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The Role of the Amygdala in Signaling Prospective Outcome of Choice

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Summary

Can brain activity reveal a covert choice? Making a choice often evokes distinct emotions that accompany decision processes. Amygdala has been implicated in choice behavior that is guided by a prospective negative outcome. However, its specific involvement in emotional versus cognitive processing of choice behavior has been a subject of controversy. In this study, the human amygdala was monitored by functional magnetic resonance imaging (fMRI) while subjects were playing in a naturalistic choice paradigm against the experimenter. In order to win, players had to occasionally choose to bluff their opponent, risk "getting caught," and suffer a loss. A critical period, when choice has been made but outcome was still unknown, activated the amygdala preferentially following the choice that entailed risk of loss. Thus, the response of the amygdala differentiated between subject's covert choice of either playing fair or foul. These results support a role of the amygdala in choice behavior, both in the appraisal of inherent value of choice and the signaling of prospective negative outcomes.

Introduction

Choices often involve risk and uncertainty. To what extent making a choice incorporates affective processing has been long debated in decision theory (Mellers et al., 1997, 1999; Damasio, 1994). Making a choice calls for appraisal of the expected outcome relating to different options. Such evaluation prior to and immediately following a choice usually evokes distinct affect. This can be demonstrated with a mundane example: if a traffic light turns yellow when we reach an intersection, we have to choose whether to stop, as required by law, or to cross the intersection. Making a choice in this case depends not only on knowing the traffic rules (i.e., the value of options), but also on our willingness to ignore them and take a risk (i.e., the value of outcome). In this case, either stopping at the yellow light (i.e., wasting time but obeying the law) or crossing the intersection (i.e., saving time but risking negative consequences) will be accompanied by a characteristic affective response.

Based on lesion studies in animals and humans, it has been suggested that an intact amygdala is essential for making motivational (i.e., affective) choices. In animals, studies using reinforced goal-directed behavioral paradigms showed that lesions to the amygdala interfere with learning to avoid an aversive outcome (Davis, 1992; LeDoux, 1996, 1998; Killcross et al., 1997; Fanselow and LeDoux, 1999), and with adjustment to varying values of reinforcement (monkeys: Malkova et al., 1997; rats: Hatfield et al., 1996). In humans, it was shown that a lesion to the medial temporal lobe interferes with affective choice behavior, as indicated by the lack of a conditioned skin conductance response (SCR) to visual stimuli paired with aversive sounds (LaBar et al., 1995, 1998). More specifically, patients with bilateral amygdala damage did not develop anticipatory SCRs when they faced a risky choice or following a negative outcome during a gambling task (Bechara et al., 1995, 1999). People and animals with bilateral amygdala damage also demonstrate poor judgment in their overall behavior. For example, monkeys with such lesions have increased tendency to approach risky objects in their environment (Kluver and Bucy, 1939; Zola-Morgan et al., 1991). Humans were found to have impaired social behavior (Tranel and Hyman, 1990) and were unable to recognize negative facial expressions, a crucial skill in judging risky social situations and evaluating prospective interactions (Adolphs et al., 1995, 1998).

Functional brain imaging provides a tool for studying the intact human amygdala and, thus, for examining its role in choice behavior. Several studies have demonstrated amygdala involvement in processing the negative valence of stimuli (Morris et al., 1996, 1999; Breiter et al., 1996; Phillips et al., 1997; Schneider et al., 1997; Whalen et al., 1998; Rotshtein et al., 2001). Imaging studies that have directly examined the role of amygdala in choice behavior have primarily employed classical conditioning or gambling paradigms. Using a conditioning paradigm in fMRI, it was shown that activation in the amygdala was greatest at the initial phase of acquisition and at extinction of emotional learning (LaBar et al., 1998; Buchel et al., 1998). The rapid habituation observed in this paradigm led to the suggestion that the amygdala is most sensitive to the novel affective aspect of a signal, such as in the initial stage of learning a conditioned choice behavior. Recently, it has been shown that the amygdala could be activated by the threat of a negative outcome, suggesting that it is not only related to the learning phase but rather to actual

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expression of a fear-conditioned response (Phelps et al., 2001). Similarly, it has been demonstrated that the amygdala is involved in evaluating the value and likelihood of a monetary or abstract outcome (Breiter et al., 2001; Zalla et al., 2000, respectively).

Evaluation of a prospective negative outcome and the response to its occurrence are not exclusively mediated by the amygdala. Rather, these processes involve several other brain regions, such as the prefrontal cortex, anterior cingulate, parietal cortex, hippocampus, and ventral striatum (LaBar et al., 1998; Buchel et al., 1998; Critchley et al., 2001; Knutson et al., 2000; Breiter et al., 2001; O'Doherty et al., 2001; Knight et al., 1999; Zalla et al., 2000; Rogers et al., 1999; Elliott et al., 1997, 2000; Leon and Shadlen, 1999). Recently, a disconnection study in monkeys indicated that motivational choice behavior, guided by the value of the outcome, is primarily dependent on the effective interaction between the amygdala and orbital prefrontal cortex (Baxter et al., 2000). Thus, it is still an open question in what way the amygdala, a major limbic junction, is pivotal for making an advantageous choice under uncertainty and risk. Bechara et al. (1999) addressed this question by measuring SCRs during a gambling task in patients with localized lesions in either the amygdala or ventromedial prefrontal (VMPF) cortex. It was found that both intact amygdala and VMPF cortex were necessary for effective goal-directed behavior, but in different ways. The amygdala was suggested to be more critical than VMPF for dealing adaptively with affective aspects of the decision process.

In this study, the intact amygdala response was monitored directly by fMRI while subjects played an interactive modified domino game against the experimenter. The subject (player) was actually involved in naturalistic choice behavior that was guided by the abstract goal of winning against the experimenter (opponent). In order to win the game, the player was sometimes forced to bluff the opponent, thereby taking the risk of getting caught and suffering an expected loss. The game thus led to making untruthful choices that were associated with greater risk.

The player's choices and the opponent's responses were interactively determined by the flow of the game, creating a natural progression of a game situation that lasted approximately 5 min, or until one of the sides won. Figure 1 illustrates the requirements and options during one round of the game (see Experimental Procedures for details and Supplemental Data at http://www.neuron.org/cgi/content/full/33/6/983/DC1 information for a short demo of the game). At the beginning of the game, one master chip and twelve game chips were assigned to the player's board. In order to win, the player had to get rid of all the assigned chips as quickly as possible. At each round of the game, the player was required to choose a chip from the board. The opponent was blind to the choice made. A chosen chip could be either a match or a nonmatch relative to the master chip (Figure 1A, red arrow). A nonmatch was a chip for which neither of the numbers matched the numbers on the master chip. Then, the opponent could either ask the player to expose the chosen chip or continue with the game. Thus, the outcome of each round depended on the combination of the player's choice (match or nonmatch) and the opponent's response (show or no-show) (Figure 1D). Note that only for a nonmatch choice the player can suffer an actual loss. Therefore, a nonmatch chip can be regarded as a foul choice, while a match chip can be regarded as a fair choice. The present game paradigm is unique, as it required that the subject actively make choices that determined the progress of the situation, and then required an ongoing involvement of the experimenter in imposing uncertainty about the consequence of each choice. Our specific interest was whether the amygdala response following each choice—but before the outcome was known—would reveal the subject's covert choice. We hypothesized that amygdala activation would reflect affective states related to both the value of the choice acted upon and the prospective opponent's response.

