REWARD AND SOCIAL VALUATION DEFICITS FOLLOWING VENTROMEDIAL PREFRONTAL DAMAGE

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ABSTRACT

Lesion and imaging studies have implicated the ventromedial prefrontal cortex (vmPFC) in economic decisions and social interactions, yet its exact functions remain unclear. Here, we investigated the hypothesis that vmPFC represents the subjective value or desirability of *future* outcomes during *social* decision-making. Both vmPFC-damaged patients and control participants acted as the responder in a single-round ultimatum game. To test outcome valuation, we contrasted concrete, immediately available gains with abstract, future ones. To test social valuation, we contrasted interactions with a human partner and those involving a computer. We found that, compared to controls, vmPFC patients substantially reduced their acceptance rate of unfair offers from a human partner, but only when financial gains were presented as abstract amounts to be received later. When the gains were visible and readily available, the vmPFC patients' acceptance of unfair offers was normal. Furthermore, unlike controls, vmPFC patients did not distinguish between unfair offers from a human agent and those from a computerized opponent. We conclude that the vmPFC encodes the expected value of abstract, future goals in a common neural currency that takes into account both reward and social signals in order to optimize economic decision-making.

INTRODUCTION

Fundamental to personal and interpersonal decision-making is the ability to represent available choices and calculate the subjective value or motivational significance of each alternative, both now and into the future (Montague & Berns, 2002; Montague, King-Casas, & Cohen, 2006). In recent years, comparative and human research has consistently identified a network of interconnected brain areas involved in aspects of reward processing, including areas within prefrontal cortex (Breiter, Aharon, Kahneman, Dale & Shizgal, 2001; O'Doherty, 2004; Volz, Schubotz, & von Cramon, 2006; Schultz, 2006). Specifically, the ventromedial sector of prefrontal cortex (vmPFC) has been described as an interface between motivation, emotion and cognition, and has been widely implicated in guiding decisions on the basis of the expected value (or utility) of competing options (Damasio, 1994; Rolls, 1999; Davidson & Irwin, 1999; Kringelbach, 2005). For example, when healthy individuals have to evaluate the obtained outcome, or when they have to estimate the desirability or subjective value of options, changes in blood flow within the vmPFC have consistently been reported (Knutson, Adams, Fong & Hommer, 2001; O'Doherty, Deichmann, Critchley, & Dolan, 2002; Gottfried, O'Doherty, & Dolan, 2003; McClure et al., 2004).

Lesion studies in several species, including humans, converge to suggest that vmPFC is critical to assign value to options (Schoenbaum, Roesch, & Stalnaker, 2006). Patients with damage to vmPFC develop enduring and severe (though relatively isolated) impairments in stimulus-reinforcement learning (Hornak et al., 2004), preference judgement (Fellows & Farah, 2007), and value-based decision-making (Bechara, Damasio, Tranel, & Damasio, 1997, Rogers et al, 1999), often described as impulsive behaviour.

Efforts to study valuation and choice in humans with vmPFC damage have been mainly focused on individual or solitary decision-making (i.e., choices made with little or no influence from others' actions and strategies). However, many real-life decision problems involve social exchanges with other individuals and a certain division of economic outcomes between them. A crisp way to examine decision-making in the context of social settings involves the use of simple bargaining games, such as the one-shot ultimatum game (Guth, Schmittberger, & Schwarze, 1982). This game is played between two anonymous persons. One player, the proposer, makes a take-it-or-leave-it offer, dividing some amount of money, say €10, between herself and another person. If the second person, the responder, accepts the division, then both people earn the specified amounts. If, however, the responder rejects it, they both get nothing. Were the responder only interested in material gains (i.e. money), she should accept any positive offer. Nevertheless, compelling evidence suggests that approximately 50% of the offers that fall below 30% of the initial endowment are rejected, and that brain areas related to both affect (anterior insula) and cognition (dorsolateral prefrontal cortex) are involved in these decisions (Sanfey, Rilling, Aronson, Nystrom, & Cohen, 2003; van't Wout, Kahn, Sanfey, & Aleman, 2005; Knoch, Pascual-Leone, Meyer, Treyer, & Fehr, 2006; Tabibnia, Satpute, & Lieberman, 2007). This evidence is generally interpreted by saying that people are not driven exclusively by self-regarding preferences based on material gains, but also by other-regarding preferences guided by fairness and equality motives (Fehr & Gatcher, 2002; Bowles, 2006). Consideration of these two classes of preferences critically influences decisions to accept or reject a certain monetary offer. Therefore, with low offers (say €1 or €2 out of the €10 available), the responder faces a conflict between accepting the money, due to its expected reward value, and rejecting it because of both anger and indignation due to the perceived unfairness of the allocation (Elster, 1998).

