European Journal of Neuroscience, Vol. 12, pp. 1764–1770, 2000

Differential amygdala responses to winning and losing: a functional magnetic resonance imaging study in humans

Tiziana Zalla,[1] Etienne Koechlin,[1] Pietro Pietrini,[1,2] Gianpaolo Basso,[1] Patrick Aquino,[1] Angela Sirigu[3] and Jordan Grafman[1]

[1]Cognitive Neuroscience Section, NINDS, National Institutes of Health, Bethesda, MD 20892-1440, USA
[2]Department of Human and Environmental Sciences, University of Pisa, Pisa, Italy
[3]Institut des Sciences Cognitives, 67 Boulevard Pinel, 69675 BRON, France

Keywords: brain, competition, emotion, motivation, punishment, reward

Abstract

The amygdala has been shown to respond to many distinct types of affective stimuli, including reward and punishment feedback in animals. In humans, winning and losing situations can be considered as reward and punishment experiences, respectively. In this study, we used functional magnetic resonance imaging (fMRI) to measure regional brain activity when human subjects were given feedback on their performance during a simple response time task in a fictitious competitive tournament. Lexical stimuli were used to convey positive 'win' or negative 'lose' feedback. The frequency of positive and negative trials was parametrically varied by the experimenters independently from the subjects' actual performance and unbeknownst to them. The results showed that the parametric increase of winning was associated with left amygdala activation whereas the parametric increase of losing was associated with right amygdala activation. These findings provide functional evidence that the human amygdala differentially responds to changes in magnitude of positive or negative reinforcement conveyed by lexical stimuli.

Introduction

Reward represents a basic goal in human and animal behaviour, regardless of species and individual differences. In animals, a limited number of brain structures, including the amygdala, prefrontal cortex and basal ganglia are involved in processing different aspects of reward information (Watanabe, 1990; Apicella *et al*., 1991; Schultz *et al*., 1995, 1997, 1998; Schultz, 1997, 1998; Kawagoe *et al*., 1998). In particular, the amygdala appears to play a critical role in processing the affective significance of a stimulus and in stimulus–reward association (Weiskrantz, 1956; Gaffan & Harrison, 1987; Nishijo *et al*., 1988; Everitt *et al*., 1991; Rolls, 1992; Schoenbaum *et al*., 1998). Some of these reports in rodents have pointed out that the amygdala is involved in memory for changes in the magnitude of reward (Coleman-Mesches *et al*., 1996; Salinas & McGaugh, 1996). The amygdala also appears to be important for working memory when the magnitude of reinforcement needs to be remembered in order to accomplish a successful performance (Kesner & Williams, 1995). Recently, Schoenbaum *et al*. (1998) have reported that in rodents, which were learning an olfactory discrimination task, neurons in both basolateral amygdala and orbitofrontal cortex fired selectively during the anticipation of reward or aversive outcomes. These data indicate that the amygdala and the orbitofrontal cortex are involved in associative learning of positive and negative outcomes related to goal-directed behaviour. Similarly, Bechara *et al*. (1999) have shown that in humans damage to the amygdala precludes the possibility of experiencing the emotional attributes of events related to reward and punishment and, thus, to use somatic state information to deliberate decisions with future consequences. The authors studied skin conductance responses during a gambling task in patients with lesions of either the amygdala or the ventromedial prefrontal cortex (Bechara *et al*., 1999). Both patient groups were impaired on the gambling task, but interestingly the patients with bilateral lesions of the amygdala, unlike patients with lesions of the ventromedial prefrontal cortex, also failed to show skin conductance responses following winning or losing money. These findings would indicate that an intact human amygdala is needed to properly respond to reward and punishment.

Appraisal of rewarding or aversive events generally provokes approach or withdrawal behaviour and elicits positive or negative emotional states, respectively. In humans, the importance of the amygdala in processing positive (i.e. happy facial expressions, pleasant pictures) or negative (i.e. fear conditioning, facial expression of fear, anger, disgust, aversive pictures, aversive auditory, olfactory or gustatory stimulations) affective states has been extensively documented (Adolphs *et al*., 1994, 1995, 1996; LaBar *et al*., 1995, 1998; Angrilli *et al*., 1996; Breiter *et al*., 1996; Irwin *et al*., 1996; LeDoux, 1996; Morris *et al*., 1996, 1998a; Phillips *et al*., 1997; 1998; Schneider *et al*., 1997; Scott *et al*., 1997; Zald & Pardo, 1997; Abercrombie *et al*., 1998; Büchel *et al*., 1998; Zald *et al*., 1998; Blair *et al*., 1999; Hamann *et al*., 1999).

In the present study, we wished to examine the functional role of the amygdala in the processing of relevant affective information associated with the amount of reward or punishment in human individuals. In a real-life situation, when outcome on a task depends on one's behavioural performance, an index of one's own performance is provided by the perception of the valence and the magnitude of the received reinforcement, i.e. variations in the amount of positive or negative feedback.

Correspondence: Dr J. Grafman, as above.
E-mail: grafmanj@ninds.nih.gov

Received 22 September 1999, revised 23 December 1999, accepted 10 January 2000

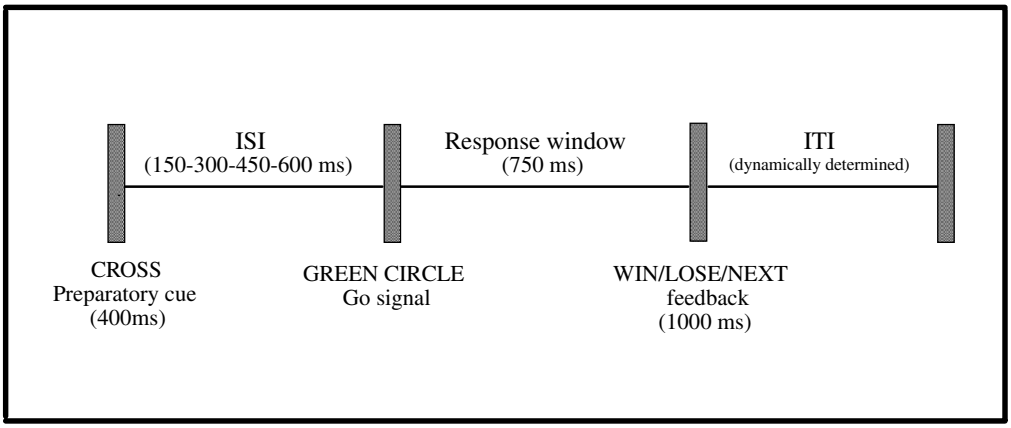

FIG. 1. Diagram showing the sequence and the timing of the trials (lasting 3 s each). A 3-s scan was acquired for each trial.

