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The contributions of lesion laterality and lesion volume to decision-making impairment following frontal lobe damage

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Abstract

Lesions to prefrontal cortex (PFC) in humans can severely disrupt everyday decision-making, with concomitant effects on social and occupational functioning. Forty-six patients with unilateral lesions to prefrontal cortex and 21 healthy control subjects were administered three neuropsychological measures of decision-making: the Iowa Gambling Task, the Cambridge Gamble Task, and the Risk Task. Magnetic resonance imaging (MRI) scans were acquired from 40 patients, with region of interest (ROI) mapping of prefrontal subregions. The frontal patients showed only limited damage in medial and orbital prefrontal cortex, but greater damage in lateral prefrontal regions of interest. Patients with right frontal lesions preferred the risky decks on the Iowa Gambling Task, and differed significantly from left frontal and control subjects. Within the right frontal group, the preference for the risky decks was correlated with the total lesion volume and the volume of damage outside of the ventromedial prefrontal region. Right and left frontal groups did not differ significantly on the Cambridge Gamble Task or the Risk Task, and performance was not associated with lesion volume. The results indicate a laterality effect on the Iowa Gambling Task, and the contribution of prefrontal regions outside the ventromedial region to task performance. The Cambridge Gamble Task and Risk Task were less sensitive to the effects of unilateral frontal lobe lesions, and may be more selectively associated with ventral prefrontal damage.

Keywords: Risk-taking; Orbitofrontal; Neuropsychology; Impulsivity

1. Introduction

Decision-making operates in conditions of response uncertainty, and entails the evaluation of the reward and punishment contingencies to each of the available response options, followed by the calculation of the optimal option (Damasio, 1994; Rolls, 1999). Subtle but systematic errors in the ability of humans to reach the mathematically optimal decision have been well documented (e.g. the Gambler's fallacy (Tversky & Kahneman, 1974) or the Wason selection task (Wason & Johnson-Laird, 1972)). However, qualitatively more severe decision-making deficits have been reported following brain injury, particularly where there is damage to the frontal lobes (Eslinger & Damasio, 1985; Satish, Streufert, & Eslinger, 1999; Shallice & Burgess, 1991). The nature of these deficits and their neuroanatomical substrates are the focus of the present study.

Bechara, Damasio, Damasio and Anderson (1994) developed the Iowa Gambling Task to assess decision-making in these patient populations. The task emphasises the contribution of emotional processing to decision-making. It requires the subject to learn the associations with reward and punishment of four card decks, in order to earn pretend money. Patients with bilateral lesions to ventromedial prefrontal cortex (PFC) were shown to be impaired on the task (Bechara et al., 1994). These patients, who also display poor decision-making in everyday life, persist in selecting from the 'risky' decks characterised by large immediate rewards but larger long-term punishments. Patients with damage to dorsolateral PFC were reported to perform within the range of healthy controls on the task (Bechara, Damasio, Tranel, & Anderson, 1998). Recent findings in a small number of patients with unilateral lesions have indicated that right-sided damage to ventromedial PFC is sufficient to impair

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performance, whereas left-sided lesions to this area do not impair decision-making (Tranel, Bechara, & Denburg, 2002).

A number of factors may contribute to deficient performance on the Iowa Gambling Task. A patient may have a genuine preference for high-risk options, or may be unable to compute the probabilities in order to discriminate risky from safe. They may be hypersensitive to reward, or insensitive to punishment, or may have difficulty learning the reward and punishment associations. More general problems with executive function may also disrupt performance in a learning context, including poor working memory and attentional inflexibility. Two novel decision-making tasks have been developed subsequently at the University of Cambridge by Rogers et al. (1999a,b), to characterise in more depth the role of PFC in decision-making. Both tasks utilise an independent trial structure to reduce learning demands, and ensure that all information needed to make each decision is displayed to the subject, to minimise working memory load.

In the Cambridge Gamble Task (Rogers et al., 1999a), subjects initially make a simple probabilistic judgment between two mutually exclusive outcomes, and then place a bet on their confidence in that decision. Four studies to date have used the Cambridge Gamble Task in groups of patients with different forms of frontal pathology. We have demonstrated increased betting in the presence of normal probabilistic judgment in three groups: (1) patients with large frontal lesions including the ventral PFC (Manes et al., 2002), (2) patients with aneurysms of the anterior communicating artery, the blood vessel that supplies ventral and medial PFC (Mavaddat, Kirkpatrick, Rogers, & Sahakian, 2000), and (3) frontal variant fronto-temporal dementia (Rahman, Sahakian, Hodges, Rogers, & Robbins, 1999), which is characterised by a disinhibition syndrome reminiscent of ventral PFC damage (Gregory & Hodges, 1996). One further study has shown decreased betting in the presence of impaired probabilistic judgment, in patients with frontal lesions including the ventral PFC (Rogers et al., 1999a). Thus altered betting on the Cambridge Gamble Task is consistently associated with damage to the ventral PFC.

The Risk Task was adapted from the Cambridge Gamble Task for use in functional imaging designs (Rogers et al., 1999b). The task again employs a probabilistic decision between two mutually exclusive outcomes, but on each trial there are fixed bets associated with either decision. The less likely outcome is always associated with the higher bet to create a situation of reward conflict. In two PET investigations using the task in healthy subjects, the contrast of the decision-making condition minus a visuo-motor control task detected significant activations in ventral PFC, and these activations were predominantly right lateralised (Rogers et al., 1999b; Rubinsztein et al., 2002). The functional imaging data therefore support the human lesion studies indicating ventral prefrontal recruitment during decision-making.