Of particular interest for the present purpose, one recent study of decision-making in the context of the ultimatum game found that vmPFC lesioned patients exhibit higher rejection rates for low offers than comparison groups (Koenigs & Tranel, 2007). Based on these findings, Koenigs and Tranel have argued that vmPFC is critical for controlling the influence of negative emotional reactions to social frustration in economic exchange. Although social emotions are tightly connected to ultimatum rejections (Elster, 1998; Sanfey et al., 2003; Xiao & Houser, 2005; van't Wout, Kahn, Sanfey, & Aleman, 2006), an alternative and equally plausible hypothesis is that vmPFC patients have diminished sensitivity to financial value of decision outcomes, especially outcomes that are abstract and far away in time. This would lessen the desirability of accepting (abstract/delayed) monetary reward, making vmPFC patients more likely to reject unfair offers. Several sources suggest this hypothesis. First, neuroimaging studies and recent models of medial prefrontal cortex suggest that information conveying hypothetical, abstract (such as gaining or losing money), or delayed outcomes engage more rostral portion of vmPFC (i.e., frontal pole or Brodmann area 10; Tanaka et al., 2004; Kringelbach, 2005; Bechara, 2005; Bechara & Damasio, 2005; Amodio & Frith, 2006; Moll et al., 2006), whereas information about salient, tangible or immediate reward (i.e., the sight or taste of food) tend to recruit more caudal vmPFC (Brodmann area 25) and adjacent subcortical regions, such as basal forebrain, and nucleus accumbens (Zink, Pagnoni, Martin-Skurski, Chappelow, & Berns, 2004; Tanaka et al., 2004; Hariri et al., 2006). It follows that damage to the vmPFC (particularly the anterior portion) should weaken the neural mechanism that enables one to make decisions based on long-term/abstract financial outcomes, thus leading to the loss of adaptive decision-making in favour of a more automatic, default reaction (i.e., prefer the fair offer and refuse the unfair one; van't Wout et al., 2005; Tabibnia et al., 2007).

Second, in standard ultimatum game protocols, including that used by Koenigs and Tranel, the intrinsically salient properties of money are typically diminished because the money is presented as an abstract visual representation (i.e., "You get €3"), and actually handed to the participant only at later time (i.e., the end of the session). In this context, monetary rewards lack the vividness and immediacy that potently elicit a motivational state of "wanting" for the anticipated reward (Berridge & Robinson, 1998). Although this may blunt the subjective value of predicted payoffs and thus affect economic exchanges in normal agents (Solnick, 2007), damage to the vmPFC should do so to a much greater extent, thereby providing an alternative explanation of Koenigs and Tranel's results.

The present research is aimed to test the hypothesis that insensitivity to abstract/future monetary outcomes is critical to explaining the greatest number of rejections in the ultimatum game after vmPFC damage. To this end, we conducted three separate treatments with an anonymous, one-shot ultimatum game, in which patients with selective vmPFC lesion, as well as neurologically healthy and brain-damaged control participants, played in the role of responders. The first treatment, termed human opponent (HO) condition, was essentially a replication of Koenigs and Tranel's experiment, in which we expected to confirm their findings. Briefly, each participant saw a screen that indicated her anonymous partner's offer (i.e., "He gets €8, You get €2"). Then subjects could accept or reject the offer by pressing the appropriate key. Finally, participants saw a screen revealing the outcome based on her response. The critical prediction concerned results of the second treatment, called human opponent with cash (HO-c) condition, which was identical to the previous treatment except that the monetary reward was presented in a motivationally salient manner. That is, the responder received, concurrently with the screen signalling the proposed split, an envelope containing the sum of money in cash that would go to her if she accepted the offer (i.e., €2). If vmPFC patients' high rejection rates result from a reduced sensitivity to abstract/future financial outcomes, then presenting tangible and immediately attainable rewards should make the option of accepting unfair offer comparatively more desirable than rejecting them, and this should be empirically observed. In contrast, if the high rate of rejections of unfair offers truly reflects poorly controlled reactions to frustration and social threats due to vmPFC lesions, then the pattern of results should not change relative to the first treatment, and be similar to that found by Koenigs and Tranel. This null finding would imply that the value of offers in conditions HO and HO-c remained the same, and therefore elicited comparable amount of social frustration and anger in vmPFC patients.

In addition to the conditions mentioned above, we also implemented a treatment in which responders played with a computer that randomly generated the offers, the computer opponent (CO) condition. This condition is particularly important because previous evidence on healthy subjects shows that, for any given level of unfair offer, rejection rates are higher for a human partner than a computer partner (Camerer, 2003, van't Wout et al., 2006; Knock et al., 2006). Sanfey et al. (2003) also found that the response of the anterior insula (a brain area involved in negative emotional states and whose activity is correlated positively with rejection rate) was greater to unfair human offers than to unfair offers made by a computer. These observations are consistent with the view that decisions in the ultimatum game are not merely a function of material gains, but also depend on other agents' outcomes and intentions (Camerer & Fehr, 2006). Accordingly, the contrast between HO and CO conditions is ideal to assess whether vmPFC is necessary for valuing social information during interactive decision-making because – except for the type of opponent player (human vs. computerized opponent) – everything else remains constant across these two conditions.

Finally, to obtain a direct measure of subjects' emotional responses during performance of the ultimatum game, we acquired subjective ratings of fairness and anger from all 3 groups of subjects immediately after each treatment. Skin conductance responses were also acquired from vmPFC patients and healthy controls in the standard (HO) condition of the ultimatum game.

Materials and Methods

Participants

Three groups of subjects participated in the study: (a) a group of patients with focal lesions involving the vmPFC (the vmPFC group, n = 7), (b) a control group of patients with damage sparing the frontal cortex (the non-FC group, n = 6), and (c) a control group of healthy subjects (the HC group, n = 14), who were matched on age, education and sex with the vmPFC group. Brain-damaged patients were recruited from the Centre for Studies and Research in Cognitive Neuroscience in Cesena. They were selected on the basis of the location of their lesion evident on CT or MRI scans. Table 1 shows demographic and clinical data, as well as the Mini-Mental Status Examination score (MMSE, Folstein, Robins, & Helzer, 1983), and the negative reciprocity score for all groups of participants. The negative reciprocity scale is a 9-item, self report questionnaire from the Personal Norm of Reciprocity Scale (Perugini, Gallucci, Presaghi, & Ercolani, 2003) used to measure individual differences in the propensity to reciprocate negative behaviour (i.e., punishing those who behave unfairly). There were no significant differences between vmPFC patients and comparison groups with regard to age, education, clinical and personality variables ($p > .05$ in all cases).