Results

Behavioral Analysis of the Game

The subjective experience reported by the subjects following the scan was that they were eager to win the game and tried to make advantageous choices to achieve that goal. An analysis of the players' choices revealed that on the average subjects chose equally between match and nonmatch chips throughout the game. Figure 2A depicts the players' nonmatch choice index and the opponent's show response index during the game (see Experimental Procedures for details on the measurements). The players' choices and the opponent's responses on average comprised of equal amounts of each option (match versus nonmatch and show versus no-show, respectively). The averaged calculated player's nonmatch choice index across all games was 0.513 (0.331 SD), and the averaged calculated opponent's show response index was 0.566 (0.341 SD). Nonetheless, there was a trend for the opponent to become biased to respond more with "Show" as the game duration approached 5 min (Figure 2A, black line). Accordingly, a one-way ANOVA of opponent's show response index by minutes of game revealed a significant effect of time ($F[4, 195] = 3.214$, $p < 0.0139$). This bias was also expressed as a statistically significant difference between the show index of the fifth minute and the hypothesized mean of 0.5 for a nonbiased opponent's responses between show and no-show ($t[14] = 2.493$, $p < 0.05$). In contrast, for the player's nonmatch choice index there was no significant change with time ($F[4, 195] = 0.615$, $p = 0.652$), and it persisted throughout around the average choice index of 0.5 (Figure 2A, light gray line). In order to further explore the relationship between the player's choice and opponent's response, a two-way ANOVA was performed with opponent's response (show index) and game duration (minutes) as factors and player's choice (nonmatch index) as the dependant variable. The main effect and interaction were not significant, suggesting that the players' responses did not change as a function of the opponent's responses.

An additional aspect of game progression was defined with respect to the number of chips left for the subject to get rid of representing the asset position (see Experimental Procedures for details). As expected, high asset

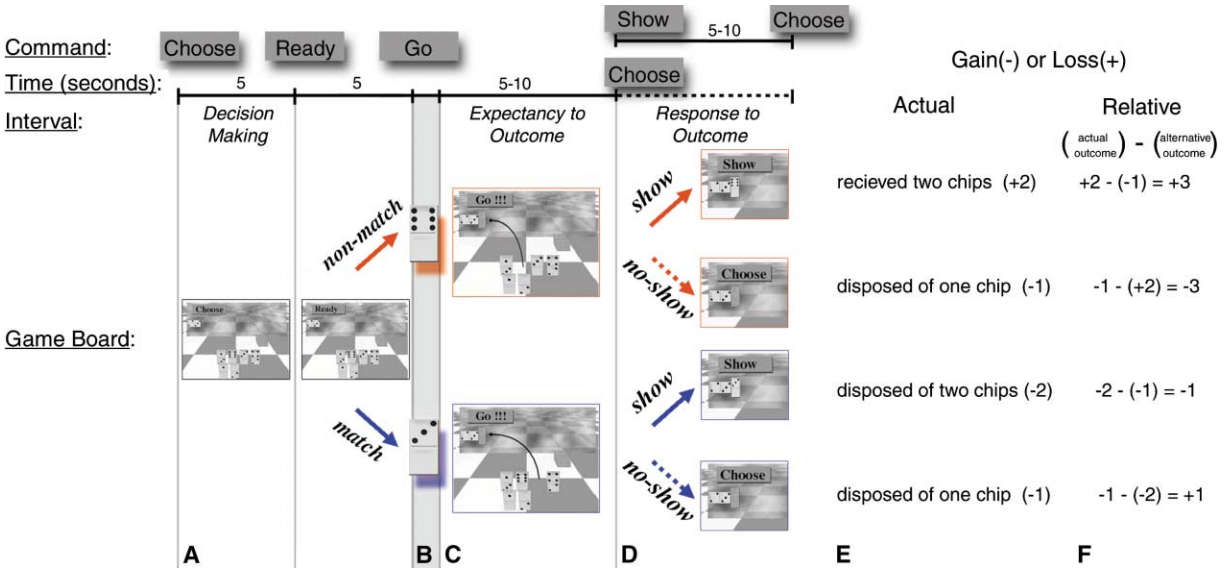

Figure 1. Game Course

Diagram indicating the temporal sequence of steps as driven by the interaction between the player and the opponent during one round in the game. The steps were divided by visually and aurally presented commands shown in gray rectangles (see Experimental Procedures for detailed description of game progress and additional information for a game demo). A representative round is depicted, where the master chip is horizontally positioned on the game board (glass-like rectangle). At the beginning of a round, the command "Choose" directs the player to mentally choose a chip from the chips assigned to him (depicted on the bottom of the board). After the command "Ready," the player is required to move the cursor to mark his chosen chip. Following the command "Go," the player is required to actually pick it and waits for the opponent's response. Having observed the subject making his choice, the opponent can ask the subject to expose the chosen chip or not to expose the chip and continue to the next turn. Accordingly, three intervals of interest were characterized during a round: "decision-making" (A), "expectancy-to-outcome" (C), and "response-to-outcome" (D). The interval from the onset of the instruction "Go" until the player's last motor action of pick, is marked in gray (B). The "expectancy-to-outcome" interval is divided into two possible events depending on the player's choice: nonmatch (red) or match (blue). Subsequently, the "response-to-outcome" interval is divided into four outcomes, depending on the two possible responses of the opponent: expose the chosen chip (filled arrows) or continue to the next turn (dotted arrows). The actual gain or loss in each round is depicted as the number of chips subtracted or added to the chips assigned initially to the player (E). The relative gain or loss is calculated as the difference between the gain or loss of the actual outcome and the alternative outcome (see Experimental Procedures for details) (F). Note that the magnitude of actual outcome is greater when opponent response with a show than a no-show, while the magnitude of counterfactual comparison (relative gain or loss) is greater when the player makes a nonmatch choice then a match choice.

was associated with early stages of the game while low asset was associated with later stages of the game. The subjects' choice behavior did not differ according to asset position. This was demonstrated in a one-way ANOVA of choice index by asset position that was not significant, and by comparison of the choice nonmatch index of the three asset positions against a hypothesized mean of 0.5 that was also not significant (Figure 2B). The proportional occurrences (number of occurrences in 30 s divided by total number of occurrences in the game) of each asset position per minute of the game are depicted in three histograms in Figure 2C.

Amygdala Activation during "Expectancy-to-Outcome" Interval

Analysis of the fMRI data revealed that while the player was expecting the outcome, the amygdala was activated differentially depending on the type of choice (i.e., nonmatch or match). These results were obtained both when the amygdala was identified structurally and functionally (see Experimental Procedures).