The selectivity of the ventral prefrontal contribution to decision-making was questioned by our recent investigation (Manes et al., 2002), in which we administered the three decision-making tasks described above to a group of patients with unilateral lesions within PFC. Neuroradiological assessment divided the group into patients with discrete orbitofrontal (including ventromedial), discrete dorsolateral, and discrete dorsomedial prefrontal lesions, and a fourth group with larger lesions affecting both dorsal and ventral aspects of PFC. The patients with orbitofrontal lesions performed in the control range on all three tasks, with the exception of deliberating for longer on two tasks. The group with large PFC lesions, in contrast, preferred the risky decks on the Iowa Gambling Task, placed higher bets on the Cambridge Gamble Task, and chose the less likely, but more rewarding, option more often on the Risk Task. However, lesion laterality was confounded in this study. In the orbitofrontal group, four of five patients had left-sided lesions, whereas in the large lesion group, four of five patients had right-sided lesions. It was therefore not possible to ascertain whether the large lesion group showed impaired decision-making because of the size of their lesions or the laterality of their lesions.

The aim of the present study was to extend the findings of Manes et al. (2002) by distinguishing the contributions of both lesion size and lesion laterality to decision-making. Patients with unilateral frontal cortex lesions were recruited from the Cambridge Cognitive Neuroscience Research Panel (CCNRP), and were combined with the Manes et al. (2002) group to provide a large group of 46 patients. The contribution of lesion laterality was examined using a three-way comparison of left frontals, right frontals, and healthy controls. The effect of lesion size was examined by correlating neuropsychological performance with lesion volume, measured by lesion tracing of magnetic resonance imaging (MRI) scans. A region of interest (ROI) analysis enabled the examination of decision-making performance in relation to the volume of damage in discrete prefrontal subregions (Aron, Fletcher, Bullmore, Sahakian, & Robbins, 2003). The markers of decision-making impairment were hypothesised to be: (1) increased selection from the risky decks on the Iowa Gambling Task, (2) increased betting on the Cambridge Gamble Task, and (3) increased choice of the less likely but higher rewarding option on the Risk Task.

2. Methods

2.1. Subjects

Patients were recruited from the Cambridge Cognitive Neuroscience Research Panel at the MRC Cognition and Brain Sciences Unit. The CCNRP is an accumulating database of volunteers with focal brain lesions. Forty-six patients with unilateral lesions in the frontal lobes were selected from the panel, for neuropsychological assessment. Twenty-four lesions were right-sided, 22 were left-sided. Lesion aetiology was tumour resection (24), haemorrhage

Table 1
Subject characteristics [mean (standard deviation, S.D.)]

	Left frontals	Right frontals	Controls	Left frontal subgroup	Right frontal subgroup
N	22	24	21	10	10
Age	53.3 (11.0)	54.3 (11.0)	50.7 (5.9)	52.8 (10.8)	58.3 (9.5)
NART	115.5 (9.7)	114.3 (6.67)	116.5 (6.7)	116.8 (10.2)	114.9 (7.1)
Gender	13 M:9 F	8 M:16 F	10 M:11 F	3 M:7 F	5 M:5 F
Lesion volume (cm^3)	35.1 (38.9)	72.8 (60.0)	–	40.3 (33.9)	38.0 (37.8)

(13), infarct (8), or abscess (1), and patients were tested on average 48.3 months (S.D. 43.8) post-onset. Twenty-six patients were receiving anticonvulsant medications, typically carbamazepine, phenytoin, or sodium valproate. Mild dysphoria was present in some patients but none met diagnostic criteria for mood disorder. Twenty-one healthy volunteers were recruited from the local community as control subjects. The National Adult Reading Test (NART; Nelson, 1982) was administered to all subjects as a measure of (premorbid) intellectual functioning. All subjects provided informed consent in accordance with the Addenbrooke's NHS Trust Local Research Ethics Committee. Controls had no history of psychiatric or neurological disease. Both controls and frontal patients were paid for their participation. Subject characteristics are displayed in Table 1.

2.2. Neuroanatomical analysis

Forty of the 46 patients also consented to receive a Magnetic Resonance Imaging scan (see Fig. 1). Of the six remaining patients (three right-sided, three left-sided), three refused to have an MRI scan for non-essential purposes, and three were unsuitable for MRI scanning for medical reasons. MRI data was acquired in a 1.5 T scanner with 3D set acquisition, using an SPGR (spin gradient echo) T1-weighted coronal sequence and a T2-weighted axial sequence. Lesions were traced onto each structural scan using MRIcro v1.34 (Rorden & Brett, 2001) to create a 3D lesion volume, and normalised to the SPM 96 (Statistical Parametric Mapping; Wellcome Department of Cognitive Neurology, London, UK) average T1 structural scan from 152 healthy subjects, using cost function masking (Brett, Leff, Rorden, & Ashburner, 2002) to exclude the lesion from the calculation of normalisation parameters. The normalised lesion volume was superimposed onto five prefrontal region of interest templates, prepared in MRIcro by Dr. Fletcher (Department of Psychiatry, Cambridge). The ROI templates depicted the inferior frontal gyrus (IFG), the middle frontal gyrus (MFG), the superior frontal gyrus (SFG), the orbital region (ORB), and the medial frontal region (MED) (see also Aron et al., 2003). Masking the patient's lesion onto the ROI template enabled the calculation of the volume of damage in each ROI, shown in Table 2.