In the vmPFC group, lesions were restricted to the vmPFC, which is defined as the medial one-third of the orbital surface and the ventral one-third of the medial surface of the frontal lobe, following the boundaries laid out by Stuss and Levine (2002). The vmPFC damage was bilateral in all cases, although often asymmetrically so, and caused by rupture of anterior communicating artery aneurysm. All vmPFC patients presented with clinical evidence of a decline in social interpersonal conduct, impaired decision-making and emotional functioning, but had generally intact intellectual abilities (see Table 2).

The non-FC patients were selected on the basis of having damage that did not involve the frontal lobe, and also spared the amygdala and the insula in both hemispheres. In this group, lesions were unilateral in 5 patients (in the left hemisphere in 3 cases, and in the right hemisphere in 2 cases) and bilateral in 1 patient, and were caused by arterial-venous malformation in 1 case, and by ischemic or hemorrhagic stroke in 5 cases. Lesion sites included the occipital lobe in 2 patients, the lateral occipito-temporal junction in 2 patients, and the lateral occipito-parietal junction in the remaining 2 patients.

All subject groups were administered a short neuropsychological battery including tests with potential sensitivity to frontal damage, as well as intelligence and memory tests (results are provided in Table 2). The groups differed significantly only in their performance on the Stroop task, with vmPFC subjects making more errors than both non-FC patients and healthy controls (Mann–Whitney U-test, $p < .05$). Patients were not receiving psychoactive drugs at the time of testing, and had no other diagnosis likely to affect cognition or interfere with participation in the study (e.g., significant psychiatric disease, alcohol misuse, history of cerebrovascular disease, focal neurological examination). Neuropsychological and experimental studies were all conducted in the chronic phase of recovery, more than a year post-onset. All lesions were acquired in adulthood. Patients gave informed consent to participate in the study according to the Declaration of Helsinki (International Committee of Medical Journal Editors, 1991) and the Ethical Committee of the Department of Psychology, University of Bologna.

Normal participants were healthy volunteers who were not taking psychoactive medication, and were free of current or past psychiatric or neurological illness as determined by history. Normal controls scored at least 28 out of 30 on the MMSE.

Lesion analysis

Lesion analysis was based on the most recent clinical computerized tomography (CT) or magnetic resonance imaging (MRI). The location and extent of each lesion were mapped by using MRIcro software (Rorden & Brett, 2000). The lesions were manually drawn by a neurologist with experience in image analysis onto standard brain template from the Montreal Neurological Institute (MNI), which is based on T1-weighted MRI scans, normalized to Talairach space. This scan is distributed with SPM99 and has become a popular template for normalization in functional brain imaging. For superimposing of the individual brain lesions, the same MRIcro software was used. Figure 1 shows the extent and overlap of the brain lesions in the brain damaged patients. Brodmann's areas (BA) affected in vmPFC group were areas 10, 11, 12, 32 (subgenual portion), and 24, with region of maximal overlap occurring in BA 10 and 11.

Ultimatum Game Tasks

We ran three treatments of a one-shot ultimatum game: the human opponent (HO) condition, the human opponent with cash (HO-c) condition, and the computer opponent (CO) condition. In each treatment, participants played 18 rounds in the role of the responder with 18 different anonymous partners, and the amount to be split in all cases was €10. All experiments took place in a quiet room in which an opaque, removable partition wall was used to create two separate settings. On either side of the wall, we placed a desk with a computer. Participants sat at one desk in front of the computer, while at the other sat an actor who played in the role of the proposer. As a result, playing partners could be separated visually, thereby providing between-subject anonymity, without separating them audibly, thus lending our set-up credibility. In all conditions, subjects’ choices were known to the experimenter, and private with regard to other subjects[1]. Before each treatment, instructions about the nature and rules of the ultimatum game were presented on the compute, and the experimenter verbalised them to ensure that participants understood them. In the instructions, it was emphasized that participants would play the game anonymously and only once with each opponent player, and that they would receive the money earned in the game. After reading the instructions, subjects were required to complete a quiz that required them to state the amount of money that each player would receive under various hypothetical circumstances. The game started once the subject successfully finished the quiz.

The HO condition was the standard ultimatum game in which the proposer and the responder interacted via a computer interface. At the beginning of each round, the actor that played the role of the proposer entered the room and sat at her position. When both proposer and responder were ready, the interaction started. Each round began with a waiting slide on the participant's computer indicating that the participant should wait for the partner's offer (see Figure 2 for schematic illustration of a typical trial). The duration of this wait period was variable (7, 8 or 9 s). Then, the offer was presented (e.g., "Partner gets €8, You get €2") for 8 s. Next, the words "Accept or reject" appeared on the screen and remained visible until a response was given. Participants were instructed to indicate whether they accepted or rejected the offer by pressing one of two different keys on the computer keyboard. Following the response, the outcome for that round, indicating how much money players had gained (e.g., "You get €2, He gets €8", if the offer was accepted, or "You get €0, He gets €0", if the offer was rejected), was presented for 6 s. Finally, a beep signaled the end of the round. The proposer went out of the room and was replaced by another actor to begin the next round.