Here, we used functional magnetic resonance imaging (fMRI) and behavioural assessment to determine brain response while healthy human subjects performed a simple reaction time task in a fictitious competitive tournament. We hypothesized that the activation of the amygdala would be modulated by changes in the frequency of positive (win) or negative (lose) feedback delivered during the experimental session. The arousing competitive context was designed to maximize the subjects' motivation and performance in pursuing the goal (i.e. winning the competition) across all the conditions, regardless of the valence and the amount of feedback received.

Preliminary results were presented in part at scientific meetings (Zalla *et al*., 1999a,b).

Materials and methods

Subjects

We studied 10 healthy right-handed volunteers (five males and five females; mean age ± SD = 25 ± 3 years; mean education ± SD = 17 ± 2 years) with no evidence or history of any medical, neurological, psychiatric disorder or treatment with psychotropic medications. All of them had normal MRI brain scan examinations. Before the experiment, subjects completed a competitive attitude scale (Ryckman *et al*., 1996) and a self-esteem scale (Rosenberg, 1989). All 10 subjects were highly competitive according to the score on this scale; eight subjects attained high and two subjects attained medium scores on the self-esteem scale.

Upon completion of the fMRI experimental session, each subject was asked to rank the relative intensity of their emotional state in response to the two kinds of feedback ('win' and 'lose') by making two marks on a 10-cm analogue scale (which ranged from 'very confident' at +5 cm to 'very frustrated' at –5 cm, and with 0 representing a neutral baseline state).

All subjects gave their written informed consent (as approved by the National Institute of Neurological Disorders and Stroke-Institutional Review Board) prior to the MRI scanning session.

Experimental task

The experiment was a detection task which required the subjects to press a button as fast as they could after the appearance of a go-stimulus (a green circle) on the computer monitor. As schematically shown in Fig. 1, at the beginning of each trial, subjects were presented with a white cross as a preparatory cue for 400 ms. Then, after a variable random delay (150, 300, 450 or 600 ms), a green filled circle (the go-stimulus) was presented on a black background and remained on the centre of the monitor during a constant time window (750 ms).

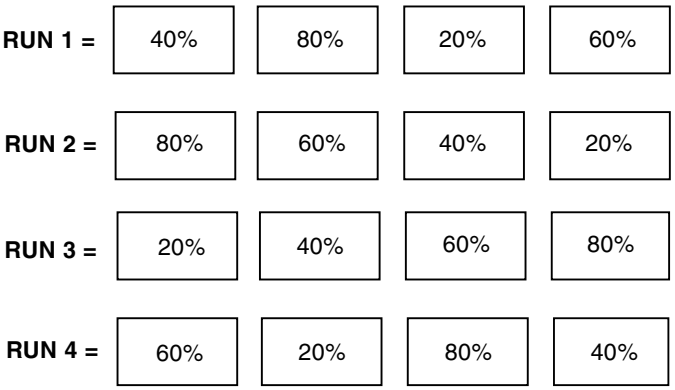

FIG. 2. Diagram of the standardized sequence of runs in the experimental block design. The experiment consisted of two sequences of four runs. Each run (lasting 2 min) consisted of four blocks of 20, 40, 60 and 80% of either 'win' or 'lose' feedback trials. Each block (lasting 30 s) was composed of 10 trials. Because 'win' and 'lose' trials were administered in separate sequences of runs, 'win' and 'lose' feedback trials were never alternated in the same block or in the same run. The order of run presentation was counterbalanced across subjects.

Following each response that fell within this time window, one of the following feedback stimuli was shown on the screen: 'WIN' to tell the subjects that they were faster than their opponents ('win trial'), 'LOSE' to tell them they were slower than their opponents ('lose trial'), and 'NEXT' for those trials where no outcome information was meant to be provided ('neutral trial', Fig. 1).

The whole experiment consisted of two sequences of four runs each and lasted for ~16 min. During one sequence of runs the subjects received only 'win' and 'next' feedback, and during the other sequence of runs, they received only 'lose' and 'next' feedback. The 'next' trials were used to vary parametrically the percentage of 'win' and 'lose' feedback delivered to the subjects to modulate the magnitude of winning and losing trials, respectively. The subjects were instructed that all the trial performances would be counted in determining the average reaction time at the end of the game, including the trials with no informative feedback. For the first sequence, each run was divided into four blocks of 10 trials each (Fig. 2). The four blocks contained, respectively, 20, 40, 60 and 80% of 'win' trials, which were alternated randomly with 'next' trials. In the second sequence, each run was again divided into four blocks of 10 trials each. The four blocks contained, respectively, 20, 40, 60 and 80% of 'lose' trials also randomly alternated with 'next' trials.

The four standard runs in each sequence were presented in a counterbalanced order (Latin square design) and each sequence was paired with a counterbalanced sequence in which the order of feedback frequency runs was reversed. All subjects believed that they were competing in a real tournament with the feedback they received contingent on their actual performance and perceived the game as a continuous sequence of trials. A post-test debriefing confirmed that they remained unaware of the parametric block design and of the true purpose of the study. The fact that the subjects knew that all the trials counted in determining their final performance and the impossibility of predicting the type of trial ensured that they maintained equal competitive performance levels across the whole experiment. Indeed, the mean response times between the win and the lose runs did not differ (294.5 ms for the win runs; 293.7 ms for the lose runs; $P > 0.05$), nor did response times change in relation to the percentage of feedback. The task was programmed using the Software Package EXPE 6 (Pallier *et al.*, 1997).