2.3. Neuropsychological assessment

Neuropsychological testing was run on an Advantech PC (Cambridge Cognition plc, Cambridge, UK) with 31 cm touch-sensitive monitor. The decision-making tasks were administered in a randomised order within a battery of other neuropsychological tasks. Decision-making tasks were not administered contiguously. Testing lasted 3–4 h and was spread over two sessions on different days. Patients were tested at home.

2.3.1. Iowa Gambling Task (Bechara et al., 1994)

The computerised version of the IGT requires the continuous selection of cards from four decks (A, B, C, D) using mouse control. The task is completed after 100 selections,

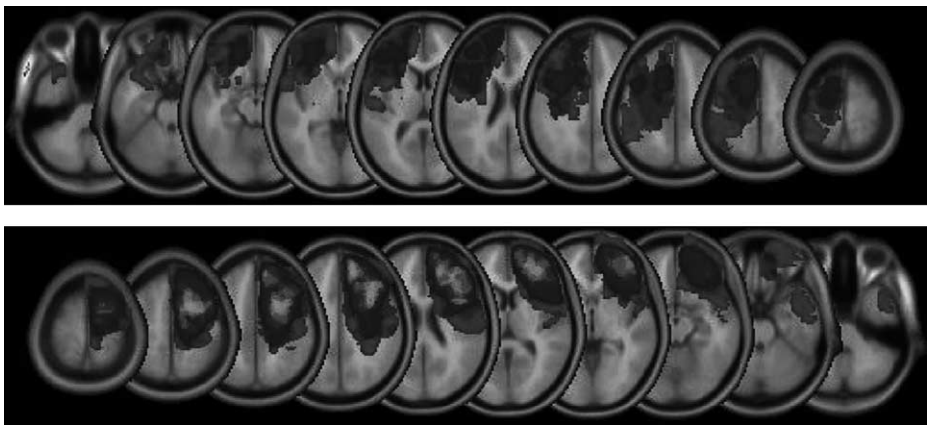

Fig. 1. Overlap of the lesions in the left frontal patients (top, $n = 19$) and the right frontal patients (bottom, $n = 21$).

Table 2
Average volume of damage in cm^3 in the six prefrontal regions of interest, in the left and right frontal groups, and the subgroups matched for total lesion volume

	Left frontals	Right frontals	Left frontal subgroup	Right frontal subgroup
Inferior frontal gyrus	4.9 (8.6)	10.2 (11.6)	5.9 (7.5)	5.5 (6.1)
Middle frontal gyrus	7.8 (10.9)	19.0 (15.4)	7.8 (8.6)	10.7 (12.5)
Superior frontal gyrus	9.2 (14.0)	17.7 (19.5)	12.6 (13.7)	10.5 (11.5)
Orbital frontal	3.8 (6.5)	6.1 (9.5)	4.1 (8.1)	1.6 (2.6)
Medial frontal	1.6 (2.5)	3.7 (5.5)	2.4 (3.3)	0.9 (1.2)

taking about 10 min. Each card selection results in the subject winning an amount of money, but some choices also result in loss. Decks A and B are characterised by large wins ($ 100 per choice) but occasional large punishments (e.g. $ 1250 on deck B), resulting in net loss with repeated selection. Decks C and D are associated with smaller wins ($ 50 per choice) but also small losses, resulting in the gradual accumulation of profit over repeated selection. The total number of choices from decks A and B over 100 selections provides a coarse measure of performance. Net score (decks (C + D) minus decks (A + B)) within each 20-choice time-block enables the assessment of learning on the task.

2.3.2. Cambridge Gamble Task (Rogers et al., 1999a)

This task uses touch-screen response and is completed in about 30 min. On each trial, the subject is presented with a mixture of 10 red and blue boxes, and must guess the colour of box that hides a single yellow token. The ratio of coloured boxes varies across 9:1, 8:2, 7:3, and 6:4 on a trial-to-trial basis, in a randomised manner. Token location is pseudo-randomised and independent on each trial; hence on a 9:1 trial the probability is 90:10. The subject indicates his decision by touching a response panel labelled 'red' or 'blue'. The subject is then invited to place a bet on their confidence in their decision, in order to increase a points score over trials. Possible bets are presented in either an ascending or descending sequence of 5, 25, 50, 75, and 95% of the points held at the time of the decision. Each bet is presented for 5 s before being replaced by the next bet, and subjects must touch the bet that they think is appropriate. Subjects complete 36 trials with the bets presented in an ascending sequence, and 36 in a descending sequence, counterbalanced for order across subjects. Disparity in betting between the ascending and descending conditions may indicate response disinhibition: the impulsive subject will respond early, and therefore place low bets in the ascending condition and high bets in the descending condition. A risk-taking subject, in contrast, must wait in the ascending condition to place a high bet. Following betting, feedback is provided in the form of a verbal Win or Lose message, the position of the yellow token is shown, and the amount bet is either added or subtracted to the subject's score.

Three dependent variables are assessed: the proportion of trials on which the subject chooses the box colour in the majority, the latency to make this decision, and the percentage of points bet on each decision. Bets are not analysed for trials where subjects choose the colour in the minority, as this would confound the betting and choice.