In the HO-c condition, the procedure was identical to the previous treatment except that, concurrent with the screen signaling the offer, the responder received from the proposer an

[1] Previous research has shown that experimenter-subject anonymity has little effect in ultimatum games, lowering rejections very slightly (Bolton and Zwick, 1995).

envelope containing the sum of money in cash that would go to her if she accepted the offer (i.e., €2). As before, subjects had to decide whether to accept or reject the offer by pressing one of the two keys on the keyboard. If the offer was accepted, the responder opened the envelope and took the money. Otherwise, the experimenter returned the envelope to the proposer. Next, the participant saw on the screen the outcome based on her accept/reject decision.

Finally, in the CO condition the procedure was the same as in the HO condition except that participants played the game with the computer as partner. An image of a computer was displayed in the waiting slide to stress the computer opponent condition. Furthermore, the instructions emphasized that offers were generated randomly by the computer.

In each treatment, offers were predetermined and presented randomly. For the present purposes, half of these offers were considered to be fair, that is, proposing fairly even split of the €10 (three offers of €6:€4, three offers of €5:€5, and three offers of €4:€6), and the remaining half of the offers were considered to be unfair, proposing unequal splits (three offers of €9:€1, three offers of €8:€2, and three offers of €7:€3). Note that subjects in all treatments faced exactly the same set of offers. Thus, behavioural differences across these three treatments cannot be attributed to differences in the offer distribution. The sequence in which subjects received the different treatments of the ultimatum game was randomized across subjects. Treatments were administered in separate sessions with an interval of at least two weeks between them. Each session lasted approximately 25 minutes.

Subjective Ratings

Following each ultimatum game treatment, responders were shown a list of all possible offers in randomized order and asked to report on a 7-point Likert-type scale to what extent they perceived an offer as fair or unfair (1 = very unfair; 7 = very fair). On a separate 7-point scale, they were asked to indicate how angry they felt towards the proposer of each possible offer (1 = not angry, 7 = very angry). Subjects were informed subsequently of their total gains from the experiment.

Psychophysical Data Acquisition

In a separate session, skin conductance responses (SCRs) were acquired during the standard, HO treatment of the ultimatum game in vmPFC patients (n = 5) and healthy controls (n = 7) who were available for this assessment. For each subject, prewired Ag/AgCl electrodes (TSD203 Model, Biopac Systems), filled with isotonic hyposaturated conductant, were attached to the volar surface of the middle and index fingertip of the nondominant hand and held firmly in place with Velcro straps. As subjects performed the ultimatum task seated in front of the computer screen, SCRs were collected continuously and stored for offline analysis on a second PC. The analog signal was recorded using the MP-150 digital converter (Biopac Systems, Goleta, CA) and fed into AcqKnowledge 3.9 recording software (Biopac Systems). The SCR data were down-sampled at 200 Hz, and a 1 Hz low-pass filter and 0.05 Hz high-pass filter were applied to the data during acquisition. Presentation of the offer in the Ultimatum Game was synchronized with the sampling computer. To analyze the SCRs to the unfair and fair offers, we computed the “area under the curve” in the 2-8 s time window after offer presentation. The “area under the curve” measurement is similar to the function of an “integral” except that, instead of using zero as a baseline for integration, a straight line is drawn between the endpoints of the selected area to function as the baseline. The area is expressed in terms of amplitude units (microsiemens, μS) per time interval (seconds). Before the start of recording, we ensured that subjects were able to generate SCRs to external stimuli, such as loud sounds (i.e., hands clapping).

RESULTS

Ultimatum Game Results

Figure 3 illustrates the group acceptance rates as a function of the monetary offers, separately for each experimental treatment. A probit regression analysis of the subjects' binary choice (accept/reject) as the dependent variable was performed on the data. This analysis assessed the probability that an event (accept or reject, in this case) occurs, given specific independent variables, such as the amount of money offered, the experimental treatment (HO, HO-c, CO), the subject groups (vmPFC, non-FC, and HC), as well as the interaction terms between each treatment and group. Furthermore, to check for the role of individual level measures on the subjects' behaviour in the ultimatum game, the demographic characteristics of participants (sex, age, education and, if the subject has a lesion, time since lesion and lesion volume), and individual scores on selected tests and questionnaires, such as MMSE, Standard Raven Matrices, Digit Span, Phonemic and Semantic Fluency, Wechsler Memory Scale, Stroop Task, Negative Reciprocity, Ratings of Fairness and Anger, were included as variables in the analysis[2].

In order to study how a change in the independent variables affects the probability of accepting an offer, we assessed the marginal effects of each variable (calculated at sample means). Note that when the variable is a category (e.g., an interaction between group and condition), the marginal effect reports the discrete change in probability of accepting with respect to a given category that is used as reference category or benchmark.

Finally, as each subject contributed more than one observation in each experimental treatment, robust standard errors (with clusters at the individual level) were used in order to

[2] We thank an anonymous referee for suggesting this analysis.

take into account that, for each individual, error terms within a given treatment might be correlated, rather than independent.

