an increased statistical power (Yassa & Stark, 2009). The last iteration of this alignment tool is ROI-Demons, which has proven to be exceptionally accurate in the alignment of hippocampal subfields for instance (<http://darwin.bio.uci.edu/~cestark/roial/roial.html>). Thirion's original demons algorithm has been implemented by Vercauteren and enforces smooth deformations by operating on a diffeomorphic space of displacement fields (Thirion, 1998; Vercauteren *et al.*, 2007). Here, we used the implementation of ROI-Demons in the DemonsRegistration command-line tool (<http://www.insight-journal.org/browse/publication/154>). Our segmented amygdalae ROIs were registered with the amygdalae of a single subject to serve as an initial model and to roughly align all amygdalae using DemonsRegistration. The resulting registered amygdalae were then averaged in SPM5 (using ImCalc) to create a first model. Subsequently, the initial non-registered amygdalae were registered with this first model and the newly registered amygdalae were averaged to create a second model. We repeated the last two steps three more times to generate a more accurate model. We finally registered our initial amygdalae ROIs with the fifth model to generate the resulting displacement fields (or transformation calculations). These individual displacement fields were then applied to each subject's normalized EPI scans to specifically normalize their amygdalae to our template amygdalae. We applied the same transformation to each subject's structural scan before averaging all the aligned structural scans, to create an amygdalae-aligned average structural brain of our 20 subjects.

Segmentation of amygdalar subregions

To date, two different techniques have been proposed to anatomically delineate human amygdalar subregions using MRI: Amunts *et al.* (2005) used post-mortem cytoarchitectonics to develop a probabilistic map of amygdala nuclei and other medial temporal lobe structures, while Solano-Castiella *et al.* (2010) used diffusion-weighted MRIs to cluster amygdala subregions based on the predominant diffusion direction. However, although both of these approaches are promising future directions, in our case neither of these segmentation methods was deemed appropriate. The Amunts amygdala map was found to extend far beyond the limits of the amygdala into the white matter of the medial temporal lobes, suggesting a mismatch between the localization of the amygdala in our sample and that in the probabilistic map. This may be due to the fact that the post-mortem brains used to derive the map were from a much older population (average age 65 years), than that used in our study (average age 23 years). Given that gross structural changes are known to occur in the brain with aging such as atrophy of brain structures and increase in ventricular size (Anderton, 1997), differences in amygdala shape and location between a younger sample (standard for fMRI studies on healthy controls) and an older sample might account for such effects, rendering the Amunts map unsuitable for our sample. The Solano-Castiella diffusion-based segmentation method yielded two distinct areas of the amygdala along a medial to lateral dimension. Unfortunately this delineation does not map clearly onto the known nuclear structure of the amygdala and the known location of the basolateral and centromedial complexes (which are better differentiated along a ventral to dorsal dimension). This might reflect the

possibility that the diffusion-based segmentation method is probably sensitive to the orientation of myelinated fibers as opposed to cytoarchitecture (Solano-Castiella *et al.*, 2010). Because of these issues, we used a manual segmentation approach to delineate the amygdala sub-structures as follows.

Amygdalar subdivisions were hand-drawn on our template amygdalae using the Atlas of the Human Brain (Mai *et al.*, 2008). We delineated three sub-areas within the amygdala – the basolateral complex comprising the basomedial, basolateral and lateral nuclei; the centromedial complex comprising the central and medial nuclei; and the cortical complex (or cortical nucleus). In its most rostral part, the amygdala is exclusively composed of the basolateral complex. The cortical nucleus appears in the dorso-medial part of the mid-rostral amygdala. The centromedial complex appears slightly more caudally than the cortical nucleus in the most dorsal part of the amygdala. The basolateral complex increases in size as one moves caudally from the anterior amygdala, has its maximal size midrostromedially and then decreases as one moves further back toward the caudal amygdala, whereas the cortical nucleus and centromedial complex slightly enlarge midrostromedially, but do not decrease in size as one moves further caudally within the amygdala. The cortical nucleus ends midcaudally, the basolateral complex ends in the caudal amygdala while the centromedial complex ends in the most caudal part of the amygdala.

To address the concern that our manual segmentation method could be prone to experimenter bias, we also performed a much more basic differentiation based on the very fundamental observation that the ventro-dorsal extent of the centromedial complex extends approximately across the top quarter of the volume of the whole amygdala, while the basolateral complex extends across the bottom three-quarters of the volume. We therefore delineated much simpler ROIs whereby the top quarter of the amygdala depicts the approximate location of the centromedial complex while the bottom three-quarters represents the approximate location of the basolateral complex. Even when using these simpler ROIs, all of the condition $\times$ subregion interactions reported in the results in the ROI comparisons were still significant at the $P < 0.05$ level. This demonstrates that our results are extremely unlikely to be due to experimenter bias in the manual segmentation of the amygdala ROIs as described above.

Computational model-based analysis

Action value learning

To best characterize the nature of learning in this task, several variants of the Rescorla Wagner/delta learning rule were considered (Rescorla & Wagner, 1972) – simple delta rule learning (Gluck & Bower, 1988) consisting of only updating the chosen action; decay reinforcement (Erev & Roth, 1998), which updates the chosen action and decays unchosen actions to 0; and fictive reinforcement learning (Myung & Busemeyer, 1992; Fudenberg & Levine, 1998), which updates the unchosen action with what would have been received had the action been selected, a model that has previously proven successful in explaining behavioral and neural activity during reversal learning (Hampton *et al.*, 2007; Glascher *et al.*, 2009). The fictive model assumes that outcomes available on the two actions are perfectly inversely correlated because of the reversal structure; for example, if the selected option on an appetitive trial resulted in no reward, then the alternate option is assumed to have provided a reward. The action values $Q(i)$ for both the selected and unselected choices were updated according to:

$$Q_j(t+1) = Q_j(t) + \alpha(R(t) - Q_j(t)) \quad (1)$$

For each of these three variants, when j is the chosen action, α is the learning rate, and $R(t)$ is the reward received on the current trial. If the 'good' outcome was obtained on the current trial, $R(t) = 1$, otherwise $R(t) = 0$. When j is the unchosen action, $\alpha = R(t) = 0$ for the simple delta rule model (resulting in no change in expectation). For both the decay and the fictive models, α is the learning rate and $R(t) = 0$ or 1 – reward received on the current trial, respectively. The new action value at trial $t + 1$ for the chosen action is based on the sum of the current action value and the prediction error between the reward obtained and the action value at time t , weighted by the learning rate.

Action selection computation

To choose which of the two actions to select, the model compares action values and probabilistically selects the action expected to give the most reward in the future. The probability $P_j(t)$ of choosing action j out of the entire set of actions at time t is given by the softmax rule (Sutton & Barto, 1998), a parameterized version of the Luce choice axiom (Luce, 1959):

$$P_j(t) = e^{Q_j(t)/\theta} / \sum_i e^{Q_i(t)/\theta} \quad (2)$$

The inverse temperature parameter θ controls the extent to which decisions are consistent. As θ approaches 0, the model predicts increasingly deterministic choice whereas larger values of θ indicate increasingly random selection.

Plots of subject choices vs. model predictions in the reward and avoidance conditions are shown in Fig. 2C,D.