Image processing and statistical analysis

Whole-brain functional MRI was conducted on a 1.5 Tesla MRI scanner (Sigma, General Electric Medical System, Milwaukee, USA). Echo-planar images were collected using a single shot, blipped, gradient echo-planar pulse sequence; TE (echo time) = 40 ms, TR (repetition time) = 3 s. Spatial resolution was set by a 64×64 voxel acquisition matrix covering a 24×24 cm field of view (FOV); thickness = 6 mm, number of slices = 18. Before functional imaging, a three-dimensional anatomical image was collected (spoiled gradient-recalled at steady-state sequence: TE = 5.4 ms, TR = 14 ms, flip angle = 20 °, number of excitations = 1, slice thickness = 6 mm, FOV = 24 × 24, acquisition matrix = 256 × 192). During each run, 44 sequential echo-planar volumes were collected.

Image processing and statistical analyses were performed using SPM96 software (Wellcome Department of Cognitive Neurology, London, UK). Brain volumes were realigned to the first volume (Friston *et al.*, 1995a). Linear normalization into the standard stereotactic space of Talairach & Tournoux (1988) was performed using a representative brain from the Montreal Neurological Institute series as a template. Residual anatomical discrepancies were reduced through spatial smoothing with an isotropic Gaussian kernel filter of 10 mm. Voxel values were adjusted through a scaling procedure. Statistical analyses were performed on a group basis according to the implementation of the general linear model for fMRI data devised by Friston *et al.* (1995b).

A complete 3-s scan was acquired for each trial; all the blocks across runs with the same percentage and valence of feedback were averaged together. Blocks with identical frequency of either positive or negative feedback presentation were modelled as four orthogonal covariates. Linear contrasts with increasing (from −1 to +1) or decreasing (from +1 to −1) weights were used to identify brain activation positively or negatively correlated with the variations in the frequency of positive and negative feedback. A Z score > 2.33, corresponding to $P < 0.001$ (uncorrected) or $P < 0.01$ (corrected), was used as a threshold for the contrasts. As the involvement of the amygdala was predicted by our hypothesis, we thought it too conservative to employ a correction for the analyses and therefore, results for activations in the amygdala are reported uncorrected (Morris *et al.*, 1996). A correction for spatial extent was adopted in the exploratory analyses for the remaining regions of the brain.

Parametric contrasts were computed in order to reveal a variation in amygdala response as a function of either increasing or decreasing win or lose trial frequency. The increase of win (or lose) feedback was determined by contrasting data from blocks with the highest rate of win (or lose) feedback (80% and 60%) with data from blocks with the lowest rate of win (or lose) feedback (40% and 20%). Conversely, the decrease of win (or lose) feedback was determined by contrasting blocks with the lowest rate of win (or lose) feedback (40% and 20%) with blocks with the highest rate of win (or lose) feedback (80% and 60%), [e.g. $+1 \times (80\%\ \text{win}) + 1/3 \times (60\%\ \text{win}) - 1/3 \times (40\%\ \text{win}) - 1 \times (20\%\ \text{win})$].

Although the words 'win' and 'lose' are associated, respectively, with positive and negative meanings, the parametric design enabled us to evaluate the amygdala's response to the effects of winning and to the effects of losing in relative terms, regardless of the semantic nature of the feedback stimuli *per se*. Thus, the relative effect of winning and the relative effect of losing were also measured on the basis of the variations in the frequency of the win and lose trial occurrence, i.e. on the win : next and lose : next ratios. Specifically, the relative effect of winning was assessed by averaging the weighted parametric increase in win trials with the weighted parametric decrease in lose trials as follows $[1 \times (80\%\ \text{win}) + 1/3 \times (60\%\ \text{win}) - 1/3 \times (40\%\ \text{win}) - 1 \times (20\%\ \text{win})] + [1 \times (20\%\ \text{lose}) + 1/3 \times (40\%\ \text{lose}) - 1/3 \times (60\%\ \text{lose}) - 1 \times (80\%\ \text{lose})]$. Conversely, the relative increase of losing was determined by averaging the weighted parametric increase in lose trials with the weighted parametric decrease in win trials as follows $[1 \times (80\%\ \text{lose}) + 1/3 \times (60\%\ \text{lose}) - 1/3 \times (40\%\ \text{lose}) - 1 \times (20\%\ \text{lose})] + [1 \times (20\%\ \text{win}) + 1/3 \times (40\%\ \text{win}) - 1/3 \times (60\%\ \text{win}) - 1 \times (80\%\ \text{win})]$.

Results

Different patterns of brain activations were associated with the variations of the frequency of either type of feedback trial (Table 1).

Parametric analyses of amygdala activation

Effect of winning

The relative effect of winning, assessed by combining the increase in win trials with the decrease in lose trials, revealed significant activation of the left amygdala ($P < 0.0001$, uncorrected for multiple comparisons; equivalent to $P < 0.01$ corrected, Table 1 and Fig. 3a).

Significant activation of the left amygdala was also identified in the individual contrasts corresponding to the increase of 'win' trials frequency ($P < 0.0001$, uncorrected, equivalent to $P < 0.01$ corrected) and to the decrease of 'lose' trials ($P < 0.0001$, uncorrected, equivalent to $P < 0.01$ corrected). Moreover, changes in mean signal in the left amygdala were significantly correlated ($r = 0.94$, $P < 0.05$) with the increase of frequencies (20, 40, 60, 80%) of 'win' trials (Fig. 4).

Effect of losing

The relative effect of losing was assessed by combining the increase of 'lose' trials with the decrease of 'win' trials. In this contrast, the right amygdala was significantly activated ($P < 0.001$, uncorrected, Table 1 and Fig. 3b). No significant amygdala activation was observed in the individual contrasts that assessed separately the decrease of 'win' trials or the increase of 'lose' trials.

Effect of the increase and decrease of informative (win and lose) trials

To control for potential effects of the parametric change in informative feedback *per se*, we also compared the averaged blocks with the highest rate of 'win' and 'lose' trials (60 and 80%) with averaged blocks with the lowest rate of 'win' and 'lose' trials (40 and 20%). No significant activation was associated with any of these conditions.