2.3.3. Risk Task (Rogers et al., 1999b)

This is an adaptation of the Cambridge Gamble Task designed initially for PET activation studies. On each trial, the subject is presented with a mixture of six red and blue boxes (5:1, 4:2, and 3:3), and must guess the colour of box that hides a yellow token. However, unlike the Cambridge Gamble Task, there is a fixed bet associated with either choice of box colour. Whilst these bets vary systematically across trials (10–90, 20–80, 30–70, 40–60, 50–50), a higher bet is always offered to the box colour in the minority, providing inherent reward conflict on each decision. For example, there may be four red boxes with a fixed bet of 20 points, or two blue boxes with a fixed bet of 80 points. By selecting the less likely colour (blue), the subject risks winning or losing more points. Two dependent variables are assessed: the proportion of trials on which the subject chooses the box colour in the majority, at both 4:2 and 5:1 box ratios, and the latency to make these decisions. Subjects complete 75 trials in total, taking approximately 15 min.

2.4. Statistical analysis

Due to some patients failing to complete each task, one-way Analysis of Variance (ANOVA) for age and NART IQ were conducted separately for each task to ensure adequate matching across groups. Proportional data from the Cambridge Gamble and Risk Tasks were arcsine transformed, as is appropriate when the variance is proportional to the mean (Howell, 1997). Untransformed values are presented in tables and figures. Analysis of variance was used to examine the effect of laterality on each of the three tasks, with a three-level between-subjects variable (controls, left frontals, right frontals), and a within-subjects variable of 20-choice time-block on the Iowa Gambling Task (five levels), box ratio on the Cambridge Gamble Task (four levels), and reward ratio on the Risk Task (five levels). Cambridge Gamble Task analysis included a second within-subjects variable (ascending versus descending condition) in the analysis of the amount bet. Risk Task analysis also included a second within-subjects variable of box ratio (4:2 versus 5:1). To examine the effect of lesion size, Pearson

correlation co-efficients were calculated for the associations between decision-making performance (collapsed across the within-subjects variables) and MRI volumes (total lesion size or region of interest damage).

3. Results

MRI lesion volumes were acquired from 19 left frontal and 21 right frontal patients. Mean volume of damage (in cm^3) in the each of the regions of interest is presented in Table 2. Lesion volume was significantly larger in the right frontal group (mean 72.8 cm^3, S.D. 60.0) than in the left frontal group (mean 35.1 cm^3, S.D. 38.9) ($t_{38} = 2.33$, $P = 0.025$). The right frontal group had significantly more damage in the middle frontal gyrus ROI only ($t_{38} = 2.63$, $P = 0.012$). Therefore to further separate the contributions of lesion size and lesion volume, a supplementary set of analyses was performed on two subgroups of 10 left frontal and 10 right frontal patients who were carefully matched for lesion volume (left mean = 40.3 cm^3, S.D. 33.9; right mean = 38.0 cm^3, S.D. 37.8), and did not differ in the extent of damage in any regions of interest (see Table 2).

3.1. Iowa Gambling Task

Forty-one frontal patients completed the task, consisting of 20 with left-sided and 21 with right-sided lesions. Left frontals, right frontals, and controls were matched for age ($F_{2,59} = 1.06$, $P = 0.354$) and NART IQ ($F_{2,59} = 0.469$, $P = 0.628$). Controls selected an average of 38.2 (S.D. 12.5) cards from decks A and B, and 61.8 (12.5) from decks C and D. This gives a mean net score (total C + D choices minus total A + B choices) of +23.6 (S.D. 25.0), indicating the development of an optimal strategy. Right frontal patients had a mean net score of −9.14 (S.D. 18.1), and maintained a preference for the risky decks throughout the task (see Fig. 2). Left frontal patients had a mean net score of +7.0 (S.D. 23.2), behaving similarly to controls in the early part of the task, but erratically in the later stages. One-way ANOVA of total net score was highly significant ($F_{2,59} = 11.3$, $P < 0.0001$). Right frontals had a lower net score than controls ($t_{40} = 4.86$, $P < 0.0001$) and left frontals ($t_{39} = 2.49$, $P = 0.017$). However, net score was also lower in left frontals than controls ($t_{39} = 2.20$, $P = 0.034$). Repeated-measures ANOVA of net score across 20-choice time-block on the task showed a highly significant effect of time-block ($F_{4,236} = 11.9$, $P < 0.0001$) and a group × time interaction ($F_{8,236} = 5.04$, $P < 0.0001$). Analysis of simple main effects showed that the effect of time-block was significant in the control ($F_{4,80} = 18.4$, $P < 0.0001$) and left frontal ($F_{4,76} = 2.93$, $P = 0.026$) groups, but not in the right frontal group ($F_{4,80} = 0.517$, $P = 0.723$), indicating that the controls and left frontals, but not right frontals, showed altered choice behaviour across the duration of the task.

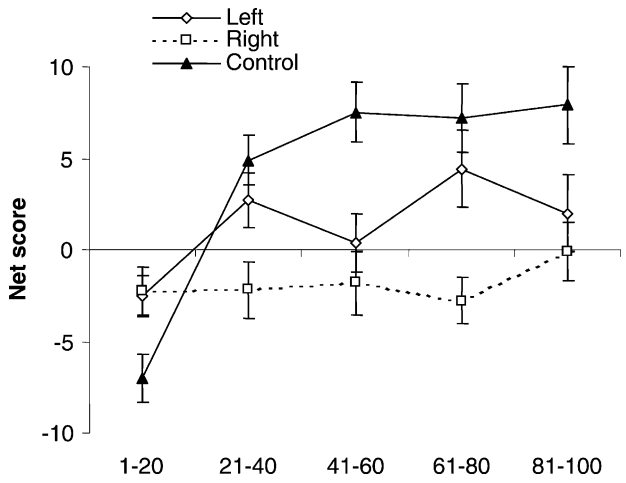

Fig. 2. Iowa Gambling Task performance in right frontals (dashed lines), left frontals (open diamonds), and controls (filled triangles), indicated by net score (decks C + D minus decks A + B) over consecutive 20-choice time-blocks of the task. Errors bars indicate standard error of the mean.