Averaged fMRI response during the "expectancy-to-outcome" interval obtained from anatomically defined region of interest (ROI) of the amygdala is presented in Figure 3A. There were no statistically significant differences between left and right amygdala for these analyses. Hereafter, the data are presented as an average for both amygdala. Events following nonmatch choices evoked an increase in signal relative to baseline and were significantly different from events following match choices. This effect was significant, as demonstrated by repeated measures ANOVA performed on choice type by time (image repetitions). The ANOVA revealed a main effect of time ($F[6, 66] = 3.890$, $p < 0.005$) and an interaction between choice and time ($F[6, 66] = 2.399$, $p < 0.05$). The signal for nonmatch choices was significantly larger than for match choices (planned contrast between nonmatch versus match choices for the duration of 7.5 s post interval onset: $F = 60.619$, $p < 0.0001$, Figure 3A).

A general linear model (GLM) was defined using the player's choices and opponent's responses as predictors. A GLM contrast with nonmatch choice as a positive predictor was used to probe for nonmatch choice-related voxels. Figure 4 shows individual parametric maps for three representative subjects. Single subject GLM analyses demonstrated robust bilateral amygdala activation for all the subjects. The time course

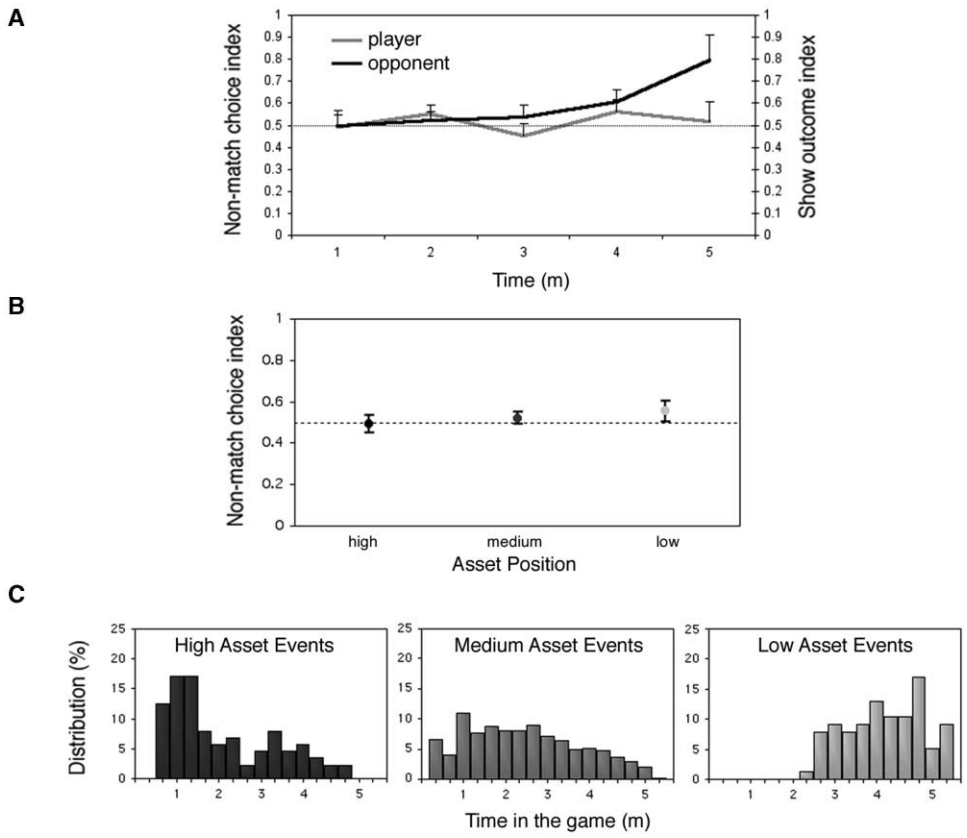

Figure 2. Behavioral Analysis of the Game

(A) Players' choices (gray) and opponent's responses (black) as a function of time. Nonmatch choice index (number of nonmatch choices divided by the number of nonmatch and match choices) and show outcome index (number of show outcomes divided by the number of show and no-show outcomes) are plotted for each minute of the game taken from all games for all the subjects. (B) Players' choices as a function of asset position (see Experimental Procedures). The mean nonmatch choice index is plotted for each one of the different asset positions. (C) Histogram of the distribution of game steps as a function of asset position. Each histogram shows the average proportion of events occurring at different times during the game for each asset position. High asset position is shown in black, medium in gray, and low in light gray. The error bars are standard error of the mean (SEM).

of activated voxels obtained for each subject was consistent with the results obtained in the structural ROI (data not shown). Figure 4 also depicts a nonmatch choice contrast obtained from 12 subjects. Both right and left amygdala were activated (left: 26 mm^3, [−22, −2, −11]; right: 13 mm^3, [29, −2, −11]; $p < 0.05$, uncorrected). Note that the smaller size of the observed foci in the group GLM was probably due to variability in location of foci between subjects. The structurally based definition of the amygdala clearly demonstrates this variability (see Table 1).

In order to test whether the amygdala activation during the "expectancy-to-outcome" interval changed as a function of the number of chips left for the subject to get rid of, fMRI signal was evaluated for each asset position and choice type (Figure 3B). The difference between fMRI signal for choice options (i.e., match versus nonmatch) decreases from high to low asset position. However, no interaction between choice type and asset position was found (two-ways ANOVA: main effect of choice type $F[1, 366] = 16.936$, $p < 0.000$, and main effect of asset position $F[2, 366] = 4.375$, $p < 0.05$). Taken together, this analysis demonstrated increased amygdala response to nonmatch choices during the "expectancy-to-outcome" interval, with greatest response at high asset position.

Amygdala Activation during "Response-to-Outcome" Interval

For the "response-to-outcome" interval, percent signal changes were first calculated from structurally defined ROIs of the amygdala. Because there was no difference in signal change between the left and right amygdala for this interval, further analyses were performed on a weighted average of the left and right amygdala. Figure 5A shows the data sorted by four possible outcomes and averaged across 7.5 s post opponent's response (Figure 1E).

A repeated measures ANOVA across hemispheres was performed with player's choice and opponent's response as factors. There was a main effect of opponent's response ($F[1, 11] = 8.376$, $p < 0.05$), but not a main effect of player's choice or interaction. In addition, planned comparisons revealed a statistically significant difference for show versus no-show outcomes collapsed across subject's choices ($F = 20.289$, $p < 0.01$, Figure 5A), such that the opponent's response of show evoked a greater response than the no-show response.