TABLE 1. Foci of maximal activations in Talairach & Tournoux (1988) coordinates

Regions of activation	*x*	*y*	*z*	*Z*-value	*P*-value
Increase of WIN and decrease of LOSE					
Left hippocampus and amygdala	–27	–21	–12	4.71	$P<0.01$ (corrected)
Left inf. frontal gyrus (BA 44)	–60	15	12	5.40	$P<0.001$ (corrected)
Right inf. frontal gyrus (BA 47)	48	18	–12	4.47	$P<0.03$ (corrected)
Increase of WIN					
Left amygdala	–36	–3	–18	3.80	$P<0.0001$ (uncorrected)
Left inf. frontal gyrus (BA 44)	–57	18	3	5.66	$P<0.0001$ (corrected)
Decrease of LOSE					
Left amygdala	–27	–15	–9	4.00	$P<0.0001$ (uncorrected)
Increase of LOSE and decrease of WIN					
Right amygdala	24	0	–15	3.13	$P<0.001$ (uncorrected)
Right globus pallidus	15	–6	–6	3.97	$P<0.0001$ (uncorrected)
Right putamen	15	9	–6	2.81	$P<0.003$ (uncorrected)

A *Z*-value > 2.33, corresponding to $P<0.001$ (uncorrected) or $P<0.01$ (corrected), was used as a threshold for the controls.

Activations in other brain regions

Effect of winning

As shown in Table 1, the effect of relative winning also revealed activations in the left inferior frontal gyrus [Brodmann's area (BA) 44] ($P<0.001$, corrected), in the left hippocampus ($P<0.01$, corrected) and in the right orbitofrontal cortex (BA 47, $P<0.03$, corrected). The individual contrast corresponding to the increase of win feedback trials was associated with a significant activation in the left inferior frontal gyrus (BA 44, $P<0.0001$, corrected, Table 1).

Effect of losing

No activation was shown by other brain regions in relation to the effect of losing. However, when the analyses were repeated without any correction for spatial extent, significant activation was observed in the right globus pallidus ($P<0.0001$, uncorrected) and the right putamen ($P<0.003$, uncorrected). Some additional activations were also seen in the right prefrontal cortex (BA 9; Tailarach coordinates $x=21$, $y=69$, $z=30$; *z*-score 3.86, $P<0.0001$, uncorrected) and the left visual association cortex (BA 18; Tailarach coordinates $x=-27$, $y=-87$, $z=3$; *z*-score 3.58, $P<0.0001$, uncorrected).

Behavioural results

Win and lose feedback runs elicited distinct subjective responses in all the subjects, according to the analogue scale that they were asked to complete immediately after the scanning session. The subjects' mean scores for 'win' and 'lose' trial sequences were equally distant from the centre point (+1.8 cm for the 'win' trial sequence and –1.9 cm for the 'lose' trial sequence) of the scale. The difference between the two scores was significant ($t_9=+6.12$, $P<0.0002$). Thus, on this scale, subjects indicated that on 'win' trials they felt relatively more confident and on 'lose' trials relatively more frustrated compared with their baseline state.

Discussion

In the current study, we investigated the role of the human amygdala in processing information about the likelihood of obtaining a reward in relation to the individual's performance on a competitive task. A parametric design was adopted to identify amygdala responses associated with the effect of winning and losing, measured as variations in the frequency of 'win' and 'lose' feedback trials. Our findings show that changes in the frequency of feedback indicating to the subjects that they were winning or losing modulate the activity of the left and right amygdala, respectively.

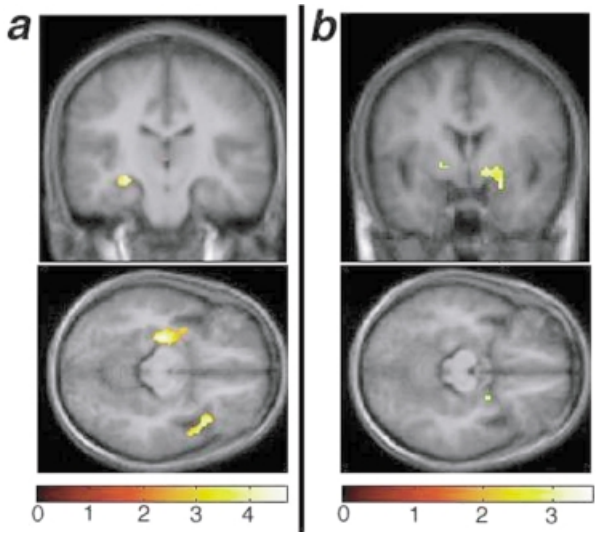

FIG. 3. Rendering of statistical parametric maps (SPM). The SPM is displayed on coronal (top) and axial (bottom) slices in a neurological orientation (the right side of the brain slice corresponds to the right hemisphere). The areas of activation are all rendered on the average structural MRI images obtained from all 10 subjects. (a) Activations associated with the effect of winning (obtained by combining the increase of 'win' trials and the decrease of 'lose' trials). The coronal and the axial views show the activation in a region encompassing the left amygdala and hippocampal complex. The axial slice also shows the activation in the right inferior frontal gyrus. (b) Activations associated with the effect of losing in the right amygdala (obtained by combining the increase of 'lose' trials and the decrease of 'win' trials).