As a general result, we found that the participants' behaviour depended on the monetary offer, as the likelihood of accepting significantly increased with the amount of money offered. More precisely, the marginal effect computed at the average offer of 2.5 euros[3] was 0.10, indicating that the probability of accepting significantly increases by 10% as the proposal increases by one euro ($z = 3.14$, $p < 0.01$).

Furthermore, the analysis revealed that the individual level measures were not significant ($p > 0.05$), with the exception of the fairness ratings. Specifically, it was found that an increase of one point in the fairness rating (computed at the average rating) significantly increased the likelihood of accepting by 18% ($z = 5.57$, $p < 0.001$), a result that is consistent with both intuition and previous literature (see Knoch et al., 2006).

More importantly for the present purposes, significant differences in the probability of accepting offers across treatments and groups were observed. Here, we first focus on the differences between groups, and then consider those within each group.

In the standard HO treatment, the analysis revealed that vmPFC patients tended to accept significantly less than both control groups. Thus, compared to the reference category (vmPFC/HO interaction), the estimated marginal effects of the non-FC/HO and HC/HO interactions were 0.46 ($z = 4.44$, $p < 0.001$) and 0.81 ($z = 3.56$, $p < 0.001$), respectively, which is perfectly consistent with previous results (Koenings and Tranel, 2007).

The HC and non-FC groups accepted significantly more than the vmPFC participants also in the CO condition (HC/CO compared to the reference category vmPFC/CO: marginal effect 0.86, $z = 4.09$, $p < 0.001$; non-FC/CO compared to reference category vmPFC/CO:

[3] Since all individuals accept offers of 5 and 6 euros, we have restricted the analysis to offers of 1, 2, 3 and 4 euros.

marginal effect 0.48, $z = 3.91$, $p < 0.001$). As in the CO treatment there is no human opponent, this finding seems to challenge the view that vmPFC patients reject because of social frustration or because they react to the perceived unfairness of the opponent.

Finally, considering the HO-c treatment and taking the vmPFC/HO-c interaction as benchmark, we found no significant difference between the probability of accepting across groups ($p > 0.05$). In other words, when the vmPFC patients were facilitated in their incentive representation of the payoffs at stake by cues signaling concrete, proximal outcomes, their behaviour could not be significantly distinguished from the other subject groups.

Turning to the effects of treatments within each group, the analysis revealed that vmPFC subjects were significantly more likely to accept an unfair offer in the HO-c than in the HO treatment (marginal effect 0.54, $z = 6.67$, $p < 0.001$), whilst there was no significant difference between HO and CO treatment ($p > 0.05$; reference category vmPFC/HO interaction for both comparisons).

Healthy participants behaved in the opposite way. Consistent with the literature (Camerer 2003), we found that normal controls were significantly more likely to accept an offer when they played in the CO condition than in the HO condition (marginal effect 0.2, $z = 3.19$, $p < 0.001$). As a new (but not unexpected) result, we found no significant difference in the probability of accepting between the HO and HO-c treatment for the HC group ($p > 0.05$; reference category HC/HO interaction for both comparisons).

For the non-FC group, we found some differences in the estimates of the probability of accepting between the three experimental treatments, but we could not assess whether they were significant[4].

[4] This is due to the fact that we did not observe enough response variability in the responses within this group, and the confidence intervals obtained were too large (in particular for the CO interaction), with the consequence that we could not reject the hypothesis of there being no significant difference among the different experimental treatments.

To sum up, vmPFC patients were more likely to reject unfair offers than comparison groups when monetary reward were not salient, both when the opponent player was human or a computer program. In contrast, vmPFC patients' acceptance rates of unfair offers were similar to subjects in the control groups when the salience of expected rewards was increased.

Subjective Rating Results

Figure 4 illustrates group mean ratings of self reported fairness and anger as a function of monetary offer, separately for each experimental treatment.

We performed a repeated measures ANOVA on fairness ratings with Group (vmPFC, non-FC and HC) as a between subjects factor, and Offer (€1, €2, €3, €4, €5 and €6) and Treatment (HO, HO-c and CO) as within subjects factors. There was a significant main effect of Offer [$F(5, 120) = 565.27$, $p < .001$], revealing that perceived fairness was modulated by offer level (specifically, offers of €5 were rated as the fairest and offers of €1 as the most unfair), and a significant Treatment by Offer interaction [$F(10, 240) = 2.31$, $p < .05$]. Pairwise comparisons (Newman-Keuls test) showed that €1 offers were judged as less unfair in the CO condition than in either the standard HO or the HO-c condition ($p < .001$). The same differences approached significance for offers of €2 (both $ps = .07$). There were no significant differences between groups.

A separate ANOVA on anger ratings revealed a significant main effect of Offer (i.e., €5 offers provoked the smallest amount of anger and €1 offers the largest) [$F(5,120) = 26.32$, $p < .001$], and a significant main effect of Treatment [$F(2,48) = 14.26$, $p < .001$] indicating that anger perceived in the CO condition was less than either in the HO or HO-c condition ($p < .001$). As before, no group difference was found. There was also a significant Treatment by Offer interaction [$F(10,240) = 8.23$, $p < .001$], which revealed that all participants when confronted with an unfair offer of €3, €2 and €1 reported smaller amount of anger in the CO condition than in either the HO or HO-c condition ($p < .001$).