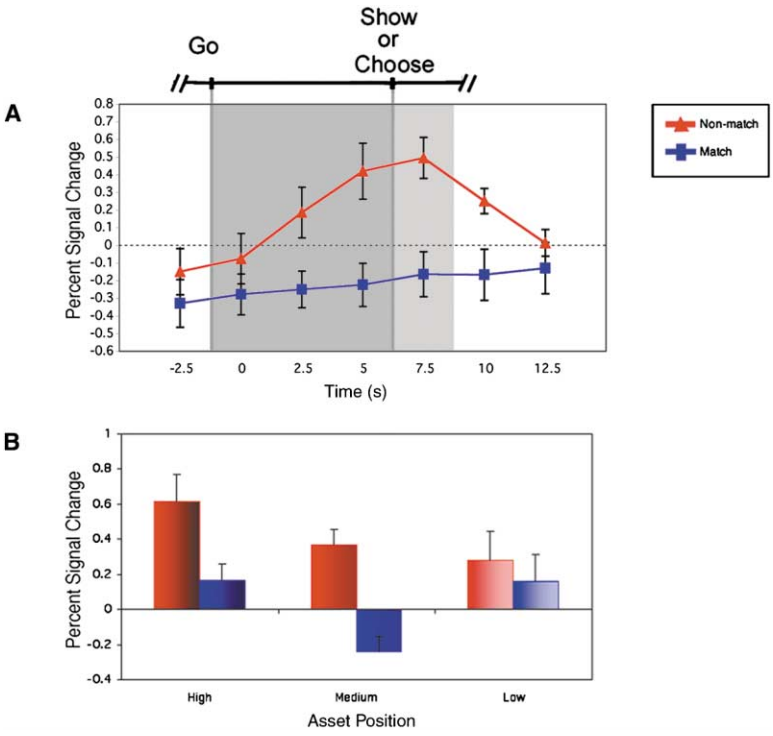

Figure 3. Amygdala Activation during the "Expectancy-to-Outcome" Interval

The graphs depict the averaged activation obtained from the amygdala region of interest bilaterally from all subjects. (A) Percent signal change is shown as a function of time for nonmatch (red) and match (blue) choices. The onset of the interval is set by the player's pick of a chosen chip and ended by the opponent response (either "Show" or "Choose"). Dark gray area represents the average duration of this interval while light gray represents the maximal duration. (B) Averaged percent signal change obtained during expectancy interval for match (blue) and nonmatch (red) events sorted by asset position in the game (i.e., low, medium, and high; see Experimental Procedures for details). The error bars are standard error of the mean (SEM).

A GLM contrast with show response (following either match or nonmatch choices) as a positive predictor was used to probe for show-related voxels in the amygdala. Both left and right amygdala contributed to the individually described signal change during the "response-to-outcome" interval. Figure 6 depicts individual parametric maps obtained for three representative subjects. The time course obtained from the show-related voxels was consistent with the results obtained in the ROI analysis for each subject (data not shown). The show effect of the group is demonstrated in a multistudy GLM for 12 subjects (Figure 6; left: 741 mm^3 [−24, −6, −10]; right: 577 mm^3 [21, −6, −12]; $p < 0.02$ uncorrected). Note that a direct comparison between nonmatch and match choices was not possible since they occurred following different temporal dynamics of the amygdala at the "expectancy-to-outcome" interval and therefore were directly influenced by different preinterval signal amplitudes. Moreover, the no-show outcome events were not perfectly symmetrical to the show outcome events, since the player immediately started to mentally select the next chip for the former, but had about 7.5 s to wait for the new round to begin (choose) following a show for the latter. This does not dismiss the possibility, however, that the player used this lag between rounds to start making his next decision.

Discussion

"Expectancy-to-Outcome": Anticipated Emotions

While the player was expecting the outcome, there was a differential activation of the amygdala according to the

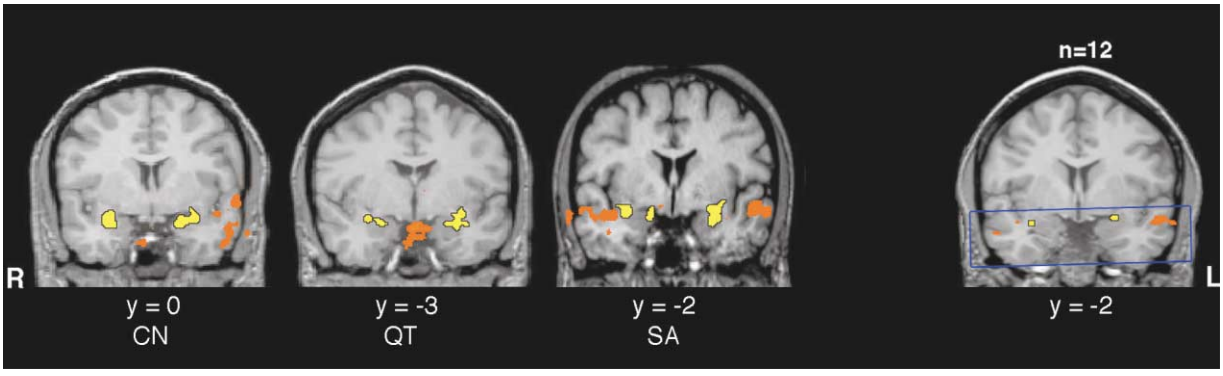

Figure 4. Parametric Maps for Nonmatch Choice Related Voxels during the "Expectancy-to-Outcome" Interval

Parametric maps of preferentially activated voxels following nonmatch choices and before outcome is known, overlaid on anatomical coronal sections. Three representative subjects' maps are shown in addition to a group average (n = 12). Significant activation within the predefined amygdala region is marked in yellow.

Table 1. Amygdala Region of Interest

	Left Amygdala				Right Amygdala			
Subject	Size	x	y	z	Size	x	y	z
BP	1440	25	−4	−14	3465	−26.5	−3	−12.5
CP	4522	18.5	−4.5	−12	3672	−18	−2.5	−12
CN	7128	20	−4.5	−15	6426	−20.5	−4.5	−15.5
EE	5610	21	−5.5	−12.5	4522	−21.5	−5	−14
GB	4356	22.5	−5	−12.5	3213	−19.5	−5	−16
HB	3888	20	−5	−17	5400	−20.5	−7	−15.5
LS	7560	19.5	−6	−12	9200	−20.5	−4	−14.5
LU	5083	19.5	−7.5	−13	3388	−18	−6	−14
QE	10164	20	−5	−15	4199	−19.5	−2	−16.5
QT	5980	19.5	−6	−17	5304	−20	−1	−16.5
SQ	4224	19.5	−4.5	−13.5	2160	−18.5	−3.5	−12.5
SA	4860	20.5	−8	−17	7182	−24	−9.5	−17.5
Anatomically defined voxels	5401.25 ± 2092.203	20.5	−5.5	−14.2	4844.25 ± 1910.11	−20.6	−4.4	−14.8

For each subject, the size (mm^3) and center of gravity (in Talairach space) of the region of interest is depicted.