Model fitting and comparison methods. The values for three free parameters were estimated for each model variant, using *fminsearch*, a simplex (Nelder & Mead, 1965) hill descent algorithm available in Matlab. Learning rates α_{rew} and α_{av} were fit separately for the reward and avoidance conditions as well as the softmax temperature parameter θ . Data from the neutral condition were not fit. Values for $Q(0)$ were set to 0.5, reflecting the idea that individuals were updating the probabilities of obtaining the outcomes, and high values of Q indicate a greater expectation for obtaining the superior outcome. Data were pooled across subjects, as this method has proven to more reliably estimate true underlying parameter values with smaller numbers (e.g. < 100) of trials per subject (Cohen *et al.*, 2008).

Parameter estimation was conducted using maximum-likelihood estimation. Here, we obtained the values for the parameters that minimized the negative log likelihood (NLL) of the data given the model (Myung, 2003). The NLL from each model was compared with that given by a baseline model that assumed random selection on each trial. Hence, the comparison was between random choice and ordered choice. The Bayesian information criterion (BIC) was used to compare the baseline model with the learning model variants. The BIC adds a penalty proportional to the number of additional free parameters to the NLL of each model, depending also on the number of degrees of freedom which, in this case, is the total number of reward and avoidance trials across all subjects (Schwarz, 1978). Note that if across all subjects each action is chosen with equal frequency – a very realistic scenario in a reversal learning task, as used here – the only hope the learning models have in outperforming the baseline model is to detect outcome-based changes in choice behavior (i.e. learning). As shown in Table 1, the decay reinforcement learning model best fit the

data. Consequently, this model variant was used in the subsequent fMRI data analysis.

State value learning

We also modelled learning of the value of the states indicated by the presentation of the visual cues at the time of trial onset. These cues indicated either a reward trial, an avoidance trial or a neutral trial. The state values were learned directly using a delta learning rule similar to that used to learn the action values; the values of the reward and avoidance state cues were updated separately.

The formula for the cue value updating is:

$$V_s(t+1) = V_s(t) + \delta \times \sqrt{U(t)/U(1)} \times (R(t) - V_s(t)) \quad (3)$$

where $V_s(t)$ is the value of the cue on trial t .

However, as the learning rate for the state values could not be estimated directly from the choice data as was the case for the action values, we adopted a reinforcement learning-based approximation of a Kalman filter to compute the trial by trial uncertainty $U(t)$ in the estimate of $V_s(t)$ for the cues and used this estimation uncertainty signal to dynamically adapt the learning rate parameter for the update of $V_s(t)$ in an approximately optimal manner. Estimation uncertainty captures the extent to which one's expectations about future reward vary over time. δ is a fixed learning rate = 0.2 and R is the reward (or outcome) obtained on each trial. The difference term represents a prediction error. The product term on the right side of the equation represents a weighted adjustment to the state value on the current trial, reflecting a dynamic adjustment of the impact of the prediction error, due to changes in the estimation uncertainty component. This state value updating was agnostic regarding the action selected. Estimation uncertainty was updated according to:

$$U(t+1) = U(t) + \delta \times ((V_s(t+1) - V_s(t))^2 - U(t)) \quad (4)$$

Note that estimation uncertainty is updated by a weighted difference of the squared deviation in state value expectations and the previous uncertainty value.

A similar procedure could have been used to generate learning rates for the action values as well as for the state values; however, for the action values, estimation of the learning rates directly from the behavioral data provided a better overall model-fit to the behavioral data than did the use of the estimation uncertainty approach [$\text{BIC}(\text{Decay RL model}) = 3751.6 < \text{BIC}(\text{estimation uncertainty model}) = 3805.8$, where a lower BIC value denotes superior performance]. Hence, we deployed estimation uncertainty for computation of the learning rate parameter in the state value case only.

fMRI data analysis

The event-related fMRI data were analysed by constructing sets of δ (stick) functions at the time of cue presentation, at the time of choice and at the time of outcome for the reward, avoidance and neutral conditions. Additional regressors were constructed by using the estimation uncertainty and estimated state values as modulating parameters at the time of cue presentation, the value for the chosen action as a modulating parameter at the time of choice and the prediction error as a modulating parameter at the time of outcome. All of these regressors were convolved with a canonical hemodynamic response function (HRF). The six scan-to-scan motion parameters derived from the affine part of the realignment procedure were

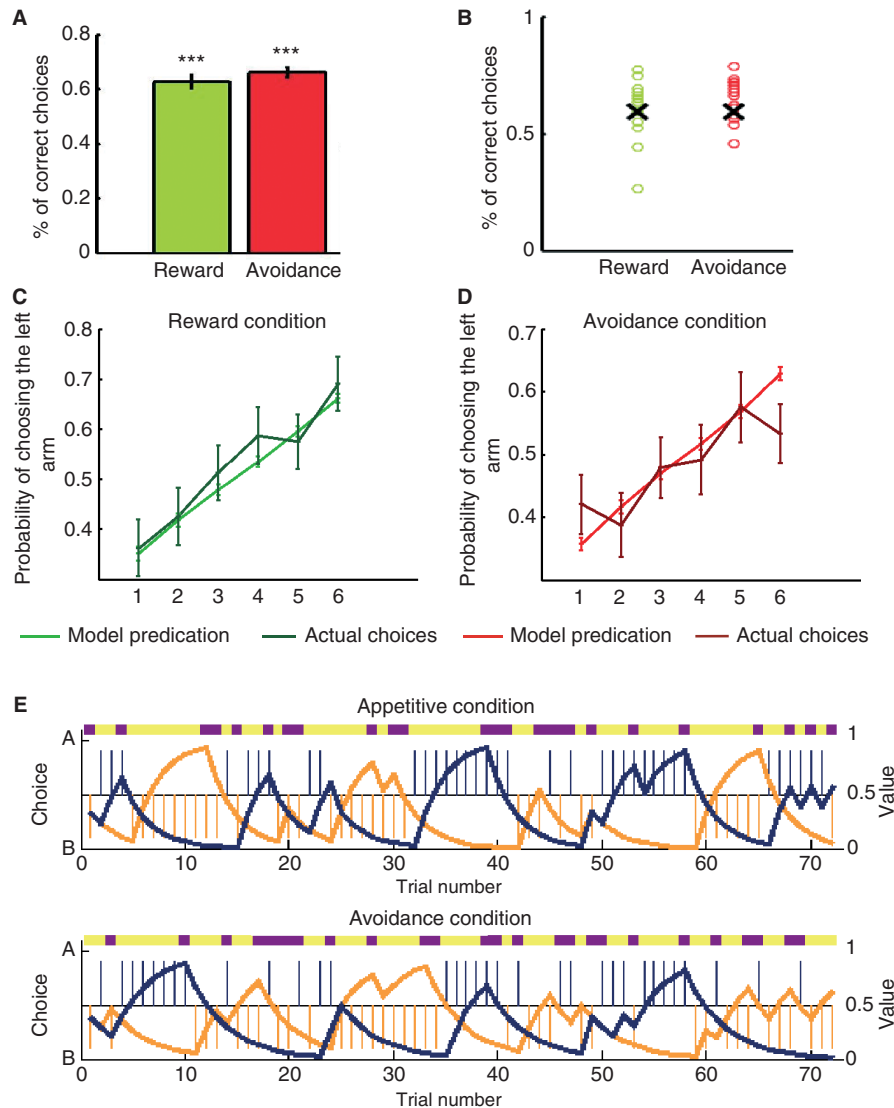


FIG. 2. Behavioral results. (A) Percentage of correct choices in the reward and avoidance conditions averaged across sessions and subjects. Error bars represent SEM. *** $P < 0.001$ as computed by a one-sample t -test comparing the mean of the correct choices for each condition against a mean of 0.5. (B) Percentage of correct choices across sessions for each subject in the reward and avoidance conditions. Each subject is represented by a circle in each condition and the black cross indicates the threshold above which subjects performed better than chance at $P < 0.05$. Note that the average percentage of correct choices does not exceed 70% because of the probabilistic nature of the task and the occurrence of reversals. (C, D) Plots of subject choices (dark colors) vs. decay RL model predictions (bright colors) in the reward (C) and Avoidance (D) conditions for six categories (category 1 representing the lowest predictions and category 6 the highest predictions). Error bars represent SEM. (E) Trial-by-trial behavioral model fit of the decay RL model for a typical subject. Actual choices of the different actions A (blue sticks) and B (orange sticks), and the model-predicted action value for each action (blue and orange lines for action A and B, respectively) are shown. The colored bar at the top shows whether subjects won 50 cents/avoided losing 50 cents in yellow or did not win 50 cents/lost 50 cents in purple in the reward and avoidance conditions, respectively.