In the analysis of the patient subgroups matched for lesion volume, one-way ANOVA of total net score was again significant ($F_{2,38} = 6.83$, $P = 0.003$). Right frontals differed significantly from controls ($t_{29} = 3.82$, $P = 0.001$) and left frontals ($t_{18} = 2.23$, $P = 0.039$), whereas left frontals did not differ significantly from controls ($t_{29} = 1.29$, $P = 0.209$). Thus performance in the matched subgroups was very similar to performance in the whole group analysis.

3.2. Gamble Task

Forty-one frontal patients completed the task, consisting of 19 with left-sided and 22 with right-sided lesions. Controls, left frontals, and right frontals were matched for age ($F_{2,59} = 0.311$, $P = 0.734$) and NART IQ ($F_{2,59} = 0.174$, $P = 0.841$). Repeated-measures ANOVA indicated that the groups did not differ in terms of the proportion of majority choices ($F_{2,59} = 0.235$, $P = 0.791$) or the latency to make these decisions ($F_{2,59} = 1.75$, $P = 0.182$). There was a significant effect of box ratio on choosing the likely colour ($F_{3,177} = 10.3$, $P < 0.0001$), such that subjects picked the likely colour more often at higher ratios. ANOVA of the amount bet revealed that subjects bet significantly more in the descend condition than the ascend condition ($F_{1,177} = 90.6$, $P < 0.0001$) and significantly more at the higher box ratios ($F_{3,177} = 82.5$, $P < 0.0001$). The main effect of group approached significance ($F_{2,59} = 2.88$, $P = 0.064$), but post-hoc comparisons were all non-significant. The group × condition interaction approached significance ($F_{2,59} = 2.97$, $P = 0.059$), as did the group × ratio interaction ($F_{6,177} = 1.97$, $P = 0.073$). As these interactions were close to significance, it was deemed appropriate to analyse the ascend and descend conditions separately (Howell, 1997). There were no significant group effects in the ascend condition, but in the descend condition, there was a

significant main effect of group ($F_{2,59} = 5.12$, $P = 0.009$) and group × ratio interaction ($F_{6,177} = 2.59$, $P = 0.020$). The right frontals placed higher bets than controls ($P = 0.006$, Tukey's), but the left frontals did not differ significantly from either group. Direct comparisons of the left and right frontal groups showed a significant difference only at the 7:3 ratio in the descend condition ($t_{39} = 2.16$, $P = 0.037$).

In the analysis of the patient subgroups matched for lesion volume, subjects again placed higher bets in the descend condition than ascend condition ($F_{1,38} = 56.2$, $P < 0.0001$) and bet more at the higher box ratios ($F_{3,114} = 46.1$, $P < 0.0001$). The main effect of group approached significance ($F_{2,38} = 2.64$, $P = 0.084$), and group interactions with condition and box ratio were not significant. Post-hoc comparisons between groups were non-significant, and the left and right subgroups did not differ significantly at any box ratio in either condition. There were no differences across groups in terms of the proportion of majority choices ($F_{2,38} = 0.154$, $P = 0.858$), but the main effect of group on latency of decision-making approached significance ($F_{2,38} = 2.88$, $P = 0.068$).

3.3. Risk Task

Forty-one frontal patients completed the task, consisting of 19 with left-sided and 22 with right-sided lesions. Controls, left frontals, and right frontals were matched for age ($F_{2,59} = 0.059$, $P = 0.942$) and NART IQ ($F_{2,59} = 0.285$, $P = 0.753$). Repeated-measures ANOVA of group × box ratio (4:2, 5:1) × reward ratio, for choice behaviour, revealed a main effect of box ratio ($F_{1,236} = 22.8$, $P < 0.0001$) such that subjects selected the likely outcome more often at the 5:1 ratio than the 4:2 ratio. There were no significant effects of group or reward ratio, or significant interaction terms. The same ANOVA model for response latency, however, showed that the main effect of group approached significance ($F_{2,59} = 2.63$, $P = 0.08$), and significant effects of box ratio ($F_{1,236} = 4.10$, $P = 0.048$), reward ratio ($F_{4,236} = 4.35$, $P = 0.002$), and reward ratio × box ratio ($F_{4,236} = 06.42$, $P < 0.0001$). To interpret this pattern of effects, the ANOVA model was repeated separately at the two different box ratios. There were no effects at the 4:2 ratio, but at the 5:1 ratio there was a significant main effect of reward ratio ($F_{4,236} = 12.3$, $P < 0.0001$), and a significant effect of group ($F_{2,59} = 3.44$, $P = 0.039$). Post-hoc comparisons indicated that both left and right frontal groups were somewhat slower than controls ($P = 0.052$ and $P = 0.095$, respectively) but there was no difference between right and left frontals ($P = 0.935$). In the analysis of the frontal subgroups matched for lesion size, the main effect of group was again only significant on latency at the 5:1 box ratio ($F_{2,37} = 4.07$, $P = 0.025$), and post-hoc comparisons revealed that the right frontal subgroup differed significantly from controls ($P = 0.020$), but the left frontals did not differ from either controls ($P = 0.447$) or right frontals ($P = 0.401$).