Skin Conductance Responses

For each subject, we divided the area under the curve measurement by 6, and then averaged the area measurements per second (μS/s) from the fair (€4, €5, and €6) vs. unfair (€1, €2, and €3) offers. A two-way repeated measure ANOVA, with Group (vmPFC patients and HC) as the between-subject factor, and Offer type (fair and unfair) as the within- subject factor, was performed on the resulting data. The analysis revealed a significant interaction between Group and Offer type [$F(1,10) = 5.8$, $p < .05$], indicating that electrodermal responses to unfair offers were significantly higher than responses to fair offers in normal controls (van't Wout et al., 2006), but not in the vmPFC group (see Figure 5). The same interaction hold if we pool only the skin responses to the unfair offers of €1 and €2 vs the fair offers of €5 and €6 [$F(1,10) = 6.2$, $p < .03$].

DISCUSSION

Recent findings have suggested that vmPFC is involved in overriding the emotional impulse to reject remunerative, yet unfair offers from noncooperative partners (Koenigs & Tranel, 2007). Based on this view, vmPFC patients would have particularly strong negative emotional responses to unfairness due to their lesion, and, therefore, would be more likely to reject low offers. However, higher rejection rates in the ultimatum game can be explained not only by stronger incentives to reject an offer, but also by lower incentives to accept it.

In the experiment presented here, we tested the specific hypothesis that the subjective value of abstract, delayed reward is degraded following vmPFC damage and no longer guides (accept/reject) decisions in bargaining situations. Based on this alternative perspective, vmPFC patients tend to reject unfair offers disproportionately not because of exaggerated emotional responses elicited by the others' unfair behaviour, but due to blunted desirability of abstract, delayed financial gains. Therefore, we manipulated the spatio-temporal proximity of monetary outcomes (i.e., the concreteness with which outcomes are presented, and how soon will be experienced) in a modified version of the ultimatum game. We predicted that increasing the motivational salience (e.g., immediacy, concreteness) of expected reward would rescue vmPFC patients' decision-making from high rejection rates.

Bargaining with a Human Partner

In the HO condition (standard ultimatum game), we found that vmPFC damage was associated with considerably higher rejection rates in response to various levels of unfair offers relative to patients with brain damage that spared vmPFC and to healthy controls. Thus, the basic results are in keeping and replicate those of Koening and Tranel, supporting the general conclusion that vmPFC plays an essential role in driving decision-making in social interactions. More importantly, however, when visual cues signaled, prior to decision-making, that anticipated monetary reward was tangible and readily available (HO-c condition), the difference in rejection rates across vmPFC patients, non-FC patients and normal participants became immaterial.

Our findings are unlikely to reflect condition differences in emotional responses driven by unfair or unequal payoff distributions, as offers were identical in the two types of treatments. This is confirmed both by acceptance rates and self reports in the two control groups, which remained unchanged across these treatments. Importantly, vmPFC patients' subjective ratings of fairness and anger, assessed immediately after each treatment, did not differ from control groups' judgments, thereby suggesting that vmPFC patients did not feel more angry or irritated towards unfair partners than comparison subjects. Likewise, clinical observation of participants during the game failed to reveal signs of intense or strong emotional reactions in the vmPFC group. Critically, recordings of skin conductance responses (SCRs) to the presented offer and prior to the choice in the standard ultimatum game (HO treatment), showed significantly blunted (rather than increased) emotional reactions to unfair offers in vmPFC patients relative to healthy controls. Thus, both self-reported ratings and psychophysiological measures failed to document negative emotional "overreactions" in vmPFC patients, as argued by Koenigs and Tranel. Indeed, accumulating evidence indicates that patients with damage to the vmPFC exhibit generally diminished emotional responsivity, blunted affect and markedly reduced social emotions (Eslinger & Damasio, 1985; Barrash, Tranel, & Anderson, 2000; Beer, John, Scabini, & Knight, 2006). In several laboratory studies, such patients show decreased levels of autonomic activity in responses to emotionally and socially meaningful stimuli (Damasio, Tranel, & Damasio, 1990). Moreover, impairments in economic and moral decision-making after vmPFC lesion have been consistently attributed to failure to generate emotional signals (Damasio, 1994; Bechara et al., 1997; Camille et al., 2004; Ciaramelli, Muccioli, Ladavas, & di Pellegrino, 2007), rather than to increased emotional/affective responses. Collectively, therefore, previous research and our current findings argue against the idea that exaggerated emotional states play an exclusive or primary role in mediating vmPFC patients' abnormal rejection pattern in the ultimatum game.

Also, the present findings cannot be explained purely in terms of difference in movement, because the motor aspect of decisions across the HO and HO-c conditions was the same (i.e., pressing one of two keys). Nor can treatment differences be ascribed to differential increase in sensorimotor arousal or responsiveness: in the HO-c condition, vmPFC patients' responses were not randomly distributed across the possible choices, but instead their decisions, like those of controls, were selectively modulated by the size of the offer.

Instead, we suggest that the consistency of vmPFC patients' choices with the other groups in the HO-c condition was due to the enhanced motivational or affective salience of expected monetary outcome. Although outcomes in the HO and HO-c treatment had the same reward value, in the standard HO treatment, gains were described to subjects as a symbolic, abstract representation of money that they would receive at a later time, and thus had weak incentive impact on decision-making (Mischel, Ebbesen, & Zeiss, 1972; Loewenstein, 1996). Humans, however, have developed greater capacity to make decisions according to outcomes that are far more abstract and far more distant in the future. This process requires them to anticipate the long-term affective consequences that may follow choices, in the absence of immediately present rewards and punishments and other affective incentives (Damasio, 1994; Mellers, Schwartz, & Ritov, 1997). As such, this process may be likened to a form of affective representational memory (Watanabe, 2007), bridging the gap between predicting cues or responses and future consequences.