included as regressors of no interest to account for residual motion effects. Finally, we included 13 additional regressors to account for physiological fluctuations (four related to heart rate, nine related to respiration) which were estimated using the RETROICOR algorithm (Glover *et al.*, 2000). Eight of the 60 (3 sessions $\times$ 20 subjects) log files could not be used to estimate these regressors due to a technical problem during data collection, and the missing physiological regressors were simply omitted for those sessions. All of these regressors were entered into a general linear model and fitted to each subject individually using SPM5. The resulting parameter estimates for regressors of interest were then entered into second-level one sample t -tests to generate the random-effects-level statistics used to obtain the results shown in Figs 3–5. All reported fMRI statistics and P -values arise from group random-effects analyses. We present all our

statistical maps at a threshold of $P < 0.005$, corrected for multiple comparisons at $P < 0.05$. To correct for multiple comparisons, we first used the 3dFWHMx function in AFNI to estimate the intrinsic smoothness of our data, within the area defined by a mask corresponding to our amygdala template. We then used the AlphaSim function in AFNI to estimate via Monte Carlo simulation an extent threshold for statistical significance that was corrected for multiple comparisons at $P < 0.05$ for a height threshold of $P < 0.005$ within the amygdala ROI. This extent threshold corresponds to $k = 26$ voxels.

In a separate analysis, we tested for responses in the amygdala to receipt of rewarding and punishing outcomes. We used exactly the same general linear model as mentioned above, except that we replaced the prediction error parametric modulators with outcome

TABLE 1. Model comparison between several variants of the delta learning model and a baseline model

Model	α_{Rew}	α_{Av}	θ	BIC
Baseline	—	—	—	3992.5
Simple	0.75	1	0.06	3849.2
Decay	0.32	0.24	1.13	3751.6
Fictive	0.25	0.44	0.26	3800.6

The simple delta rule learning consists of only updating the chosen action, decay reinforcement updates the chosen action and decays unchosen actions to 0, and fictive reinforcement updates the unchosen action with what would have been received had the action been selected. A smaller BIC value indicates a better fit, and therefore the decay reinforcement learning model best fitted the data.

parametric modulators. In the reward condition, on any trial where a reward was obtained, this modulator was set to 1, whereas any time a no-reward was obtained the modulator was set to -1 . For the avoidance condition, any time no punishment was obtained, the regressor was set to 1, and when a punishment was obtained it was set to -1 . Similar activation patterns were obtained in amygdala in response to outcomes (reward vs. no-reward; no punishment vs. punishment) as were obtained for prediction errors. This may be largely due to the fact that for this task, prediction errors and outcomes are intrinsically strongly correlated. However, to discriminate between them, we used a Bayesian model selection procedure (BMS) to test which signal (prediction error or outcome) better accounted for the observed activity. For the reward condition, we included voxels in this model comparison that were significantly correlated with either the outcome parametric regressors for the outcome model or the reward prediction error signal in the prediction error model. This allowed us to input only those voxels responsive either to prediction errors or to outcomes and to avoid a non-independence bias in the voxel selection. The same approach was adopted for the avoidance condition. Using the `spm_BMS` function in SPM8, we found that activity at the time of outcome was better explained by the prediction error signal at the time of outcome than by the receipt of outcomes themselves (Reward condition – exceedance probability = 0.739; Avoidance condition –

exceedance probability = 0.742). Consequently, we interpret activity at the time of outcome as pertaining to prediction errors and not outcome values *per se*.

ROI analyses

Functional ROIs were defined using the MarsBaR toolbox (<http://marsbar.sourceforge.net/>). All ROIs are functional clusters of interest as they appeared on the statistical maps of a given contrast. Percentage signal change was extracted for each subject from each of these ROIs and then averaged across subjects to plot action values (Fig. 3B), prediction error (Fig. 4B) and estimation uncertainty (Fig. 5C) according to six categories (category 1 corresponding to the lowest values and category 6 corresponding to the highest values).

Beta estimates from different amygdalar subregions, namely the basolateral complex and centromedial complex, were estimated for each subject for both the reward and the avoidance conditions. These were then averaged across subjects and beta estimates from the action value contrasts are plotted in Fig. 3C and those from the estimation uncertainty contrasts are plotted in Fig. 5D. Repeated-measures ANOVA showing the interactions subregion $\times$ condition were performed in SPSS 16.0. Note that because the volume of the basolateral and centromedial ROIs is substantially different (the basolateral is approximately three times larger than the centromedial ROI), when directly comparing the ROIs there is a possible violation of the sphericity assumption in the general linear model due to potential differences in the variance distributions. To account for this, we equalized the volume of the ROIs in an unbiased way by defining a sphere of the same volume of the centromedial ROI, placing this in the geometric centroid of the basolateral ROI and then performing the comparison between these two identical volumes. Nevertheless, even when taking the whole extent of the basolateral complex as the ROI, all the ROI effects reported in the Results remained significant at $P < 0.05$ both for the estimation uncertainty contrast and for the action value contrast. Thus, all the results reported are robust to differences in the ROI volumes.

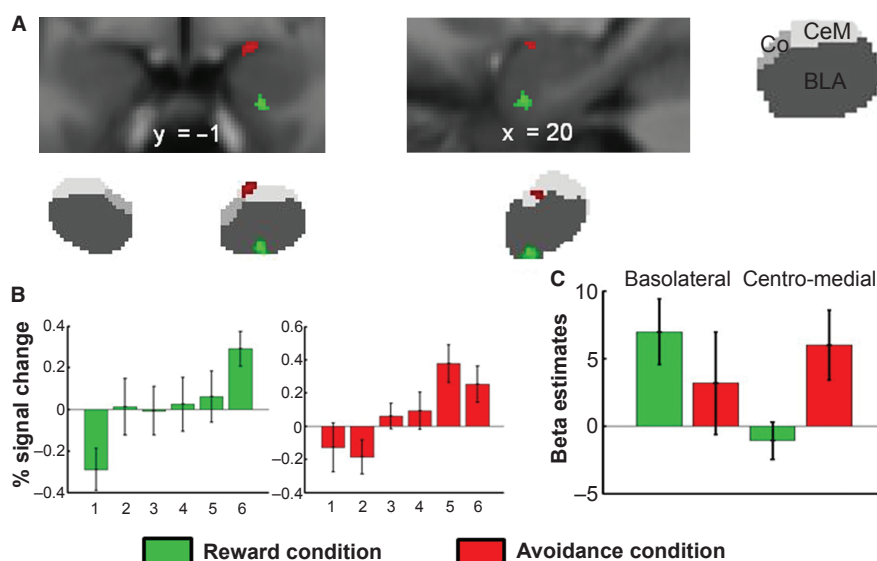


FIG. 3. Action reward value signals. (A) Blood oxygen level-dependent (BOLD) signals correlating with the magnitude of the expected reward value of the chosen action were found in the basolateral complex in the reward condition (in green) and in the centromedial complex in the avoidance condition (in red). (B) Plots showing the percentage signal change for six categories of action values (category 1 representing the lowest action values, and category 6 representing the highest action values) in the reward (green) and avoidance (red) conditions in the clusters activated. (C) Beta estimates showing an interaction between the subregion (basolateral vs. centromedial) and the condition (reward vs. avoidance) ($P < 0.05$).