Although many animal and human studies, including functional brain imaging ones, have explored the role of the amygdala in processing stimuli with positive and aversive content in a variety of conditions, to date only one recently published study has linked the amygdala to the perception of reward and punishment in humans (Bechara *et al*., 1999). In this study by Bechara *et al*. (1999), patients with bilateral lesions of the amygdala were found to lack skin conductance responses following positive or negative reinforcement (gaining or losing money in a gambling task). The results of our study are consistent with, and further expand, these findings by Bechara *et al*. (1999) by providing, for the first time in healthy human subjects

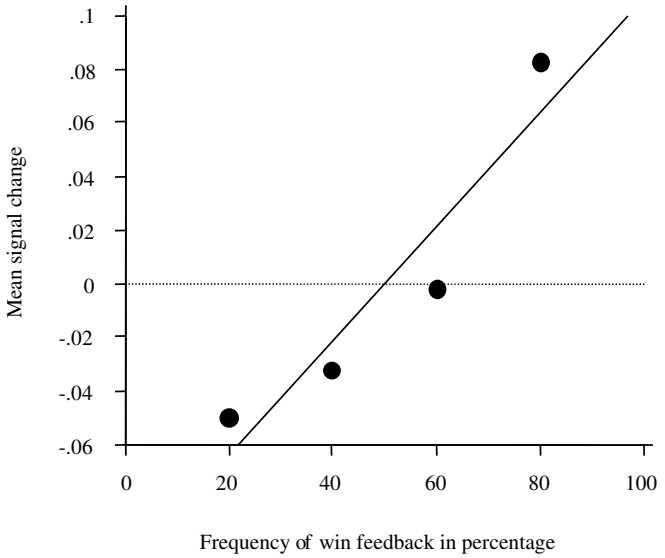

FIG. 4. Correlation plot reporting the relationship between mean fMRI signal changes (in percentage) and frequencies (20, 40, 60, 80%) of win feedback trials for all 10 subjects in the left amygdala. The per cent signal change encompasses a relative range from +0.1 to –0.1 with the number '0' in the vertical axis representing the averaged signal across feedback percentages.

with intact brains, a demonstration that the amygdala functionally responds to both positive (winning) and negative (losing) conditions.

In addition, our results also point to a distinct involvement of the left and right amygdala in relation to positive and negative situations, respectively. Although in need of replication and validation in a larger sample of subjects, this differential left/right amygdala response is in agreement with results from animal and human studies suggesting a distinct role of the left and right hemisphere with regard to positive and negative emotional states (Sackeim *et al*., 1982; Davidson *et al*., 1990; Coleman-Mesches & McGaugh, 1995; Davidson, 1995, 1998; Coleman-Mesches *et al*., 1996; Salinas & White, 1998). Indeed, the results of the debriefing and the behavioural scale completed by the subjects upon termination of the study showed, as expected, that winning was associated with a positive emotional response (increased self-confidence and gratification) and losing with an opposite reaction (decreased self-confidence and frustration). Evidence in rodents suggests that the right amygdala is more involved than the left in consolidation of memory storage for aversive experience based on reward reduction (Coleman-Mesches & McGaugh, 1995; Salinas & White, 1998). Clinical, electroencephalographic and neuroimaging studies support the role of the left hemisphere in expressing approach-related positive affect, and that of the right hemisphere in withdrawal-related negative affect (Sackeim *et al*., 1982; Davidson *et al*., 1990; Davidson, 1995, 1998). Patients with left brain damage frequently show dysphoric mood, depression and hopelessness, whereas patients with lesions in the right hemisphere show euphoric mood and happiness as a result of a disinhibition of centres in the opposite side of the brain.

The role of the amygdala in the regulation of mood and emotions has also been investigated in psychiatric disorders. A study by Rauch *et al*. (1996) in patients with post-traumatic stress disorder (PTSD) showed an over-responsiveness of the right amygdala associated with PTSD symptomatic states and the absence of habituation to intense emotional stimuli, compared with normal controls. Using positron emission tomography, Abercrombie *et al*. (1998) reported that in depressive patients, right amygdala metabolism was positively correlated with negative affects. Consistent with these results, our data support the notion of a different involvement of the amygdala in mediating positive and negative affective states.

The involvement of the human amygdala in responding to other emotionally charged stimulations has been extensively demonstrated in the case of perception of natural stimuli, primarily by using facial expressions (Adolphs *et al*., 1994, 1995, 1996; Breiter *et al*., 1996; Morris *et al*., 1996, 1998a, 1998b; Blair *et al*., 1999) or olfactory, gustatory and auditory stimulations (Scott *et al*., 1997; Zald & Prado, 1997; Zald *et al*., 1998). To our knowledge, however, no previous study yet has reported a differential functional activity of the amygdala related to processing lexical stimuli signalling rewarding and aversive events. In two previous studies with positron emission tomography, the neural substrate of reward was investigated by using abstract forms of reinforcement in relation to successful or unsuccessful performance in humans. The first study (Elliott *et al*., 1997) employed words to provide positive or negative feedback about the subject's performance while, in the second study (Thut *et al*., 1997), the word 'ok' or a number indicating the amount of money were delivered. In neither of these experiments, though, was the amygdala activated. The lack of a social competitive context in the two studies cited above may contribute to explain the absence of amygdala activation in processing salient verbal feedback. On the contrary, the competitive setting and the final ranking in our study provided the subjects with the context in which the words 'win' and 'lose' acted as emotional elicitors. In support of this interpretation, Cahill *et al*. (1995) and Cahill & McGaugh (1998) have shown that the amygdala is involved in an emotional memory task when the stimuli are arousing. Further, patients with lesions of the amygdala retain the ability to identify emotional words or sentences, suggesting that the amygdala is not necessarily involved in processing lexical items with emotional semantic content (Phelps *et al*., 1997). In the authors' view, the amygdala would become involved only when emotional words or sentences are capable of eliciting an arousal response.

In addition to the amygdala, we found different activations in other brain structures, including the prefrontal and orbitofrontal cortex, the hippocampus and the ventral striatum, in response to the effects of winning and losing. During winning, among the cortical areas activated, we found a significant activation in the Broca's area (BA 44) and the right inferior frontal gyrus (BA 47). Besides its function in producing linguistic output (Wise *et al*., 1991), Broca's area is involved in programming and controlling manual sequential production (Roland, 1985; Fox *et al*., 1988). However, evidence from previous studies does not help to disambiguate the specific role of this area in our task. The involvement of frontal cortical areas in processing rewarding and aversive stimuli in relation to a goal is supported by several previous reports. For instance, patients with lesions of the dorsolateral prefrontal cortex are impaired in planning action in that they are unable to judge the instrumental value of an event in order to reach a goal (Sirigu *et al*., 1995). In particular, the orbitofrontal cortex plays a crucial role in emotional responses and in predicting reward or punishment events (Rolls, 1996; Schoenbaum *et al*., 1998; Schultz *et al*., 1998). Bechara *et al*. (1997) reported that patients with damage to the ventral region of the prefrontal cortex are impaired in decision-making while performing a gambling task, compared with normal subjects. Contrary to normals, these patients failed to generate anticipatory skin conductance responses whenever they were unconsciously making a risky choice and were unable to act in accordance with the advantageous strategy. However, unlike patients with amygdala damage, patients with damage to the ventromedial prefrontal cortex generated skin conductance responses after receiving a reward or a punishment (Bechara *et al*., 1999). The results from these studies suggest that the prefrontal cortex is