A growing corpus of neuroscientific evidence suggests that vmPFC is critical to the ability to form and maintain expectations about the desirability or motivational value of abstract/future states and rewards, thus organizing behaviour toward the acquisition of motivationally significant goals on a long time scale (Damasio, 1994; Mobini et al., 2002; Tanaka et al. 2004; Schoenbaum et al., 2006; Kable & Glimcher, 2007). Damage to the vmPFC, particularly its anterior aspect, would therefore reduce the motivational value of future prospects and result in an inability to adapt behaviour according to the long-term consequences of decisions (i.e., "myopia for the future"; Damasio, 1994). By contrast, such damage is less likely to disrupt the subjective valuing of imminent and tangible outcomes, suggesting that other brain areas may be critical for choices involving immediate gains or losses (Tanaka et al., 2004; Bechara & Damasio, 2005; Kringelbach, 2005).

Our findings are highly consistent with this view. For each unfair offer level, vmPFC patients' acceptance rate critically depended on whether monetary reward was visible and immediately attainable (i.e., out of sight becomes literally out of mind), despite that both fairness and material gains being identical across HO and HO-c treatments. Conversely, non-FC patients and healthy individuals' choices were not influenced by the presentation mode of payoffs, resulting in similar accept/reject rates across the two types of treatments. This suggests that vmPFC damage affects the subjective valuing of abstract/delayed monetary outcomes that enables subjects to implement more "rational" (i.e., forward looking) decisions when self interest and fairness motives are at odds, in the ultimatum game. This conclusion is highly congruent with recent neuroimaging findings revealing the involvement of the vmPFC in difficult choices that require the weighing of costs and benefits of actions for the purpose of decision-making (Arana et al., 2003; de Quervain et al., 2004; De Martino, Kumaran, Seymour, & Dolan, 2006; Knutson, Rick, Wimmer, Prelec, & Loewenstein, 2007). Furthermore, our result is reminiscent of the findings of classical consumer research showing that consumer decision-making is strongly influenced by changing the presentation mode of available options from real to symbolic (i.e., photographs), but only when consumer processing resources are depleted by a concurrent task (Shiv & Fedorikhin, 1999).

Finally, it should be noted that it remains an open question whether vmPFC patients' higher acceptance rate in the HO-c treatment was related to physical proximity of reward at the time of decision-making (e.g., the sight of concrete sums of money in envelopes), or to its temporal proximity, (e.g., the immediacy of reward delivery), as these two aspects of reward were not separated in our saliency manipulation. Future neuropsychological studies should include experimental conditions that isolate changes in decision-making related to reward visibility from changes related to time to reward (for example, by using visible but not immediately attainable reward), to address whether vmPFC plays a different role in these processes.

Bargaining with a Computer Partner

Another important result of the present study concerns the comparison between the HO and CO treatments across the groups of participants. We found that, following vmPFC damage, rejection rates were not modulated at all by the type of opponent player present in the environment. That is, patients with lesion in the vmPFC did not distinguish between unfair offers intentionally generated by human agents and those randomly caused by a computer program. Instead, their choices were merely sensitive to the unequal distribution of gains, no matter how this distribution was generated. In stark contrast, control participants were more likely to reject low offers when they believed that they were interacting with people than a computer opponent (Sanfey et al., 2003), thus revealing that normal economic decisions are driven by factors beyond mere material utility, for instance altruistic punishment, the propensity to take costly actions to punish unfair behaviour from human defectors (Fehr & Gächter, 2002; Seymour, Singer, & Dolan, 2007). Together, these results suggest a critical role for vmPFC in valuing the social element of an economic exchange.

Importantly, subjects in all groups perceived a low offer as less unfair in the computer than in the human opponent condition, and there were no differences in fairness and anger judgments between vmPFC patients and comparison groups. Thus, lesion of vmPFC only affects behavioural responses to low offers but not to fairness or anger judgments. This suggests that an explicit knowledge of social norms and rules is intact and normally accessible following vmPFC damage. Despite this retained knowledge, however, vmPFC patients fail in valuing social information when the implications of another individual’s presence must be taken into account before acting (Damasio, 1994; Koenigs et al, 2007).

As such, the present findings are consistent with previous lesion studies reporting that damage of vmPFC and adjacent prefrontal areas may impair social valuation processes and mechanisms designed for mediating social exchange with other conspecifics (Bechara & Damasio, 2005; Rudebeck, Buckley, Walton, & Rushworth, 2006), including the ability for making inferences about the mental states of others (Stuss, Gallup, & Alexander, 2001), and empathize with them (Shamay-Tsoory, Tomer, Berger, & Aharon-Peretz, 2003). In line with this, considerable neuroimaging research has documented increased activation in medial prefrontal areas when human subjects play interactive decision-making games, as long as they believe they are playing against a person rather than a computer (McCabe, Houser, Ryan, Smith, & Trouard, 2001; Rilling et al., 2002, Gallagher, Jack, Roepstroff, & Frith, 2002). Thus, the current study supports the hypothesis that vmPFC is essential for determining future behaviour on the basis of the anticipated value of financial as well as 'social' goals (Bechara & Damasio, 2005; Moll et al., 2006), which suggests that the brain relies on common valuation mechanisms to guide decision-making in diverse domains (Montague et al., 2006).