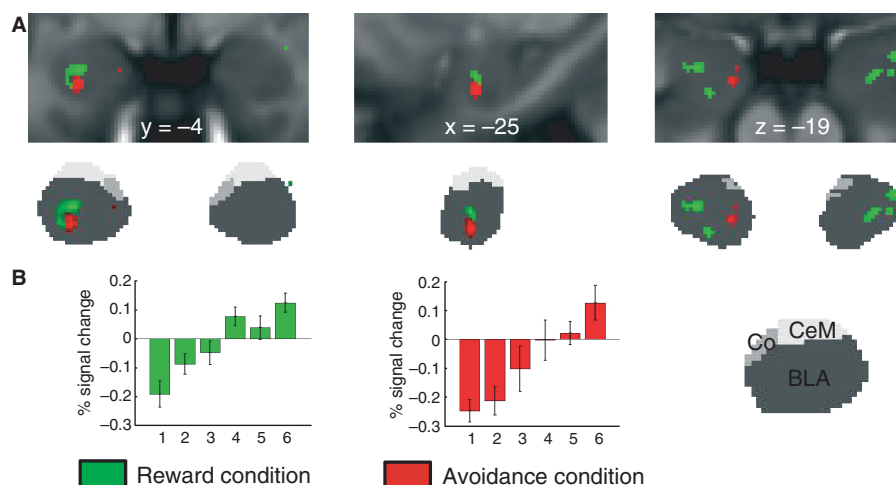


FIG. 4. Reward prediction error signals. (A) BOLD signals correlating with the magnitude of the reward prediction error at the time of outcome were found in the basolateral complex in both the reward (in green) and avoidance (in red) condition. (B) Plots showing the percentage signal change for six categories of prediction error values (category 1 representing the lowest prediction error values, and category 6 representing the highest prediction error values) in the reward (in green) and avoidance (in red) conditions in the clusters activated.

Results

Behavioral results

Subjects showed behavioral evidence of learning in both the reward and the avoidance conditions in that they favored choice of the reward-maximizing or loss-minimizing action over the alternative actions (Fig. 2A). To further show that subjects were able to learn the task, we demonstrated that overall they performed better than would be expected by chance in both conditions (Fig. 2B). We fitted a variant of a reinforcement learning model (RL) to generate trial-by-trial estimates of the computations necessary to underpin performance on such a task, including the expected future reward corresponding to individual actions at the time of choice, and prediction errors signaling the difference between expected and actual outcomes used to facilitate updating of the estimated expected reward for each action. This model performed significantly better than a baseline model choosing purely randomly, even after adjusting for additional free parameters (Table 1). Figure 2C,D shows the RL model predictions vs. participants' actual choices in the reward and avoidance conditions, respectively. The trial-by-trial estimates of the action values for a typical subject are represented in Fig. 2E.

fMRI results

We found evidence for a number of distinct computational signals within the amygdala in the reward and avoidance conditions in our fMRI data. Our results are reported using a height threshold of $P < 0.005$, with an extent threshold significant at $P < 0.05$ corrected for multiple comparisons.

Action-value signals

We first examined BOLD activity in the amygdala at the time of choice. In the reward condition, an area on the ventral border of the right anterior amygdala was found to show significant correlations with the expected reward signal for the action chosen on each trial, according to the RL model (Fig. 3A in green, MNI $[x\ y\ z]$ $[20\ -1\ -26]$, $T = 5.29$, $k = 27$ voxels). A spatially distinct, far dorsal region of the right amygdala was found to be positively correlated with the

action value signal in the avoidance condition (Fig. 3A in red, $[x\ y\ z]$ $[18\ -2\ -12]$, $T = 5.35$, $k = 52$ voxels), such that the greater the activity in that area, the less an aversive outcome is predicted to occur. We next performed an independent ROI analysis using our amygdala template, subdivided according to the approximate anatomical locations of the basolateral complex, the centromedial complex and the cortical nucleus defined in the atlas of Mai *et al.* (2008). We tested for a subregion (basolateral vs. centromedial) $\times$ condition (reward vs. avoidance) interaction on the averaged parameter estimates for our action value signal within the designated amygdalar ROIs. This analysis yielded a significant subregion $\times$ condition interaction ($F_{1,19} = 7.06$, $P < 0.05$) such that the basolateral amygdala showed greater correlation with action value in the reward condition while the centromedial complex showed a significantly greater correlation with action value in the avoidance condition (Fig. 3C). We also looked for areas correlating negatively with action value in both the reward and the avoidance conditions; that is, areas showing an increase in activity the less reward was predicted to occur given the chosen action, according to the RL model. We found significant activity in a region of anterior dorso-medial amygdala in the possible vicinity of the cortical amygdala nucleus in the reward condition ($[x\ y\ z]$ $[17\ 3\ -15]$, $T = 4.23$, $k = 32$ voxels).

Reward prediction error signals

Next, we examined amygdala activity at the time of outcome. We tested for amygdala activity correlating with reward prediction errors during the reward and avoidance conditions. We found activity positively correlating with prediction error during both the reward and the avoidance conditions within the basolateral complex ROI (reward condition: $[x\ y\ z]$ $[-25\ -4\ -19]$, $T = 5.24$, $k = 47$; $[x\ y\ z]$ $[22\ -8\ -16]$, $T = 5.13$, $k = 140$; $[x\ y\ z]$ $[-21\ -11\ -19]$, $T = 4.50$, $k = 96$; $[x\ y\ z]$ $[28\ -1\ -19]$, $T = 4.27$, $k = 47$; avoidance condition: $[x\ y\ z]$ $[-25\ -5\ -23]$, $T = 5.01$, $k = 38$; $[x\ y\ z]$ $[-15\ -6\ -21]$, $T = 4.88$, $k = 39$; $[x\ y\ z]$ $[29\ -11\ -14]$, $T = 4.29$, $k = 31$). Some areas correlating with reward prediction errors in both conditions were closely adjacent but non-overlapping at our statistical threshold (Fig. 4A). Most of these activities were located in the lateral portion of the basolateral complex, in an area consistent with the lateral nucleus of the amygdala. We also replicated previous findings of reward prediction error activity in the