responsible for assessing the positive or negative value of events that we use to make an optimal choice. As suggested by Damasio (1995), cognitive processes supported by ventromedial prefrontal cortex may be responsible for monitoring somatic markers related to reward and punishment encoded by the amygdala. In human subjects, processing of information that conveys the amount of success or failure in an ongoing activity is crucial for them to adjust their behaviour and achieve a goal. In our task, the performance-based ranking, which motivated the competition among the subjects, provided them with a goal in relation to which the frequency of 'win' and 'lose' trials acquired a positive or negative valence. In this context, the amygdala would be covertly involved in evaluating the positive and negative aspects of events relative to a baseline state and may be crucial in detecting the amount of reward by computing variations of their occurrence. The activation found in our subjects in the orbitofrontal cortex during the winning condition is consistent with this observation although it is not clear why no similar activation was seen during the losing condition.

In addition to the left amygdala, the contiguous hippocampal formation was also activated in response to winning. As previous studies have shown (Kesner & Williams, 1995; Cahill & McGaugh, 1998), the amygdala and the hippocampus are both involved in learning associations between a stimulus and the primary reinforcer.

The relative increase of losing was also associated with some (uncorrected) activation in the globus pallidus and in the putamen. The basal ganglia dopamine neurons are known to be modulated by various aspects of reinforcement, e.g. reward expectation (Apicella *et al*., 1991; Schultz *et al*., 1995, 1997; Shidara *et al*., 1998). Because of their direct anatomical connections with the limbic system, the basal ganglia provide the neural mechanisms responsible for linking the reward-related information processed in limbic structures with behavioural responses (Everitt *et al*., 1991). In our task, while keeping the subject's reaction time constant, the activation in the globus pallidus and in the putamen in response to the decrease of reward might be associated with motivational changes. This interpretation is consistent with the previous evidence assessing the role of basal ganglia in the motivational aspects of attention and action selection (Graybiel, 1995; Kawagoe *et al*., 1998).

In summary, the findings of this functional brain study demonstrate that in humans the activation of the amygdala is modulated by changes in the frequency of positive and negative feedbacks. Furthermore, our results are the first to show that the left and right human amygdala respond differentially to the magnitude of positive and negative lexical feedback, respectively. We suggest that such an asymmetric activation may be due to differential involvement of the left and right amygdala in the expression of the positive and negative emotions associated with succeeding and failing in a competitive context.

Acknowledgements

This study was funded by the NINDS-NIH intramural program, the Fondation Bettencourt-Schueller (T. Z.) and the GIS-CNRS, Sciences de la Cognition (T. Z., A. S.). The authors wish to thank Michael E. Goldberg for his helpful comments on the manuscript and Milan Makale for technical support with MRI scanning.

Abbreviations

BA, Broadmann's area; fMRI, functional magnetic resonance imaging; FOV, field of view; PTSD, post-traumatic stress disorder.

References

Abercrombie, H.C., Schaefer, S.M., Larson, C.L., Oakes, T.R., Lindgren, K.A., Holden, J.E., Perlman, S.B., Turski, P.A., Krahn, D.D., Benca, R.M. & Davidson, R.J. (1998) Metabolic rate in the right amygdala predicts negative affect in depressed patients. *Neuroreport*, **9**, 3301–3307.

Adolphs, R., Tranel, D., Damasio, H. & Damasio, A.R. (1994) Impaired recognition of emotion in facial expressions following bilateral damage to the human amygdala. *Nature*, **372**, 669–672.

Adolphs, R., Tranel, D., Damasio, H. & Damasio, A.R. (1995) Fear and the human amygdala. *J. Neurosci.*, **15**, 5879–5891.

Adolphs, R., Damasio, H., Tranel, D. & Damasio, A.R. (1996) Cortical systems for the recognition of emotion in facial expressions. *J. Neurosci.*, **16**, 7678–7687.

Angrilli, A., Mauri, A., Palomba, D., Flor, H., Birbaumer, N., Sartori, G. & di Paola, F. (1996) Startle reflex and emotional modulation impairment after a right amygdala lesion. *Brain*, **119**, 1991–2000.

Apicella, P., Ljungberg, T., Scarnati, E. & Schultz, W. (1991) Responses to reward in monkey dorsal and ventral striatum. *Exp. Brain Res.*, **85** (3), 491–500.

Bechara, A., Damasio, H., Tranel, D. & Damasio, A.R. (1997) Deciding advantageously before knowing the advantageous strategy. *Science*, **275**, 1293–1295.

Bechara, A., Damasio, H., Damasio, A.R. & Lee, G.P. (1999) Different contributions of the human amygdala and ventromedial prefrontal cortex to decision making. *J. Neurosci.*, 19 (13), 5473–5481.

Blair, R.J., Morris, J.S., Frith, C.D., Perrett, D.I. & Dolan, R.J. (1999) Dissociable neural responses to facial expressions of sadness and anger. *Brain*, **122**, 883–893.

Breiter, H.C., Etcoff, N.L., Whalen, P.J., Kennedy, W.A., Rauch, S.L., Buckner, R.L., Strauss, M.M., Hyman, S.E. & Rosen, B.R. (1996) Response and habituation of the human amygdala during visual processing of facial expression. *Neuron*, **17**, 875–887.

Büchel, C., Morris, J., Dolan, R. & Friston, K.J. (1998) Brain systems mediating aversive conditioning: an event-related fMRI study. *Neuron*, **20**, 947–957.

Cahill, L., Babinsky, R., Markowitsch, H.J. & McGaugh, J.L. (1995) The amygdala and the emotional memory. *Science*, **377**, 295–296.