type of chip chosen by the player. Following a nonmatch choice, there was a positive response in the amygdala that was significantly larger then the response observed following a match choice (Figure 3A, Figure 4). Such differential amygdala responses occurred before the outcome was known, thus revealing the subject's covert choice to play fair or foul (i.e., choosing a match or a nonmatch chip). However, this pattern of amygdala response could also represent affective proposition related to prospective response of the opponent (show or no-show) and consequently the possible outcomes (loss or gain, small or large). The affective characteristic of a nonmatch choice could be related to guilt evoked by its untruthful value or to the tension evoked by the

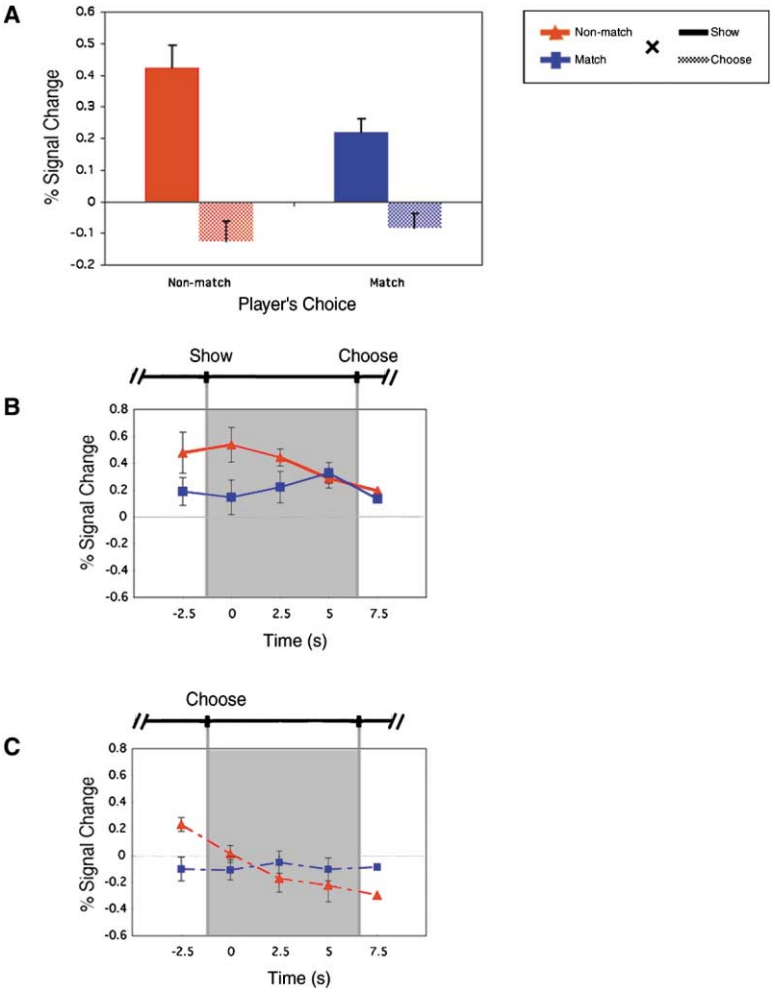

Figure 5. Amygdala Activation during the "Response-to-Outcome" Interval

Average activation obtained from the amygdala region of interest bilaterally for all subjects. (A) Averaged activation for the 7.5 s after either the "Show" outcome (filled) or "Choose" (dotted) as a function of subject choice (nonmatch in red and match in blue). (B) Time course of the amygdala region activation during the "response-to-outcome" interval following a show outcome, and (C) no-show ("Choose") outcome. The error bars are standard error of the mean (SEM).

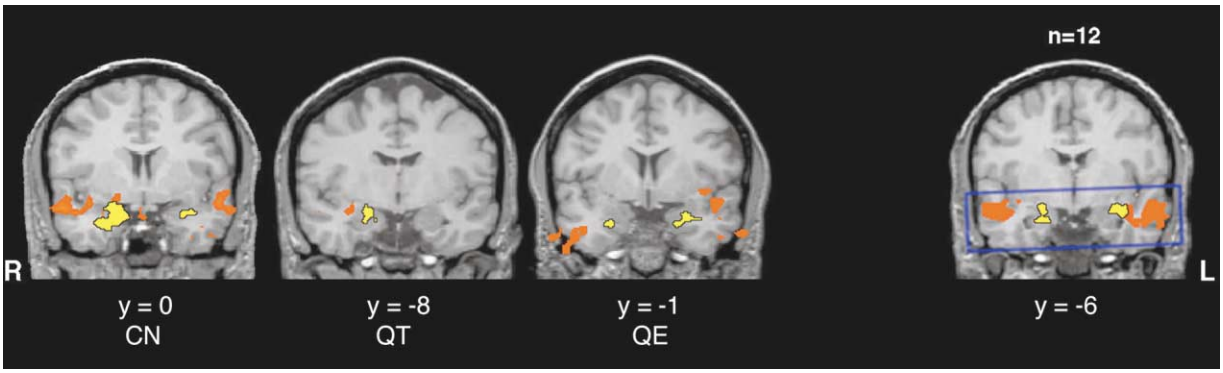

Figure 6. Parametric Maps for Show Outcome Related Voxels during the "Response-to-Outcome" Interval

Parametric maps of voxels preferentially activated following a show outcome are overlaid on coronal sections. Three representative subjects' maps are shown in addition to a group average (n = 12). Significant activation within the predefined amygdala region is marked in yellow.

risk of being exposed and the subsequent loss. In the present game paradigm, players were forced to occasionally make a nonmatch choice; thus, it is unlikely that they felt guilty about it. However, they could have felt shame for the prospect of "being caught" when bluffing. The risk of greater loss following a nonmatch choice could also provoke negative emotion that would influence the amygdala response. In our game paradigm, both choices entailed risk of loss, although of different magnitudes (i.e., large loss following a request to show a nonmatch choice versus a small loss when not requested to show a match choice; Figures 1E and 1F). Therefore, it is suggested that the amygdala is most affected by the prospective magnitude of loss and not just by a risk of any loss.

According to the somatic marker hypothesis, risky choices evoke anticipatory SCRs that represent the affective attributes in the process of decision-making (Damasio, 1994; Bechara et al., 1999). Moreover, decision affect theory suggests that it is not the actual emotion, but rather anticipated emotion, that interacts with the choice process. More specifically, it proposes that risky choices evoke anticipated emotions that relate to either regret (a feeling evoked by considering the player's own choice) or disappointment (a feeling evoked by considering alternative options of the opponent's response) (Loomes and Sugden, 1982, 1986; Loomes et al., 1989; Mellers et al., 1997, 1999).

Recently, another study demonstrated greater positive response of the amygdala when subjects were presented with the prospect of a bad monetary outcome (Breiter et al., 2001). This study and our data suggest that the amygdala is involved in the process of attaching affect to appraisal of prospective negative outcome. However, the origin of this affect in each study might be different. In our study, subjects were engaged in active choice behavior between fair and foul that determined the dominating negative valence of the prospective outcome; thus, their main anticipated emotion was most likely regret (Mellers et al., 1999). In the Breiter et al. (2001) study, subjects did not make any choice. Thus, their negative anticipated emotions could be mainly disappointment (Mellers et al., 1999). Therefore, depending on the involvement of active choice, either anticipated regret (with choice) or disappointment (without choice) could account for the amygdala larger activation to prospective negative outcome. Direct experimental comparison between "expectancy-to-outcome" with and without choice would further delineate the contribution of the value of choice by itself to the amygdala response.