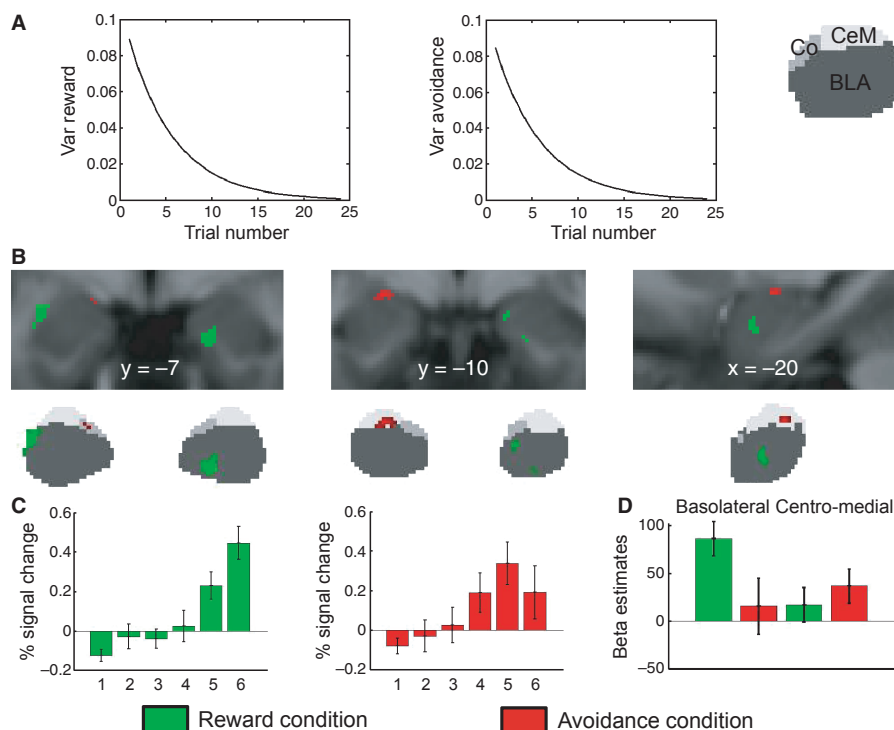


FIG. 5. Estimation uncertainty signals. (A) Plots showing the variance (or estimation uncertainty) estimated by our RL-based approximation of a Kalman filter averaged across all sessions and subjects in the reward (left) and avoidance (right) conditions. Note that these plots show exponential decline over non-contiguous trials, as the trial types were interleaved. (B) BOLD signals correlating with the magnitude of the estimation uncertainty of the cue were found in the basolateral complex in the reward condition (in green) and in the centromedial complex in the avoidance condition (in red). (C) Plots showing the percentage signal change for six categories of estimation uncertainty values (category 1 representing the lowest estimation uncertainty values, and category 6 representing the highest estimation uncertainty values) in the reward (in green) and avoidance (in red) conditions in the clusters activated. (D) Beta estimates showing an interaction between the subregion (basolateral vs. centromedial) and the condition (reward vs. avoidance) ($P < 0.01$).

ventral striatum (which though not the focus of the study was also contained within the field of view of our imaging protocol) during both the reward ($[x\ y\ z]$ $[8\ 7\ -5]$, $T = 4.08$) and avoidance conditions ($[x\ y\ z]$ $[18\ 13\ -11]$, $T = 3.76$) (McClure *et al.*, 2003; O'Doherty *et al.*, 2003). Finally, we also tested for an unsigned prediction error in a separate analysis, but did not find evidence for significant correlations with this signal in the amygdala at the time of outcome.

State-value signals

We then examined activity at the time of the initial cue presentation at the beginning of each trial. We looked for regions correlating with the average reward expected at the time of presentation of this initial cue. For this, we assumed that the value of each cue was learned through trial and error in the same way that action values are learned at the time of choice by means of a reward prediction error. We found activity correlating positively with the cue reward value during the avoidance condition in the centromedial complex ($[x\ y\ z]$ $[-18\ -12\ -10]$, $T = 4.29$, $k = 30$), such that activity increased the more reward (or less punishment) expected on that trial. No area showed a significant negative correlation with expected reward in the avoidance condition and no region of the amygdala was found to correlate either positively or negatively with expected reward at the time of cue presentation in the reward condition. The fact that we found evidence of this signal in the avoidance but not in the reward condition is difficult to interpret at this stage, and further investigation is needed to elucidate the mechanisms by which estimation uncertainty in reward and avoidance learning operate in the amygdala.

Estimation uncertainty signals

Finally, we looked for evidence of a signal widely reported in prior fMRI studies of conditioning in which amygdala activation shows an initial signal increase during the early stages of learning that subsequently decreases or habituates over the course of learning (Buchel *et al.*, 1998; LaBar *et al.*, 1998; Schiller *et al.*, 2008; Davis *et al.*, 2010). One possible explanation is that this signal reflects the 'estimation uncertainty' of the cue, i.e. the extent to which attention should be paid to the cue during learning, which can be used to set the rate at which learning occurs. In a Bayesian framework such as that instantiated in a Kalman filter (Dayan *et al.*, 2000), the learning rate of a cue is set using a computation of the variance in the estimation of expected reward. Here, we used a reinforcement learning-based approximation of a Kalman filter to compute the trial-by-trial uncertainty in the estimate of expected reward for the cues during both the reward and the avoidance conditions and generated a model-based prediction for the estimation uncertainty over the course of learning. This signal approximated an exponential decay over the course of learning such that it was high during initial learning on each session when new cues were presented, but then decreased as the estimated predicted reward became more accurate, thus minimizing estimation uncertainty (Fig. 5A). We tested for regions within the amygdala correlating with estimation uncertainty separately for the reward and avoidance conditions. Analogous to the results obtained for the expected value at the time of choice, we found distinct regions of amygdala to be correlated with our estimation uncertainty metric in the reward and avoidance conditions. Although a number of clusters in the basolateral complex were correlated with

estimation uncertainty in the reward condition ($[x\ y\ z]$ $[17\ -7\ -23]$, $T = 5.55$, $k = 59$; $[x\ y\ z]$ $[-31\ -5\ -17]$, $T = 4.43$, $k = 81$; $[x\ y\ z]$ $[-18\ -2\ -24]$, $T = 3.96$, $k = 39$), a region of dorsal amygdala in the vicinity of the centromedial complex was found to be correlated with estimation uncertainty in the avoidance condition ($[x\ y\ z]$ $[-21\ -10\ -11]$, $T = 5.66$, $k = 46$) (Fig. 5B). Moreover, in an independent ROI analysis, we found a significant subregion $\times$ condition interaction ($F_{1,19} = 11.94$, $P < 0.01$) (Fig. 5D), with the basolateral amygdala being significantly more involved in representing estimation uncertainty during the reward condition, and the centromedial amygdala being more involved in representing estimation uncertainty during the avoidance condition.

Discussion

We provide evidence for at least partly distinct contributions of the basolateral and centromedial amygdala complexes during two fundamental forms of instrumental conditioning – reward and avoidance learning.

Although such a dissociation has never been reported in human studies before to our knowledge, the present results may relate to prior lesion evidence for a differential contribution of basolateral and centromedial complexes in mediating the influence of appetitive and aversive Pavlovian cues on the conditioned potentiation and suppression of instrumental feeding behavior (Holland *et al.*, 2002; Petrovich *et al.*, 2009). It is possible that there are some similarities in the types of processes being recruited here and in those previous studies. In the present case, visual cues presented at the beginning of each trial served as discriminative stimuli signaling whether or not the subject was in a rewarding or avoidance context, which may be similar to the means by which the Pavlovian stimuli in the conditioned potentiation and suppression paradigms recruited appetitive or aversive motivational processes. Furthermore, the process of selection of an instrumental response in the reward and avoidance conditions might involve the need to promote responding to a previously rewarded action in the reward condition, while suppressing responding to a previously punished action in the avoidance condition.