Cahill, L. & McGaugh, J.L. (1998) Mechanisms of emotional arousal and lasting declarative memory. *Trends Neurosci.*, **21**, 294–299.

Coleman-Mesches, K. & McGaugh, J.L. (1995) Differential involvement of the right and left amygdalae in expression of memory for aversively motivated training. *Brain Res.*, **670**, 75–81.

Coleman-Mesches, K., Salinas, J.A. & McGaugh, J.L. (1996) Unilateral amygdala inactivation after training attenuates memory for reduced reward. *Behav. Brain Res.*, **77**, 175–180.

Damasio, A.R. (1995) On some functions of the human prefrontal cortex. In Grafman, J., Boller, F. & Holyoak, K.J. (eds), *Structures and Functions of the Human Prefrontal Cortex.* Ann. NY Acad. Sci., Vol. 15, no. 769, New York, pp. 241–251.

Davidson, R.J., Ekman, P., Saron, C.D., Senulis, J.A. & Friesen, W.V. (1990) Approach-withdrawal and cerebral asymmetry: emotional expression and brain physiology. I. *J. Pers. Soc. Psychol.*, **58**, 330–341.

Davidson, R.J. (1998) Affective style and affective disorders: perspectives from affective neuroscience. *Cognition Emotion*, **12**, 307–330.

Davidson, R.J. (1995) Asymmetric brain function, emotion and affective style. In Davidson, R.J. & Hugdahl, K. (eds), *Brain Asymmetry*. MIT Press, Cambridge, MA, USA, pp. 361–387.

Elliott, R., Frith, C.D. & Dolan, R.J. (1997) Differential neural response to positive and negative feedback in planning and guessing tasks. *Neuropsychologia*, **35**, 1395–1404.

Everitt, B.J., Morris, K.A., O'Brien, A. & Robbins, T.W. (1991) The basolateral amygdala-ventral striatal system and conditioned place preference: further evidence of limbic–striatal interactions underlying reward-related processes. *Neuroscience*, **42**, 1–18.

Friston, K.J., Holmes, A.P., Poline, J.-B., Grasby, P.J., Williams, S.C.R., Frackowiak, R.S. & Turner, R. (1995a) Analysis of fMRI time-series revisited. *Neuroimage*, **2**, 45–53.

Friston, K.J., Ashburner, J., Frith, C.D., Poline, J.-B., Heather, J.D. & Frackowiak, R.S. (1995b) Spatial registration and normalization of images. *Hum. Brain Mapp.*, **2**, 1–25.

Fox, P., Petersen, S., Posner, M. & Raichle, M. (1988) Is Broca's area language-specific? *Neurology*, **38** (Suppl. 1), 172.

Graybiel, A.M. (1995) Building action repertoires: memory and learning functions of the basal ganglia. *Curr. Opin. Neurobiol.*, **5**, 733–741.

Gaffan, D. & Harrison, S.J. (1987) Amygdalectomy and disconnection in visual learning for auditory secondary reinforcement by monkeys. *Neuroscience*, **7**, 2285–2292.