The observed hypersensitivity of amygdala to negative anticipated emotions are in accord with findings in awake cats, showing increased firing rate and greater neuronal synchronization in the lateral amygdala during anticipation of noxious stimuli (Pare and Collins, 2000). In another study, unit recordings in rats indicated that neurons in the amygdala signal not only the value of an already received reinforcement, but also the expectancy to negative outcome even before learning has been established. Moreover, the majority of neurons in the amygdala fired more when a negative outcome was expected than when a positive outcome was expected (Schoenbaum et al., 1998). It was proposed that such prelearning differential amygdala activity to prospective value of outcome provides an important cue for avoiding aversive outcomes in the early stages of learning. Our subjects participated in an over-learned risky choice behavior, and no strategy seemed to be acquired throughout the game by the player (Figure 2A). Thus, the specific response of the amygdala to expected large negative outcome was obtained beyond the learning phase of the game. Such data provide additional support for the claim that the human amygdala is involved in the actual expression and not solely in the acquisition of anticipated negative emotions (Phelps et al., 2001; Bechara et al., 1995).

Furthermore, amygdala damage has been shown to lead to difficulty in making advantageous choices under uncertainty in a gambling task with a monetary outcome (Bechara et al., 1999). This difficulty corresponded to a lack of anticipatory SCRs before choosing from a disadvantageous card deck. It was assumed that the impairment in making an advantageous choice in these patients was related to their inability to encode and anticipate the negative value of an outcome that is related to their choice and, thus, to avoid it. Our fMRI data support this proposal by showing that the strongest activation of the intact amygdala occurred while sub-

jects expected the outcome of largest negative magnitude. This outcome was directly related to their risky choice of bluffing the opponent.

"Expectancy-to-Outcome": Value of Choice

Anticipated negative emotions were assumed to be associated with, and possibly generated by, a cognitive process of inferring subjective value to a choice in terms of loss or gain probability and cost (Kahneman and Tversky, 1979). However, this perceived value of choice could have changed with game progression. Interestingly enough, in our study, when events during the "expectancy-to-outcome" interval were divided according to their asset positions, there was a significant asset effect in addition to the choice effect (Figure 3B). Amygdala response following a nonmatch choice decreased with asset changing from high (many chips left to be disposed) to low (few chips left to be disposed). Furthermore, the difference in activation between match and nonmatch choices was getting smaller as asset decreased. Based on this finding, it is tempting to suggest that the amygdala response while the subject was expecting the outcome was affected not only by the expected magnitude of immediate negative outcome, but also by the size of asset. Asset position in the game could reflect the likelihood of winning the game. At low asset position where the game seems to be close to the end, match and nonmatch choices would be perceived as similarly critical for winning the game. Thus, it is suggested that the amygdala is most sensitive to the difference between choices when the player is more engaged in immediate outcome evaluation (i.e., high or medium asset position). In fact, most of our subjects reported after scanning that when they reached the stage of having fewer chips (i.e., low asset position) they felt less anxious about the outcome of every step and were more focused on achieving their final goal of winning the game. Thus, the change in the value of choice could be accountable for the decrease in amygdala response at low asset position. Altogether, the asset analysis proposes that human amygdala may be most effective at signaling the value of a choice with respect to the immediate expected outcome.

There are, however, two alternative interpretations for the asset effect. It could either be the mere effect of prolonging the game, or a tendency of the opponent to respond more with the show option toward the end of game. The effect of lengthening the game could be related to the known neural habituation phenomenon in the amygdala. It was suggested that such habituation reflects the role of the amygdala as predictor of the value of choice in terms of outcome in a novel situation (Quirk et al., 1997; Buchel et al., 1998; LaBar et al., 1998). However, the pattern of activation of match choices demonstrates an increase in activation from medium to low asset. Thus, it seems less likely that this effect can be explained solely by habituation. The second interpretation posits that the change in the opponent's response pattern affected the amygdala response. Nonetheless, similar nonmatch choice index of the player at the three asset positions (Figure 2B) and the lack of correspondence between player's choice and opponent's response (Figure 2A) demonstrate that the player did not change his choice pattern according to the opponent response.

"Response-to-Outcome": Sensitivity to Opponent's Response

Following either match or nonmatch choices, the amygdala was more activated when the opponent asked the player to reveal the chosen chip (show outcome) than when was not (no-show outcome) (Figure 5A). Thus, in contrast to the "expectancy-to-outcome" interval, during the "response-to-outcome" the amygdala was tuned more to the type of opponent's response than the player's choice. Accordingly, amygdala response seems to correspond to the magnitude of the outcome rather than to its direction (gain or loss). As is shown in Figure 1E, the magnitude of gain or loss of show outcome was greater than that of the no-show outcome, irrespective of the subject's choice (match or nonmatch). Furthermore, the amygdala response did not seem to correlate with the possible valence of experienced emotions due to counterfactual comparisons (Mellers et al., 1999). A counterfactual comparison can be regarded as the process of comparing the actual with the alternative outcome. For example, in the case of the opponent's "Show" request, the experienced emotion could be either of positive valence (i.e., satisfaction) when it follows a match choice, or of negative valence (i.e., disappointment) when it follows a nonmatch choice. Such relatively low sensitivity of the amygdala to valence of outcome is in accordance with animal and human data suggesting a role for the amygdala in evoking somatic responses to both punishment and reward (Hatfield et al., 1996; Bechara et al., 1999). Moreover, recent fMRI studies showed a change in activation of the amygdala with magnitude of either loss or gain in gambling tasks (Zalla et al., 2000; Breiter et al., 2001).

The value of outcome could also be affected for better or worse by the magnitude of the alternative outcome (i.e., represented by the difference between the actual and alternative outcomes). In our game, the largest relative loss was experienced following show nonmatch (see Experimental Procedures; Figure 1F). Although the amygdala response was slightly larger for show nonmatch than show match, it was not statistically significant (Figure 5A). Hence, overall there was no effect of relative outcome. This finding is in agreement with a previous study showing that different magnitudes of counterfactual comparisons, even when determined by the experimental paradigm and not by the subject, did not affect the amygdala response to outcome (Breiter et al., 2001). We conclude that the actual magnitude of outcome was more likely to contribute to the amygdala response than valence or magnitude of counterfactual comparisons. However, in the current study the magnitude of actual outcome and type of opponent's response were dovetailed and therefore it was not possible to characterize their specific contribution.