Expected reward signals were present in the far ventral amygdala in the vicinity of the basolateral nucleus during reward learning, but although we also found expected value signals during avoidance learning, these signals were located very dorsally within the boundaries of the likely location of the centromedial complex. Although expected reward signals have been reported previously in amygdala in fMRI studies (Elliott *et al.*, 2004; Yacubian *et al.*, 2006), they have hitherto not been localized to a specific nucleus.

In both subregions, the signals we found are ‘reward expectations’, in that they increased the more reward is predicted to occur and the more a loss is predicted to be avoided. Notably, we did not find evidence for aversive-going signals in the avoidance condition at all. Such a result would appear puzzling in the light of considerable evidence of a role for amygdala in aversive learning, especially fear conditioning (Buchel *et al.*, 1998; LaBar *et al.*, 1998; LeDoux, 2003; Schiller *et al.*, 2008). However, monetary loss is a secondary reinforcer and thereby may be processed very differently from more biological reinforcers such as aversive tastes or shock. Indeed, other conventional resolution fMRI studies have also found a lack of increasing activation in amygdala during increasing predictions of monetary loss (Delgado *et al.*, 2008), suggesting that the human amygdala may show signal increases during predictions of some types of aversive reinforcers such as shock but not necessarily during anticipation of monetary loss. An important next step will be to assess

amygdala responses in these different subregions during learning with other types of aversive reinforcers such as unpleasant tastes or foot shocks, in both Pavlovian and instrumental contexts, to provide learning situations more analogous to that studied in the rodent and non-human primate literature. An alternative explanation for the absence of signals positively correlated with aversiveness could relate to limits in the spatial resolution offered by fMRI (even with a high-resolution protocol). In the event that populations of neurons with rewarding and aversive signaling properties are spatially intermingled within parts of the amygdala as shown in several electrophysiological studies in rodents and monkeys (Schoenbaum *et al.*, 1998; Paton *et al.*, 2006; Shabel & Janak, 2009), a comparison between appetitive and aversive predicting events might not yield a significant signal change in those areas, even though such neuronal populations are present. In future studies, multivariate fMRI analysis techniques that allow one to detect distributed voxel encoding might aid in the identification of such populations in human amygdalar subregions, if present.

Interestingly, the signed prediction error signals we found in the basolateral complex for both the reward and avoidance conditions were particularly (but not exclusively) located in the lateral portion of this complex, corresponding to the likely location of the lateral amygdalar nucleus. This area is often considered to be the ‘gateway to the amygdala’ in that it receives inputs from a variety of sensory modalities (LeDoux, 2003, 2007). Plasticity has also been reported to occur within this region of the amygdala during conditioning protocols (Blair *et al.*, 2001; LeDoux, 2007). The presence of reward prediction errors in this region as measured by BOLD signal could be occurring due to inputs into the amygdala from dopaminergic neurons arising from the ventral tegmental area (Schultz, 2002), which could therefore contribute to modifying plasticity during affective learning. Prediction error signals have previously been reported in basolateral nucleus in non-human primates, as well as in rodents (Belova *et al.*, 2007) although in some cases the signals were unsigned rather than signed as we observed here (Roesch *et al.*, 2010).

We also observed signals resembling ‘an estimation uncertainty’ computation from a learning process that could be used to set the level of attention allocated to a particular cue, and/or modify the learning rate to that cue. Other possible explanations could be proposed to account for such a decreasing response profile within the amygdala during learning, such as a more generalized cue-novelty response or arousal response. However, the finding that these signals were located in different regions of the amygdala depending on whether the learning was occurring in a reward or avoidance context is difficult to interpret in terms of a non-specific novelty or arousal signal. The presence of cue-estimation uncertainty signals in the human amygdala is broadly consistent with previous reports that parts of the amygdala mediate the allocation of attention to cues during learning such as in orienting (Gallagher *et al.*, 1990; Roesch *et al.*, 2010).

The main finding of the study is that within the human amygdala, basolateral and centromedial complexes appear to be differentially involved in reward and avoidance learning, respectively. The specific involvement of these complexes in these different types of learning might relate to the different patterns of emotional response engendered during the two learning types – while the reward learning condition might engender appetitive preparatory and/or consumatory responses, the avoidance learning condition may evoke greater aversive and/or stress-related responses. Drawing analogies with the animal literature, it is interesting to note that the basolateral amygdala, ventromedial prefrontal cortex and hippocampus are the main sources of input to the ventral striatum, with the densest projections within the nucleus accumbens (Russchen *et al.*, 1985; Fudge *et al.*, 2002; Haber &

Knutson, 2010). Because of these convergent fibers, the ventral striatum is considered a 'limbic-motor interface', a key structure processing emotional and motivational information and further driving action output (Everitt *et al.*, 1999; Haber & Knutson, 2010). Moreover, the basolateral amygdala has been shown to be acting on dopamine-dependent mechanisms of the ventral striatum to mediate the effects of stimulus-reward associations on behavior (Cador *et al.*, 1989), suggesting that the basolateral amygdala may be involved in reward learning through its interaction with the ventral striatum. On the other hand, the central nucleus of the amygdala has repeatedly been shown to be uniquely capable of influencing a widespread system of structures including the hypothalamus, midbrain (especially the periaqueductal gray matter) and lower brainstem, via extensive projections shown to be remarkably consistent in rats, cats and monkeys (Price, 2003). These different structures, particularly the periaqueductal gray matter, control and modulate visceral functions through their influence on autonomic function. Therefore, it has been suggested that the central nucleus contributes to the organization of the defense response and the production of fight or flight reactions by integrating the autonomic components of the behavior (Price & Amaral, 1981). Interestingly, a recent neuroimaging study has shown that distal threat elicited activity in lateral amygdala (consistent with the anatomical location of the basolateral complex) and ventromedial prefrontal cortex (a brain region repeatedly involved in reward processing) while proximal threat elicited activity in dorsal amygdala (consistent with the anatomical location of the centromedial complex) and periaqueductal gray matter (Mobbs *et al.*, 2007). Thus, the differential presence of value signals in these different areas of the amygdala may pertain to a different role for these regions in mediating appetitive and aversive responding, respectively. However, it should be noted that the signals found in the avoidance condition in the centromedial complex are not aversive *per se*, but rather reward-related (increasing the more avoidance is predicted to be successful).

These findings suggest that amygdala subregions might be differentially recruited as a function of different types of learning, namely reward and avoidance learning. It is entirely feasible and indeed likely that reward vs. avoidance is not the only dimension on which these amygdala complexes might be differentially engaged. Although our findings emphasize partly distinct contributions of the basolateral and centromedial complexes as a function of the type of instrumental conditioning involved, our computational fMRI analysis revealed that the form of the computations within these two areas appears to be similar. We observed expected reward signals in both of these structures during reward and avoidance learning and we also observed expected uncertainty signals in both of these areas. These findings suggest that these areas are not necessarily engaged in qualitatively different computations, but rather highlight the fact that similar computations in these regions operate on reward and avoidance learning.

The present findings also have important implications for better understanding the neuronal and psychological mechanisms underlying avoidance learning and its relationship to reward learning. Kim *et al.* (2006) reported that medial orbitofrontal cortex was recruited during successful avoidance of a monetary loss in a similar manner to that found during receipt of monetary gain, thereby concluding that avoidance learning depends in part on overlapping neuronal processes to that involved in learning about reward. The present results add to these findings by suggesting that within the amygdala, these two different forms of learning may not rely on entirely overlapping circuitry even if this is the case in the orbitofrontal cortex. However, the fact that the representations predominantly pertained to predictions about reward and successful avoidance in both the basolateral and the

centromedial complexes is broadly consistent with the suggestion that, mechanistically, reward and avoidance learning may recruit similar computational processes albeit implemented in partly distinct neural circuits.