3.4. Associations between decision-making performance and lesion volume

To restrict the number of correlational analyses, associations with lesion volume were only computed for the three discriminatory variables, i.e. those showing a significant main effect of group in the main ANOVA analyses: total net score on the Iowa Gambling Task, average amount bet in the descend condition of the Gamble Task, and average latency at the 5:1 box ratio on the Risk Task.

The total net score on the Iowa Gambling Task correlated with the total lesion volume in the right frontal patients ($r_{19} = -0.510$, $P = 0.026$) such that larger lesions were associated with increased preference for the risky decks. This association was not significant in the left frontal patients ($r_{17} = 0.045$, $P = 0.865$). Total net score also did not correlate with the volume of damage in any of the left frontal regions of interest (all $P > 0.10$). In the right frontal group, total net score correlated with the extent of damage in the middle frontal gyrus ROI ($r_{19} = -0.458$, $P = 0.049$), the superior frontal gyrus ROI ($r_{19} = -0.529$, $P = 0.020$), and the medial prefrontal ROI ($r_{19} = -0.456$, $P = 0.050$). However, given that the volumes of damage in these three ROIs were all significantly intercorrelated (e.g. SFG and MFG: $r_{19} = 0.821$, $P < 0.0001$), and were also each significantly correlated with total lesion volume, it was not possible to determine whether one region was driving the association. To specifically examine the impact of ventromedial prefrontal damage, a ventromedial volume (ORB + MED) and a non-ventromedial volume (IFG + MFG + SFG) were computed. In the right frontal group, total net score correlated with non-VM damage ($r_{19} = -0.544$, $P = 0.016$), but not with VM damage ($r_{19} = -0.230$, $P = 0.343$). Neither volume correlated with total net score in the left frontal group (both $P > 0.10$).

Average amount bet in the descend condition of the Gamble Task was not correlated with total lesion volume in the right frontal ($r_{19} = 0.292$, $P = 0.225$) or left frontal ($r_{17} = -0.009$, $P = 0.972$) groups, and was not correlated with volume of damage in any regions of interest in right or left prefrontal cortex (all $P > 0.10$). On the Risk Task, the average response latency at the 5:1 box ratio was not correlated with total lesion volume in the right frontal ($r_{19} = -0.254$, $P = 0.293$), or left frontal ($r_{16} = 0.286$, $P = 0.283$) groups. Average latency was correlated with the volume of damage in left SFG ($r_{16} = 0.563$, $P = 0.023$), but in no other ROIs in left or right prefrontal cortex (all $P > 0.10$).

4. Discussion

The present investigation sought to dissociate the contribution of lesion size and lesion laterality to deficits in decision-making in patients with unilateral frontal lobe lesions. Three neuropsychological measures of decision-making were employed: the Iowa Gambling Task (Bechara

et al., 1994), the Cambridge Gamble Task (Rogers et al., 1999a) and the Risk Task (Rogers et al., 1999b). Patients with right frontal lesions demonstrated severe impairment on the Iowa Gambling Task. They selected more cards from the 'risky' decks that are characterised by large immediate rewards but larger long-term punishments, compared to both healthy controls and patients with left frontal lesions. The right-sided group preferred the risky decks to the safe decks over the course of the task, and resembled patients with ventromedial PFC damage reported previously by Bechara et al. (1994) and Tranel et al. (2002). Patients with left-sided lesions differed significantly from both controls and the right frontal group. The left frontals showed a significant effect of learning across the duration of the task, and this is clearly apparent over the first two blocks (see Fig. 2). Left frontals preferred the safe decks to the risky decks, on average, from the second time-block onwards. Hence left frontals displayed a similar, only weaker, profile to controls on the task. A number of extraneous cognitive factors including distractibility and loss of attentional set could lead to less-pronounced implementation of a successful strategy on the Iowa Gambling Task, and may account for the difference between the left frontal group and controls.

On the Cambridge Gamble Task, patients with unilateral frontal lesions performed similarly to control subjects in terms of probabilistic judgment (choosing the box colour in the majority) and decision-making latency, and there were no effects of laterality on these measures. Patients with frontal damage showed a small effect on the betting stage of the Cambridge Gamble Task (see Fig. 3). This effect was significant only in the condition where the bets are presented in a descending sequence. The right frontals placed higher bets than controls in this condition, but the left frontals did not differ significantly from either group. In the descending condition, inhibitory control is required to avoid placing a high, inappropriate bet, and subjects must delay responding for 10–20 s in order for the bet to drop significantly. Measures of motor inhibition including the Go-No Go task (Garavan, Ross, & Stein, 1999; Konishi et al., 1999) and Stop Signal task (Aron et al., 2003) have previously been associated with right prefrontal cortex function. However, a simple deficit in motor inhibition in the Gamble Task should also be associated with *reduced* betting in the ascend condition, where the response must be delayed to avoid placing an inappropriately low bet. No group effects were apparent in the ascend condition, and the frontal deficit may therefore involve response disinhibition in the context of high reward. Post-hoc comparisons indicated no significant difference between right and left frontal groups, and the present data therefore do not indicate a pronounced laterality effect on the Gamble Task.