Hamann, S.B., Ely, T.D., Grafton, S.T. & Kilts, C.D. (1999) Amygdala

activity related to enhanced memory for pleasant and aversive stimuli. *Nature Neurosci.*, **2**, 289–293.
Kawagoe, R., Takikawa, Y. & Hikosaka, O. (1998) Expectation of reward modulates cognitive signals in the basal ganglia. *Nature Neurosci.*, **1**, 411–416.
Kesner, R.P. & Williams, J.M. (1995) Memory for magnitude of reinforcement: dissociation between the amygdala and hippocampus. *Neurobiol. Learn. Mem.*, **64**, 237–244.
Irwin, W., Davidson, R.J., Lowe, M.J., Mock, B.J., Sorenson, J.A. & Turski, P.A. (1996) Human amygdala activation detected with echo-planar functional magnetic resonance imaging. *Neuroreport*, **7**, 1765–1769.
LaBar, K.S., LeDoux, J.E., Spencer, D.D. & Phelps, E.A. (1995) Impaired fear conditioning following unilateral temporal lobectomy in humans. *J. Neurosci.*, **15**, 6846–6855.
LaBar, K.S., Gatemby, 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.E. (1996) *The Emotional Brain*. Simon & Schuster, New York.
Morris, J.S., Frith, C.D., Perrett, D.I., Rowland, D., Young, A.W., Calder, A.J. & Dolan, R.J. (1996) A differential neural response in the human amygdala to fearful and happy facial expressions. *Nature*, **383**, 812–815.
Morris, J.S., Friston, K.J., Buchel, C., Frith, C.D., Young, A.W., Calder, A.J. & Dolan, R.J. (1998a) A neuromodulatory role for the human amygdala in processing emotional facial expressions. *Brain*, **121**, 47–57.
Morris, J.S., Öhman, A. & Dolan, R.J. (1998b) Conscious and unconscious emotional learning in the human amygdala. *Nature*, **393**, 467–470.
Nishijo, H., Ono, T. & Nishino, H. (1988) Single neuron responses in amygdala of alert monkey during complex sensory stimulation with affective significance. *J. Neurosci.*, **8**, 3570–3583.
Pallier, C., Dupoux, E. & Jeannin, X. (1997) EXPE: an expandable programming language for psychological experiments. *Behav. Res. Meths, Instruments Computers*, **29**, 322–327.
Phelps, E.A., LaBar, K.S. & Spencer, D.D. (1997) Memory for emotional words following unilateral temporal lobectomy. *Brain Cogn.*, **35**, 85–109.
Phillips, M.L., Young, A.W., Senior, C., Brammer, M., Andrew, C., Calder, A.J., Bullmore, E.T., Perrett, D.I., Rowland, D., Williams, S.C., Gray, J.A. & David, A.S. (1997) A specific neural substrate for perceiving facial expressions of disgust. *Nature*, **389**, 495–498.
Phillips, M.L., Young, A.W., Scott, S.K., Calder, A.J., Andrew, C., Giampietro, V., Williams, S.C., Bullmore, E.T., Brammer, M. & Gray, J.A. (1998) Neural responses to facial and vocal expressions of fear and disgust. *Proc. R. Soc. Lond. B. Biol. Sci.*, **265**, 1809–1817.
Rauch, S.L., van der Kolk, B.A., Fisler, R.E., Alpert, N.M., Orr, S.P., Savage, C.R., Fischman, A.J., Jenike, M.A. & Pitman, R.K. (1996) A symptom provocation study of posttraumatic stress disorder using positron emission tomography and script-driven imagery. *Arch. Gen. Psychiatry*, **53**, 380–387.
Roland, P.E. (1985) Cortical organization of voluntary behavior in man. *Neurobiology*, **4**, 155–167.
Rolls, E.T. (1992) Neurobiological aspects of emotion, memory and mental dysfunction. In Aggleton, J.P. (Ed.) *The Amygdala*, Wiley-Liss, New York, pp. 143–165.
Rolls, E.T. (1996) The orbitofrontal cortex. *Philos. Trans. R. Soc. Lond. Biol. Sci.*, **351**, 1443–1444.
Rosenberg, M. (1989) *Society and the Adolescent Self Image*. Wesleyan University Press, Middletown, CT, USA.
Ryckman, R.M., Hammer, M., Kaczor, L.M. & Gold, J.A. (1996) Construction of a personal developmental competitive attitude scale. *J. Pers. Assess.*, **66**, 374–385.
Sackeim, H.A., Greenberg, M.S., Weiman, A.L., Gur, R.C., Hungerbuhler, J.P. & Geschwind, N. (1982) Hemispheric asymmetry in the expression of positive and negative emotions. Neurologic evidence. *Arch. Neurol.*, **39**, 210–218.
Salinas, J.A. & McGaugh, J.L. (1996) The amygdala modulates memory for changes in reward magnitude: involvement of the amygdaloid GABAergic system. *Behav. Brain Res.*, **80**, 87–98.
Salinas, J.A. & White, N.M. (1998) Contributions of the hippocampus, amygdala, and dorsal striatum to the response elicited by reward reduction. *Behav. Neurosci.*, **112**, 812–826.
Schneider, F., Grodd, W., Weiss, U., Klose, U., Mayer, K.R., Nagele, T. & Gur, R.C. (1997) Functional MRI reveals left amygdala activation during emotion. *Psychiatry Res.*, **76**, 75–82.
Schoenbaum, G., Chiba, A.A. & Gallagher, M. (1998) Orbitofrontal cortex and basolateral amygdala encode expected outcomes during learning. *Nature Neurosci.*, **1**, 155–159.
Schultz, W., Romo, R., Ljungberg, T., Mirenowicz, J., Hollerman, J.R. & Dickinson, A. (1995) Reward-related signals carried by dopamine neurons. In Houk, J.C., Davis, J.L. & Beiser, D.G. (eds), *Models of Information Processing in the Basal Ganglia.* A Bradford Book, MIT Press, Cambridge, MA, USA, pp. 233–248.
Schultz, W. (1997) Dopamine neurons and their role in reward mechanisms. *Curr. Opin. Neurobiol.*, **7**, 191–197.
Schultz, W., Dayan, P. & Montague, P.R. (1997) A neural substrate of prediction and reward. *Science*, **275**, 1593–1599.
Schultz, W., Tremblay, L. & Hollerman, J.R. (1998) Reward prediction in primate basal ganglia and frontal cortex. *Neuropharmacology*, **37**, 421–429.
Schultz, W. (1998) Predictive reward signal of dopamine neurons. *J. Neurophysiol.*, **80** (1), 1–27.
Scott, S.K., Young, A.W., Calder, A.J., Hellawell, D.J., Aggleton, J.P. & Johnson, M. (1997) Impaired auditory recognition of fear and anger following bilateral amygdala lesions. *Nature*, **385**, 254–257.
Shidara, M., Aigner, T.G. & Richmond, B.J. (1998) Neuronal signals in the monkey ventral striatum related to progress through a predictable series of trials. *J. Neurosci.*, **18**, 2613–2625.
Sirigu, A., Zalla, T., Pillon, B., Grafman, J., Agid, Y. & Dubois, B. (1995) Selective impairments in managerial knowledge following pre-frontal cortex damage. *Cortex*, **31**, 301–316.
Talairach, J. & Tournoux, P. (1988) *Co-Planar Stereotaxic Atlas of the Human Brain.* Thieme Medical Publisher, New York.
Thut, G., Schultz, W., Roelcke, U., Nienhusmeier, M., Missimer, J., Maguire, R.P. & Leenders, K.L. (1997) Activation of the human brain by monetary reward. *Neuroreport*, **8**, 1225–1228.
Watanabe, M. (1990) Prefrontal unit activity during associative learning in the monkey. *Exp. Brain Res.*, **80**, 296–309.
Weiskrantz, L. (1956) Behavioral changes associated with ablation of the amygdaloid complex in monkeys. *J. Comp. Physiol. Psychol.*, **49**, 381–391.
Wise, R., Chollet, F., Hadar, U., Friston, K., Hoffner, E. & Frackowiak, R. (1991) Distribution of cortical networks involved in word comprehension and word retrieval. *Brain*, **114**, 1803–1817.
Zald, D.H. & Pardo, J.V. (1997) Emotion, olfaction and the human amygdala: amygdala activation during aversive olfactory stimulation. *Proc. Natl Acad. Sci., USA*, **94**, 4119–4124.
Zald, D.H., Lee, J.T., Fluegel, K.W. & Pardo, J.V. (1998) Aversive gustatory stimulation activates limbic circuits in humans. *Brain*, **121**, 1143–1154.
Zalla, T., Koechlin, E., Pietrini, P., Basso, G., Aquino, P. & Grafman, J. (1999a) Distinct left and right activation in winning and losing situations. *Biol. Psychiatry*, **45**, 111S–112S.
Zalla, T., Koechlin, E., Pietrini, P., Basso, G., Aquino, P. & Grafman, J. (1999b) Differential amygdala activation to verbal stimuli during winning and losing perception. *Neuroimage*, **9**, S370.