Amygdala Response throughout the Game: From Motivation to Action

In this study, the profile of amygdala activation was characterized during an interactive game, by either the player's choice (expectancy interval) or the opponent's

response (outcome interval). In a SCRs companion study (see Supplemental Data at http://www.neuron.org/cgi/content/full/33/6/983/DC1) an overall effect of player's choice was demonstrated during both expectancy and outcome intervals. This finding suggests that the choice-dependant response of the amygdala during the "expectancy-to-outcome" interval was correlated with arousal and thus could fit with the somatic marker hypothesis of decision-making. On the other hand, the amygdala response to outcome was different from the SCRs by not being related to player's choice. This discrepancy calls for an additional nonarousal related mechanism that could inflect the amygdala response in choice behavior in respect to actual outcome.

One possible explanation for the difference between fMRI and SCRs data could be related to the extensive interconnections between the amygdala and prefrontal cortex. It has been shown that when the amygdala and orbital prefrontal cortex were disconnected, monkeys were unable to adjust their choice behavior when facing change in values of the reward outcomes. In contrast, the disconnection did not affect motivation to avoid aversive stimuli and to prefer food reinforcement. These findings support the established idea that motivational significance is coded by the amygdala and then transferred to prefrontal cortex for the control of action (Schoenbaum et al., 1998).

Effective interactions between the amygdala and prefrontal cortex have been proposed to be critical for appropriate social behavior (Rolls, 1999). Clearly, this is dependent on sufficiently active amygdala. Monkeys with bilateral lesions of the amygdala exhibited inappropriate responses to social stimuli rather than difficulties in actual emotional expression (Meunier et al., 1999). In humans, damage to the amygdala is characterized not only by inappropriate emotional behavior, but also by a tendency to impose danger on the self and others (Bechara et al., 1999). Correspondingly, an abnormal response of the amygdala during an aversive conditioning task was found in antisocial personality disorder (Schneider et al., 2000). In the current study, the tuning of the amygdala to the player's choice on the one hand and to the opponent's response on the other hand underscores its significance in shaping appropriate social behavior. For example, the observed sensitivity of the amygdala to the expected value of an outcome was based on previously learned rules of the game. In addition, the response to the actual magnitude of the outcome was related to the type of opponent's response, suggesting that the amygdala is involved in evaluating possible outcome of choice. Taken together, the data suggest that the amygdala is capable of directing motivation by signaling the prospective consequences of a choice. Moreover, it can provide guidance for future actions in accordance with the actual outcome of the choice.

Experimental Procedures

Subjects

Thirteen right-handed healthy subjects (seven females; aged 18–46) participated in the experiment. Subjects provided written informed consent prior to the scanning session. All procedures were approved by the Tel Aviv Sourasky Medical Center human rights committee. One male subject was excluded from the final analysis due to substantial artifacts in the MR BOLD signal (see below).

Game Rules and Objectives

The domino game presented below is a two-person game with diametrically opposed preferences. In the game, the subject is the player and the experimenter is the opponent. There are twenty-eight domino chips, where each chip is composed of two numbers from zero to six (all possible combinations of 0, 1, ..., 6 without repetitions). In the beginning of each game, twelve random chips are assigned to the player and placed face up at the bottom of the board, four undisclosed chips are assigned to the bank, and one chip is placed face up on the board and is the master chip. No other chips are used. Each assigned chip can be either a match or a nonmatch relative to the master chip. A match is a chip in which at least one number out of the two matches one of the numbers on the master chip (lower arrow, Figure 1A). A nonmatch is a chip in which none of the numbers on it matches the numbers on the master chip (upper arrow, Figure 1A). Approximately half of the assigned chips will be nonmatch. To win the game, the player has to get rid of all the chips assigned to him. One round in the game can be described in terms of the following steps:

(1) Each round starts with the command "Choose." The player then makes one of two decisions called pick match choice or pick nonmatch choice.
(2) Following the command "Ready," the player moves the cursor to the chosen chip.
(3) Following the command "Go," the player picks the chip as quickly as possible. Once picked, the chip is automatically placed facedown on the game board (demonstrated by the curved arrows, Figure 1C).
(4) Having observed the player make his pick, the opponent makes one of two decisions called show and no-show.
(5) If the opponent decides no-show, the round is over and the command "Choose" is presented (step 1). If he decides to ask the subject to expose the chip, the command "Show" is presented and the chip is turned face up. If it is a nonmatch, the player will get the chip back and two additional chips (from the bank or randomly from the previously disposed chips if the bank is empty). If it is a match, one additional chip from the chips assigned to the player is randomly picked and moved to the board.

Rounds in the game continue until the player got rid of all of his chips (win), or either 320 s have passed (lose) or the player got all the chips from the bank and the board (i.e., there are no more chips for him to get and therefore he loses).

The first two steps of a round are both of fixed duration (5 s). The duration of the third step is determined by the player's response time after the "Go" command. The average response time was 829 ms (328.259 SD) where response times for nonmatch were not significantly different from match choices (Nonmatch: 812 ms $\pm$ 306 SE, Match: 846 ms $\pm$ 361 SE; $t[11] = 0.913$, $p = 0.381$). Once picked, the chosen chip is placed facedown beside the master chip (demonstrated by curved arrows, Figure 1C). Subsequently, the player was waiting for the opponent's response for 5–10 s (step 4, "expectancy-to-outcome" interval, Figure 1C). Note that the duration of this interval was not of fixed duration and was controlled by the opponent's response. The average duration of the "expectancy-to-outcome" interval was 6394 ms (748 SD) when followed by the "Show" command, and 6701 (837 SD) when followed by "Choose" command (no-show outcome). The duration of show and no-show outcomes did not differ significantly.

The number of chips removed or added to the player's assigned chips in a round reflects the actual gain or loss, respectively. A relative gain or loss of a player was defined as the difference between the two possible outcomes (show and no-show) as determined by the opponent's response (Figure 1F).

Based on the player's choice and the opponent's response, there were four possible outcomes (step 5, "response-to-outcome" interval, Figures 1D and 1E, from top to bottom):

(1) Show nonmatch: The player chose a nonmatch chip and was

asked to show it. As a consequence, the player suffers a loss by getting back the picked chip plus two additional chips (i.e., +2). The player has a relative loss of three, since he could have disposed of one chip [i.e., (+2) − (−1) = +3].

(2) No-show nonmatch: The player chose a nonmatch chip and was asked to proceed with the game and choose another chip. This outcome is an actual gain of the one chip that was picked (i.e., −1), but a relative gain of three because the nonmatch choice was not exposed [i.e., (−1) − (+2) = −3].

(3) Show match: The player chose a match chip and was asked to show it. As a consequence, the player has an actual gain of two, since he got disposed of the picked chip and one additional random chip from his assigned chips (i.e., −2). However, the relative gain is only one [i.e., (−2) − (−1) = −1].

(4) No-show match: The player chose a match chip but was asked to proceed with the game and choose another chip. This outcome is an actual gain of the one chip that was picked (i.e., −1), but a relative loss of one chip, since the match choice was not exposed [i.e., (−1) − (−2) = +1].