To sum up, we have demonstrated that the rejection rates of vmPFC patients in bargaining encounters strictly depend on the motivational, affective salience of the expected outcome. Reward was salient because of its immediacy and physical proximity. If vmPFC patients' deficit was simply due to poorly controlled emotions to unfairness, there should be no difference between immediate/concrete and remote/abstract presentation of outcome. The difference argues strongly for a role of incentive saliency in modulating vmPFC patients' behaviour in the ultimatum game task. Furthermore, we have shown that vmPFC is critical for the normal valuation of social stimuli during an economic exchange with another person.

These findings are highly compatible with current theories maintaining that vmPFC is a critical neural substrate for assigning motivational value to competing options to guide future behaviour, both in personal and societal decision-making (Bechara & Damasio, 2005). We believe that our account is more parsimonious than interpretation proposing that vmPFC damage may lead to different emotion impairments (i.e., blunted affect vs irritation and anger) in different circumstances (Koenigs et al., 2007; Koenigs & Tranel, 2007). Finally, the reported findings provide evidence for theoretical approaches to social cognition and decision-making that emphasize the pivotal role of medial prefrontal cortex in the integration of multiple signals to generate adaptive behaviour (Montague & Berns, 2002).

Acknowledgements

This work was supported by a PRIN grant (nr. 2005111741) from MIUR to G. di Pellegrino. We thank Ellen Peters, Elisa Ciaramelli, India Morrison, Steve Wise and two anonymous referees for their helpful comments on an earlier draft of the manuscript. We also thank Randolph Bruno, Roberto Golinelli, Norberto Pignatti, Simona Valmori for statistical advice, and Irene Cristofori for collecting part of the data.

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Table 1. Summary data for participants [mean (standard deviation)]

Group	Sex (M/F)	Age at test (year)	Education (year)	Time since lesion (year)	Lesion volume (cc)	MMSE	Negative Reciprocity
vmPFC (n=7)	6/1	53.7 (8.0)	11.7 (4.1)	4.8 (3.2)	43.8 (15)	27.3 (2.1)	3.19 (0.5)
non-FC (n=6)	4/2	45.2 (6.2)	13.3 (3.2)	3.2 (1.2)	38.5 (13.5)	28.7 (1.2)	3.30 (0.5)
HC (n=14)	10/4	51.1 (4.1)	12.2 (3.3)	-	-	29.7 (0.6)	3.27 (1)

MMSE = Mini-Mental State Examination

Table 2. Results of selected neuropsychological tests [mean (standard deviation)]

Group	**SRM**	**Digit Span Forward**	**Phonemic Fluency**	**Semantic Fluency**	**WMS**	**Stroop Task Errors°**
vmPFC	42 (11.6)	5 (1.1)	21.7 (8.4)	41.8 (12.8)	87.2 (4.9)	6.5 (4.2)°
non-FC	48.2 (8.1)	5.1 (0.9)	23.6 (6.5)	42.2 (3.3)	94 (5.3)	2.5 (1)
HC	46.5 (3.4)	5.4 (0.9)	27.6 (5.5)	43.0 (4)	98.9 (5.2)	2.3 (1)

° Values that differ significantly between groups. SRM = Standard Raven Matrices (scores in percentile values), WMS = Wechsler Memory Scale,

Captions to figures

Figure 1. Location and overlap of brain lesions. The panel shows the lesions of the 7 patients with vmPFC damage projected on the same 7 axial slices and on the mesial view of the standard Montreal Neurological Institute brain. The level of the axial slices has been marked by white horizontal lines on the mesial view of the brain. Z-coordinates of each axial slice are given. The colour bar indicates the number of overlapping lesions. In each axial slice, left hemisphere is on left side. Maximal overlap occurs in the ventral and anterior portions of the medial prefrontal cortex (Brodmann areas 10 and 11 and 32).

Figure 2. Schematic diagram of a single round of the ultimatum game. From left to right, Waiting screen: 7-9 s, Partner's offer: 8 s, Subject's decision: indefinite, Outcome: 6 s. In this example, the partner's offer was rejected. The original screens were in Italian.

Figure 3. Mean acceptance rates as a function of ultimatum game offer for all 3 groups of subjects. Panel A shows the results for the human opponent (HO) condition, Panel B shows the results for the human opponent with cash (HO-c) condition, Panel C shows the results for the computer opponent (CO) condition. Error bars indicate standard errors of the mean. HC = healthy controls; non-FC = non frontal patients; vmPFC = ventromedial prefrontal patients.

Figure 4. Mean subjective ratings of fairness (1 = very unfair; 7 = very fair; left panels) and anger (1 = not angry, 7 = very angry; right panels) as a function of ultimatum game offer for all 3 groups of subjects (see text for details). Top panels show the results for the human opponent (HO) condition, middle panels show the results for the human opponent with cash

(HO-c) condition, bottom panels show the results for the computer opponent (CO) condition. Error bars indicate standard errors of the mean. These data show that there were no differences in fairness and anger judgments across the three groups of subjects in all treatments of the ultimatum game. HC = healthy controls; non-FC = non frontal patients; vmPFC = ventromedial prefrontal patients.

Figure 5. Mean skin conductance responses of vmPFC patients and healthy controls, measured as “area under the curve” in the 2-8 s time window after presentation of fair (€6, €5, €4) and unfair offers (€3, €2, €1), in the human-opponent (HO) condition of the ultimatum game.