Conclusions

Collectively, our findings suggest the existence of a number of distinct computational signals within the basolateral and centromedial complexes, thereby providing new insight into the functional contributions of these amygdalar subregions in associative learning. The adoption of a high-resolution fMRI approach has allowed us to localize these signals to different amygdalar regions in a manner not hitherto possible in human neuroimaging studies of associative learning. More generally, we show how the high-resolution fMRI approach can, when combined with quantitative computational modeling, contribute to the circuit-level analysis of amygdala function with a level of fidelity hitherto only achievable in animal lesion and neurophysiology studies.

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Abbreviations

BIC, Bayesian information criterion; BMS, Bayesian model selection; BOLD, blood oxygen level-dependent; fMRI, functional magnetic resonance imaging; HRF, hemodynamic response function; MTL, medial temporal lobe; NLL, negative log likelihood; RL, reinforcement learning; ROI, region of interest.

References

- Adolphs, R. (2008) Fear, faces, and the human amygdala. *Curr. Opin. Neurobiol.*, **18**, 166–172.
- Amunts, K., Kedo, O., Kindler, M., Pieperhoff, P., Mohlberg, H., Shah, N.J., Habel, U., Schneider, F. & Zilles, K. (2005) Cytoarchitectonic mapping of the human amygdala, hippocampal region and entorhinal cortex: intersubject variability and probability maps. *Anat. Embryol. (Berl)*, **210**, 343–352.
- Anderton, B.H. (1997) Changes in the ageing brain in health and disease. *Philos. Trans. R. Soc. Lond. B. Biol. Sci.*, **352**, 1781–1792.
- Bechara, A., Damasio, H. & Damasio, A.R. (2003) Role of the amygdala in decision-making. *Ann. NY Acad. Sci.*, **985**, 356–369.
- Belova, M.A., Paton, J.J., Morrison, S.E. & Salzman, C.D. (2007) Expectation modulates neural responses to pleasant and aversive stimuli in primate amygdala. *Neuron*, **55**, 970–984.
- Blair, H.T., Schafe, G.E., Bauer, E.P., Rodrigues, S.M. & LeDoux, J.E. (2001) Synaptic plasticity in the lateral amygdala: a cellular hypothesis of fear conditioning. *Learn. Mem.*, **8**, 229–242.
- Buchel, C. & Dolan, R.J. (2000) Classical fear conditioning in functional neuroimaging. *Curr. Opin. Neurobiol.*, **10**, 219–223.
- Buchel, C., Morris, J., Dolan, R.J. & Friston, K.J. (1998) Brain systems mediating aversive conditioning: an event-related fMRI study. *Neuron*, **20**, 947–957.
- Cador, M., Robbins, T.W. & Everitt, B.J. (1989) Involvement of the amygdala in stimulus-reward associations: interaction with the ventral striatum. *Neuroscience*, **30**, 77–86.
- Cardinal, R.N., Parkinson, J.A., Hall, J. & Everitt, B.J. (2002) Emotion and motivation: the role of the amygdala, ventral striatum, and prefrontal cortex. *Neurosci. Biobehav. Rev.*, **26**, 321–352.
- Cohen, A., Sanborn, A. & Shiffrin, R. (2008) Model evaluation using grouped or individual data. *Psychon. Bull. Rev.*, **15**, 692.
- Corbit, L.H. & Balleine, B.W. (2005) Double dissociation of basolateral and central amygdala lesions on the general and outcome-specific forms of pavlovian-instrumental transfer. *J. Neurosci.*, **25**, 962–970.