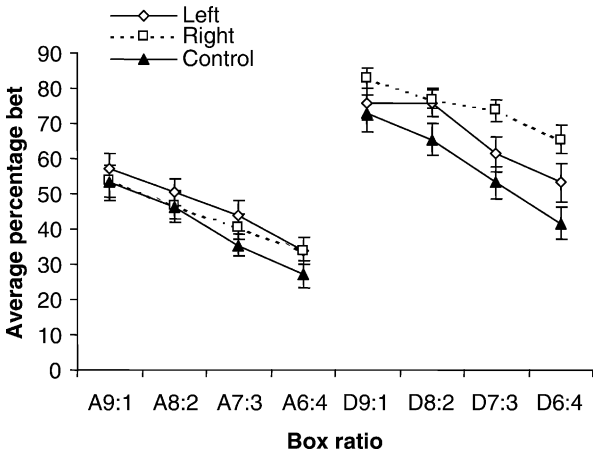

Fig. 3. The amount bet by subjects on the Gamble Task, as a percentage of the points held on that trial, in right frontals (dashed lines), left frontals (open diamonds), and controls (filled triangles). Errors bars indicate standard error of the mean.

Both right and left frontal groups showed similar decision-making to control subjects on the Risk Task, where the less likely option on each trial offers a higher (fixed) reward. However, lesions to either hemisphere were associated with longer latencies to make these decisions. The effect of group was only significant at the 5:1 box ratio, but frontal latencies were also non-significantly slower at the 4:2 box ratio, and also on the Cambridge Gamble Task (see Table 3). At the 5:1 box ratio, all groups showed exaggerated response latencies when 70 points were offered at a probability of one in six, against 30 points at a probability at five in six (see Fig. 4). This effect is also clearly apparent in eight subjects in the behavioural data in the

Table 3
Decision-making performance in left and right frontal patients, and healthy controls [mean (S.D.)], averaged across within-subjects variables

	Left frontals	Right frontals	Controls	Left frontal subgroup	Right frontal subgroup
Iowa Gambling Task					
Total risky choices	46.5 (11.6)	54.6 (9.0)	38.2 (12.5)	44.4 (12.5)	54.3 (6.4)
Gamble Task					
Percent likely choice	86.2 (17.0)	90.1 (15.0)	89.2 (13.9)	86.4 (16.1)	91.1 (10.0)
Percent bet	56.4 (15.1)	59.2 (10.9)	49.4 (14.8)	54.5 (14.1)	61.2 (8.8)
Latency (ms)	3395 (1211)	3557 (1792)	2777 (1163)	3124 (750)	3836 (1413)
Risk Task					
Percent likely choice	82.2 (15.3)	76.7 (18.4)	86.8 (14.8)	83.9 (15.2)	72.4 (20.7)
Latency (ms)	3357 (1638)	3131 (1222)	2421 (1218)	2998 (1204)	3558 (1391)

Rogers et al. (Rogers et al., 1999b) PET study, suggesting that this condition provided particularly strong conflict of reward against probability. However, in the present data reward ratio did not interact with the group effect, and it is therefore likely that the lengthened response times in the frontal patients are a general effect of psychomotor slowing following brain injury.

The contributions of lesion laterality and lesion size to decision-making performance remained confounded in the group of 46 patients tested in the present study, as lesion volume was significantly larger in the right frontal patients than the left frontal patients. It is unclear whether this is difference is simply spurious, or underpinned by a bias in patient recruitment or a direct pathological mechanism; for example, the association of language disorders with left frontal lesions. To circumvent this confound in the present data, two subgroups of 10 patients were selected from the right and left frontal groups who were carefully matched for lesion volume. The effects in the subgroup analysis were largely consistent with the full group analysis. The right frontal subgroup remained significantly impaired on the Iowa Gambling Task and preferred the risky decks overall, whilst left frontals did not differ significantly from either group, presumably due to reduced power. On the Cambridge Gamble Task, the effect of group on the amount bet only approached significance and the three groups did not differ in post-hoc comparisons; presumably because of a combination of the small effect size and reduced power. On the Risk Task, the effect of group was again only significant on response latency at the 5:1 ratio, where the right frontals also differed significantly from controls. This latter result is possibly unreliable, given that in the full group analysis the latency effect in the two frontal groups appeared roughly comparable (see Fig. 4).

The acquisition of MRI scans from frontal patients in the present study enabled lesion volumes to be computed, as well as the volume of damage in discrete regions of interests within prefrontal cortex. The ROI approach has yielded a pronounced association between Stop Signal reaction time, a well-validated measure of response inhibition, and the extent of damage in right inferior frontal gyrus (Aron et al., 2003), which is highly consistent with a number of functional imaging studies (Garavan et al., 1999; Konishi et al., 1999). This approach may provide a useful alternative to the coarse parcellation of neuropsychological patients into small subgroups based on region of damage. Performance on the Iowa Gambling Task was shown to be significantly correlated with the overall lesion volume in the right-sided patients, and the volume of damage in ROIs in right middle frontal gyrus, right superior frontal gyrus, and right medial prefrontal cortex. These four volumes associated with the Iowa Gambling Task were all intercorrelated, and due to insufficient power it was not possible to ascertain whether damage in one ROI was driving the association. However, the summed volume of damage in the dorsal and lateral ROIs remained significantly correlated with the net score on the task in the right frontal patients, clearly indicating a prefrontal contribution to the Iowa Gambling Task outside of the ventromedial region. Consistent with the laterality effect shown in the group analysis, there were no significant associations between Iowa Gambling Task net score and lesion volume in the left frontal patients, or with any regions of interest in left prefrontal cortex.