The utility of the player as defined by the difference between the show and no-show outcomes reflects the counterfactual comparisons (Mellers et al., 1999). In our design, outcome of a nonmatch choice leads to a larger counterfactual comparison magnitude (relative gain or loss of 3) than outcome of a match choice (relative gain or loss of 1).

Game Course Analyses

Each subject (player) played an average of 4.8 games (2.03 SD) with the same experimenter—I.K. (opponent). The average duration of a game was 220 s (45.177 SD), where the shortest game duration was 63 s and the longest was 319 s. 83.4% of the games lasted from 3 to 5 min, where 1 min games comprised only 3.7% and 2 min games merely 12.9% of all games. 3, 4, and 5 min games constituted 24%, 33.4%, and 26% of all games, respectively.

The average number of rounds per game was 10.51 (2.89 SD). Games that lasted 1 min or less were considered outliers and therefore were excluded from all later behavioral and fMRI analyses (comprised 3.7% of all games; calculated index: 0.1667 ± 0.237 SD, not shown in Figure 2A).

Three intervals were highlighted for brain analyses: The "expectancy-to-outcome" interval was defined as starting after the selected chip was placed beside the master chip and ending when the opponent responded (Figure 1C). The fMRI response during this interval was sorted according to the player's choice. To characterize the player's choices, a nonmatch choice index was defined as the division of nonmatch choices by the sum of match and nonmatch choices. This index represents a nonbiased choice when equal to 0.5 (exactly half of the events were nonmatch choices), a biased choice for match when smaller than 0.5 or to nonmatch when greater than 0.5.

The "response-to-outcome" interval was defined as starting after the opponent's response (either a "Show" or "Choose" command, Figure 1D), and lasting for 7.5 s (average duration of the interval: 7144 ms ± 749 SD). The "response-to-outcome" interval following a "Choose" command (i.e., outcome of no-show) was similarly defined. Finally, for this interval fMRI events were sorted according to the player's choice and the opponent's response. The opponent's responses were characterized with a show outcome index. The index was calculated by dividing the number of show outcomes by the sum of show and no-show outcomes.

A third interval was defined as baseline for calculation of percent signal change (Figure 1A). The "decision-making" interval was defined as starting after the command "Choose" and ending before the "Ready" command. This interval occasionally included the "response-to-outcome" interval following a choose outcome.

An additional analysis was done by sorting each game round according to the number of chips left for the subject to get rid of (asset position). Three different asset positions were defined: (1) low asset (# chips ≤ 4); (2) medium asset (4 < # chips ≤ 12); and (3) high asset (# chips > 12). Medium asset position comprised 78% of all game rounds and was used as a control for the two other asset classes. The high and low asset classes comprised 10% and 12% of the remaining game rounds, respectively.

fMRI Experimental Procedure

The subjects were given detailed instructions of the game's rules and practiced playing against the experimenter (I.K.) for a few rounds. Thus, when put in the scanner the game's rules were fully learned. The same experimenter (I.K.) ran all sessions and played against all subjects. The experimenter was blind to the specific chips assigned to the subject, as well as the choices made by the subject if not exposed. The experimenter heard instructive sounds and, thus, knew the type of chip when the subject was asked to expose it. The subject was aware of the fact that he played against the experimenter.

The stimuli were projected onto a tangent screen mounted in front of the subject's eyes in the scanner, and viewed through a tilted mirror. The commands for the player were presented visually by words shown on the left corner of the board and aurally via headphones. The subject played the game using a button box with three possible key-presses (move left, move right, and pick). The experimenter response was presented visually to the player accompanied by a characteristic sound. Game presentation and response acquisition were controlled by a Pentium II PC using in-house software written in Visual C++ and Directx3.0 (Microsoft Corp.).

MRI Scanning

Blood oxygenation level dependent (BOLD) contrast was obtained with gradient-echo echo-planar imaging (EPI) sequence (TR = 2500, TE = 55, FA = 90) on a 1.5T Signa Horizon LX 8.25 GE echospeed scanner. In order to allow for a large number of acquisitions and improve the signal-to-noise ratio, we used a small number of slices centered on the amygdala (LaBar et al., 1998). Four functional slices of 5 mm thickness with 1 mm gap and the corresponding spin-echo T1 weighted anatomical images were acquired for each run (i.e., one game). The amygdala was anatomically detected clearly in two to three slices. Considering the image resolution of fMRI and the signal-to-noise ratio in this area of the brain, it was not possible to reliably sort out subregions touching the amygdala nuclei such as substantia innominata and periamygdaloid cortex (Breiter et al., 1996; Whalen et al., 1998). Therefore, we only present data obtained from a predefined amygdala region (see below). A 3D spoiled gradient echo sequence was acquired on each subject, in order to allow for volume statistical analyses of signal changes during the game.

Image Analysis

All fMRI data were processed using the BrainVoyager3.9 software package (http://www.brainvoyager.com) (Dierks et al., 1999; Goebel et al., 1998). Prior to statistical analysis of signal, all functional images were evaluated for quality of EPI. One subject was excluded from image analyses due to significant artifacts of functional images. For each subject (n = 12), the 2D functional images were superimposed on 2D anatomical images and incorporated into the 3D data set through trilinear interpolation. The complete data set was transformed into Talairach space (Talairach and Tournoux, 1988). Pre-processing of functional scans included head movement assessment (scans with head movement of >1.5 mm were omitted), high-frequency temporal filtering and removal of linear trends.

First, ROIs of the amygdala were defined anatomically for each subject. Amygdala borders were determined on the axial view and were limited by the tip of lateral ventricles. Group average for the ROI approach was based on a random effects model. The average size of the ROIs was 5401.25 mm (2092.203 SD) for the left amygdala and 4844.25 mm (1910.11 SD) for right amygdala. The center of the structurally defined clusters was 20.5, −5.5, −14.2 and −20.6, −4.4, −14.8 for left and right amygdala, respectively (see Supplemental Data at http://www.neuron.org/cgi/content/full/33/6/983/DC1). Table 1 for single subject data shows the average size and center of gravity for the individual anatomical ROIs. In addition to ROI analysis, parametric maps were calculated separately for each subject using a GLM (Friston et al., 1995), with game events as predictors. A lag of 7.5 s (i.e., three repetitions) was used to account for the hemodynamic response delay. Although we employed an event-related design, we assumed no overlap of the hemodynamic re-

sponses between events since inter-event intervals lasted 10–15 s. To create a parametric map, EPI images were transformed to Talairach space, Z-normalized, and concatenated, and statistical tests were done on the concatenated time courses. Parametric maps for each subject and for a group average (n = 12) were derived using a fixed effects model, applied separately for events of "expectancy-to-outcome" and "response-to-outcome" intervals (Figures 4 and 6, respectively).

Further statistical analyses on fMRI signal that were obtained from both approaches were done with StatView 5.0.1 (SAS Institute Inc.). The baseline for calculating percent signal changes of the hemodynamic responses was defined as the average signal obtained from all "decision making" intervals. This interval essentially represents the process of thinking about the next step (subjects were unable to move the cursor until the ready command appeared).

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