- Davis, M. & Whalen, P.J. (2001) The amygdala: vigilance and emotion. *Mol. Psychiatry*, **6**, 13–34.
- Davis, F.C., Johnstone, T., Mazzulla, E.C., Oler, J.A. & Whalen, P.J. (2010) Regional response differences across the human amygdaloid complex during social conditioning. *Cereb. Cortex*, **20**, 612–621.
- Dayan, P., Kakade, S. & Montague, P.R. (2000) Learning and selective attention. *Nat. Neurosci.*, **3** (Suppl), 1218–1223.
- Delgado, M.R., Li, J., Schiller, D. & Phelps, E.A. (2008) The role of the striatum in aversive learning and aversive prediction errors. *Philos. Trans. R. Soc. Lond. B. Biol. Sci.*, **363**, 3787–3800.
- Elliott, R., Newman, J.L., Longe, O.A. & William Deakin, J.F. (2004) Instrumental responding for rewards is associated with enhanced neuronal response in subcortical reward systems. *Neuroimage*, **21**, 984–990.
- Erev, I. & Roth, A. (1998) Predicting how people play games: reinforcement learning in experimental games with unique, mixed strategy equilibria. *Am. Econ. Rev.*, **88**, 848–881.
- Everitt, B.J., Parkinson, J.A., Olmstead, M.C., Arroyo, M., Robledo, P. & Robbins, T.W. (1999) Associative processes in addiction and reward. The role of amygdala-ventral striatal subsystems. *Ann. NY Acad. Sci.*, **877**, 412–438.
- Fudenberg, D. & Levine, D. (1998) Learning in games. *Eur. Econ. Rev.*, **42**, 631–639.
- Fudge, J.L., Kunishio, K., Walsh, P., Richard, C. & Haber, S.N. (2002) Amygdaloid projections to ventromedial striatal subterritories in the primate. *Neuroscience*, **110**, 257–275.
- Gallagher, M., Graham, P.W. & Holland, P.C. (1990) The amygdala central nucleus and appetitive Pavlovian conditioning: lesions impair one class of conditioned behavior. *J. Neurosci.*, **10**, 1906–1911.
- Glascher, J., Hampton, A.N. & O'Doherty, J.P. (2009) Determining a role for ventromedial prefrontal cortex in encoding action-based value signals during reward-related decision making. *Cereb. Cortex*, **19**, 483–495.
- Glover, G.H., Li, T.Q. & Ress, D. (2000) Image-based method for retrospective correction of physiological motion effects in fMRI: RETROICOR. *Magn. Reson. Med.*, **44**, 162–167.
- Gluck, M.A. & Bower, G.H. (1988) From conditioning to category learning: an adaptive network model. *J. Exp. Psychol. Gen.*, **117**, 227–247.
- Haber, S.N. & Knutson, B. (2010) The reward circuit: linking primate anatomy and human imaging. *Neuropsychopharmacology*, **35**, 4–26.
- Hampton, A.N., Adolphs, R., Tyszka, M.J. & O'Doherty, J.P. (2007) Contributions of the amygdala to reward expectancy and choice signals in human prefrontal cortex. *Neuron*, **55**, 545–555.
- Holland, P.C. & Gallagher, M. (2003) Double dissociation of the effects of lesions of basolateral and ventral amygdala on conditioned stimulus-potentiated feeding and Pavlovian-instrumental transfer. *Eur. J. Neurosci.*, **17**, 1680–1694.
- Holland, P.C., Petrovich, G.D. & Gallagher, M. (2002) The effects of amygdala lesions on conditioned stimulus-potentiated eating in rats. *Physiol. Behav.*, **76**, 117–129.
- Hsu, M., Bhatt, M., Adolphs, R., Tranel, D. & Camerer, C.F. (2005) Neural systems responding to degrees of uncertainty in human decision-making. *Science*, **310**, 1680–1683.
- Insausti, R., Juottonen, K., Soininen, H., Insausti, A.M., Partanen, K., Vainio, P., Laakso, M.P. & Pitkanen, A. (1998) MR volumetric analysis of the human entorhinal, perirhinal, and temporopolar cortices. *AJNR Am. J. Neuroradiol.*, **19**, 659–671.
- Killcross, S., Robbins, T.W. & Everitt, B.J. (1997) Different types of fear-conditioned behaviour mediated by separate nuclei within amygdala. *Nature*, **388**, 377–380.
- Kim, H., Shimojo, S. & O'Doherty, J.P. (2006) Is avoiding an aversive outcome rewarding? Neural substrates of avoidance learning in the human brain *PLoS Biol.*, **4**, e233.
- LaBar, K.S., Gatenby, J.C., Gore, J.C., LeDoux, J.E. & Phelps, E.A. (1998) Human amygdala activation during conditioned fear acquisition and extinction: a mixed-trial fMRI study. *Neuron*, **20**, 937–945.
- LeDoux, J. (2003) The emotional brain, fear, and the amygdala. *Cell. Mol. Neurobiol.*, **23**, 727–738.
- LeDoux, J. (2007) The amygdala. *Curr. Biol.*, **17**, R868–R874.
- Luce, R.D. (1959) On the possible psychophysical laws. *Psychol. Rev.*, **66**, 81–95.
- Mai, J.K., Paxinos, G. & Voss, T. (2008) *Atlas of the Human Brain*. Elsevier, Amsterdam.
- McClure, S.M., Berns, G.S. & Montague, P.R. (2003) Temporal prediction errors in a passive learning task activate human striatum. *Neuron*, **38**, 339–346.
- Miller, M.I., Beg, M.F., Ceritoglu, C. & Stark, C. (2005) Increasing the power of functional maps of the medial temporal lobe by using large deformation diffeomorphic metric mapping. *Proc. Natl Acad. Sci. USA*, **102**, 9685–9690.
- Mobbs, D., Petrovic, P., Marchant, J.L., Hassabis, D., Weiskopf, N., Seymour, B., Dolan, R.J. & Frith, C.D. (2007) When fear is near: threat imminence elicits prefrontal-periaqueductal gray shifts in humans. *Science*, **317**, 1079–1083.
- Myung, I.J. (2003) Tutorial on maximum likelihood estimation. *J. Math. Psychol.*, **47**, 90–100.
- Myung, I. & Busmeyer, J. (1992) Measurement-free tests of a general state-space model of prototype learning. *J. Math. Psychol.*, **36**, 32–67.
- Nelder, J. & Mead, R. (1965) A simplex method for function minimization. *Comput. J.*, **7**, 308.
- O'Doherty, J.P., Dayan, P., Friston, K., Critchley, H. & Dolan, R.J. (2003) Temporal difference models and reward-related learning in the human brain. *Neuron*, **38**, 329–337.
- Paton, J.J., Belova, M.A., Morrison, S.E. & Salzman, C.D. (2006) The primate amygdala represents the positive and negative value of visual stimuli during learning. *Nature*, **439**, 865–870.
- Pearce, J.M. & Hall, G. (1980) A model for Pavlovian learning: variations in the effectiveness of conditioned but not of unconditioned stimuli. *Psychol. Rev.*, **87**, 532–552.
- Petrovich, G.D., Ross, C.A., Mody, P., Holland, P.C. & Gallagher, M. (2009) Central, but not basolateral, amygdala is critical for control of feeding by aversive learned cues. *J. Neurosci.*, **29**, 15205–15212.
- Phelps, E.A. (2006) Emotion and cognition: insights from studies of the human amygdala. *Annu. Rev. Psychol.*, **57**, 27–53.
- Price, J.L. (2003) Comparative aspects of amygdala connectivity. *Ann. NY Acad. Sci.*, **985**, 50–58.
- Price, J.L. & Amaral, D.G. (1981) An autoradiographic study of the projections of the central nucleus of the monkey amygdala. *J. Neurosci.*, **1**, 1242–1259.
- Rescorla, R.A. & Wagner, A.R. (1972) A theory of Pavlovian conditioning: variations in effectiveness of reinforcement and nonreinforcement. In A.H., Black & W.F., Prokasy (Eds), *Classical Conditioning II: Current Research and Theory*. Appleton Century-Crofts, New York, pp. 64–99.
- Roesch, M.R., Calu, D.J., Esber, G.R. & Schoenbaum, G. (2010) Neural correlates of variations in event processing during learning in basolateral amygdala. *J. Neurosci.*, **30**, 2464–2471.
- Russchen, F.T., Bakst, I., Amaral, D.G. & Price, J.L. (1985) The amygdalo-striatal projections in the monkey. An anterograde tracing study. *Brain Res.*, **329**, 241–257.
- Schiller, D., Levy, I., Niv, Y., LeDoux, J.E. & Phelps, E.A. (2008) From fear to safety and back: reversal of fear in the human brain. *J. Neurosci.*, **28**, 11517–11525.
- Schoenbaum, G., Chiba, A.A. & Gallagher, M. (1998) Orbitofrontal cortex and basolateral amygdala encode expected outcomes during learning. *Nat. Neurosci.*, **1**, 155–159.
- Schultz, W. (2002) Getting formal with dopamine and reward. *Neuron*, **36**, 241–263.
- Schwarz, G. (1978) Estimating the dimension of a model. *Ann. Stat.*, **6**, 461–464.
- Seymour, B. & Dolan, R. (2008) Emotion, decision making, and the amygdala. *Neuron*, **58**, 662–671.
- Seymour, B., O'Doherty, J.P., Koltzenburg, M., Wiech, K., Frackowiak, R., Friston, K. & Dolan, R. (2005) Opponent appetitive-aversive neural processes underlie predictive learning of pain relief. *Nat. Neurosci.*, **8**, 1234–1240.
- Shabel, S.J. & Janak, P.H. (2009) Substantial similarity in amygdala neuronal activity during conditioned appetitive and aversive emotional arousal. *Proc. Natl Acad. Sci. USA*, **106**, 15031–15036.
- Solano-Castiella, E., Anwender, A., Lohmann, G., Weiss, M., Docherty, C., Geyer, S., Reimer, E., Friederici, A.D. & Turner, R. (2010) Diffusion tensor imaging segments the human amygdala *in vivo*. *Neuroimage*, **49**, 2958–2965.
- Sutton, R. & Barto, A. (1998) *Reinforcement Learning*. MIT Press, Cambridge, MA.
- Thirion, J.P. (1998) Image matching as a diffusion process: an analogy with Maxwell's demons. *Med. Image Anal.*, **2**, 243–260.
- Vercauteren, T., Pennec, X., Perchant, A. & Ayache, N. (2007) Non-parametric diffeomorphic image registration with the demons algorithm. *Med. Image Comput. Assist. Interv.*, **10**, 319–326.
- Yacubian, J., Glascher, J., Schroeder, K., Sommer, T., Braus, D.F. & Buchel, C. (2006) Dissociable systems for gain- and loss-related value predictions and errors of prediction in the human brain. *J. Neurosci.*, **26**, 9530–9537.
- Yassa, M.A. & Stark, C.E. (2009) A quantitative evaluation of cross-participant registration techniques for MRI studies of the medial temporal lobe. *Neuroimage*, **44**, 319–327.