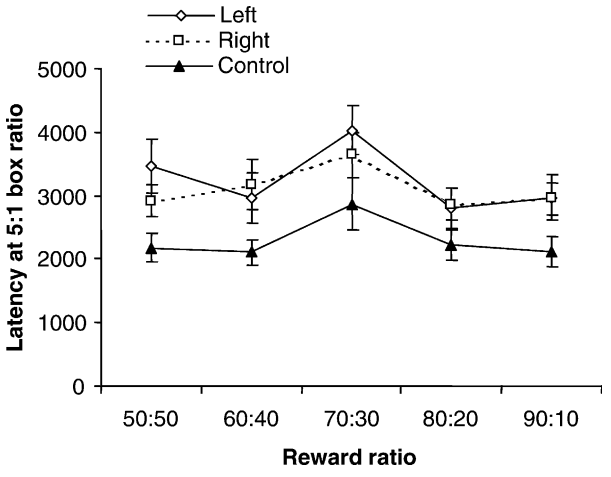

Fig. 4. Response latency on the Risk Task, at the 5:1 box ratio, in right frontals (dashed lines), left frontals (open diamonds), and controls (filled triangles). Errors bars indicate standard error of the mean.

Betting behaviour on the Gamble Task was not associated with total lesion volume in either the right or left frontal groups, and was not associated with the volume of damage in any prefrontal regions of interest. Response latency on the Risk Task was also not correlated with total lesion volume, but did correlate with the volume of damage in left SFG. SFG contains a number of key motor regions and so it is consistent that damage in these regions should correlate with a generic slowing in response time. However, given that the right frontal subgroup matched for lesion volume showed a significant increase in Risk Task latency, it seems likely that either response latency conflates several processes lateralised to right and left PFC, or that the association with left SFG volume does not reflect a laterality effect.

In the present study, the volume of damage in the orbital region of interest did not correlate with the magnitude of decision-making effects on any of the three tasks. Whilst this a provocative finding, it is important to consider that the average volume of damage to the orbital ROI was small in both the left and right frontal groups, and the distribution of volumes within the orbital ROI was heavily skewed (i.e. towards zero damage). Patients with frontal damage including the ventral PFC have been shown to place higher bets relative to controls on the Cambridge Gamble Task in three previous studies (Manes et al., 2002; Mavaddat et al., 2000; Rahman et al., 1999). The effect on the Cambridge Gamble Task in the present study must be considered small in comparison, given that the right frontal patients only differed significantly from controls in the descend condition,

whereas the number of patients tested is considerably larger than in the previous studies. We would interpret the small effects in the present study as due to minimal levels of orbital PFC involvement. This interpretation is supported by the lack of a correlation with total lesion volume, or volume of damage in IFG, MFG, or SFG, where damage was greater on average. Similarly, our previous study (Manes et al., 2002) showed that large frontal lesions including the ventral PFC impaired decision-making on the Risk Task, supporting two PET studies showing ventral prefrontal activations (Rogers et al., 1999b; Rubinsztein et al., 2002). We would infer that the Risk Task may be more selectively disrupted by orbitofrontal damage, which was minimal in the present group of patients.

In contrast to the effects on the Cambridge Gamble and Risk Tasks, performance on the Iowa Gambling Task was significantly disrupted by unilateral frontal lesions that largely spared the orbital and medial prefrontal ROIs. The Iowa Gambling Task deficit was dependent upon the laterality of the lesion, such that right-sided lesions closely resembled the ventromedial PFC profile described previously (Bechara et al., 1994). These findings are consistent with recent data from Tranel et al. (Tranel et al., 2002), showing right-lateralised Iowa Gambling Task deficits in seven patients (four right, three left) with unilateral lesions to ventromedial PFC. These cases are unusual because damage in the vicinity of the medial wall is inherently likely to be bilateral. However, our data strongly indicate that right-sided damage *outside* the ventromedial region may also be associated with Iowa Gambling Task impairments. This extends the findings of our previous study (Manes et al., 2002), which showed that patients with discrete dorsolateral and dorsomedial PFC lesions were impaired on the Iowa Gambling Task. It remains possible that frontal lesions outside the ventromedial PFC region may contribute indirectly to task deficits by disconnecting input to the ventral areas that are more crucially implicated in decision-making. However, against this interpretation, a recent PET study from Ernst et al. (2002) showed widespread (and predominantly right-lateralised) frontal activations in dorsolateral PFC, anterior cingulate, and orbitofrontal cortex during performance of the Iowa Gambling Task. Further research is needed to investigate how these diffuse frontal activations contribute to decision-making. It remains important to clarify whether discrete right-sided ventral prefrontal lesions, and also bilateral ventral prefrontal lesions, impair Iowa Gambling Task performance to a greater extent than non-selective right frontal lesions.

In conclusion, the present study has demonstrated differential contributions of lesion laterality and lesion size across three measures of decision-making, in patients with unilateral frontal lobe lesions. Patients with right frontal lesions preferred the risky decks on the Iowa Gambling Task, and within the right frontal group, the preference for the risky decks was correlated both with the total lesion volume, and the volume of damage outside the ventromedial prefrontal region. Patients with left frontal lesions preferred the safe decks, and differed significantly from the right frontal patients. The Cambridge Gamble Task and the Risk Task were less sensitive than the Iowa Gambling Task to unilateral frontal lobe damage, and there was no clear evidence of laterality or volume effects. On the Cambridge Gamble Task, the right frontal group placed higher bets than controls in the descending condition where inhibitory control is required. However, the right frontal group did not differ significantly from the left frontal group, and betting behaviour was not correlated with lesion volumes. Decision-making on the Risk Task was unaffected by unilateral frontal lesions, although response latencies were lengthened in both right and left frontal groups. The limited effects on the Cambridge Gamble Task and the Risk Task are presumably concordant with the relative sparing of orbital and medial prefrontal cortex in this case series.

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