Cerebral Cortex January 2005;15:58–63
doi:10.1093/cercor/bhh108
Advance Access publication June 24, 2004

Different Underlying Impairments in Decision-making Following Ventromedial and Dorsolateral Frontal Lobe Damage in Humans

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Ventromedial prefrontal cortex (VMF) damage can lead to impaired decision-making. This has been studied most intensively with the Iowa gambling task (IGT), a card game that asks subjects to overcome an initial attraction to high-payoff decks as losses begin to accrue. VMF subjects choose from the high risk decks more often than controls, but the fundamental impairments driving poor performance on this complex task have yet to be established. There is also conflicting evidence regarding the role of the dorsolateral prefrontal cortex (DLF) in this task. The present study examined whether poor performance on the IGT was specific for VMF damage and whether fundamental impairments in reversal learning contributed to IGT performance. We found that both VMF and DLF damage leads to impaired IGT performance. The impairment of VMF subjects, but not of DLF subjects, seems to be largely explained by an underlying reversal learning deficit.

Keywords: dorsolateral prefrontal cortex, gambling, lesion, reversal learning, ventromedial prefrontal cortex

Introduction

The role of prefrontal cortex in human decision-making has become a recent focus of study (Godefroy and Rousseaux, 1997; Rogers *et al.*, 1999b; Satish *et al.*, 1999; Bechara *et al.*, 2000a; Sanfey *et al.*, 2003). Two observations have particularly spurred this work: individuals with damage to the ventromedial prefrontal cortex (VMF) may be especially prone to impulsive decision-making in real life and these same patients are impaired on laboratory decision-making tasks that require balancing rewards, punishments and risk (Bechara *et al.*, 1994, 1997, 2000b; Rogers *et al.*, 1999b; Sanfey *et al.*, 2003). The most widely used task, hereafter referred to as the Iowa gambling task (IGT), takes the form of a card game in which participants select cards from one of four decks in an effort to win play money. Two of the decks are associated with large wins, but occasional even larger losses. The other two conceal smaller wins, but even smaller losses. As the game proceeds, normal individuals generally learn to avoid the risky decks, instead adopting a conservative strategy of accepting smaller wins to avoid large losses. In contrast, Bechara and colleagues found that a group of patients with bilateral VMF damage persistently chose more cards from the high risk decks (Bechara *et al.*, 1994, 1997). This pattern of performance has been ascribed to a failure to develop a 'gut feeling' about the high risk decks, a theory termed the somatic-marker hypothesis (Bechara *et al.*, 1997).

Pathologically risky decision-making is a feature of other disorders, notably addiction and psychopathy. Abnormal IGT performance has been reported in substance abusers, compulsive gamblers, and psychopaths (Petry *et al.*, 1998; Mitchell, 1999; Grant *et al.*, 2000; Bechara *et al.*, 2001, 2002; Cavedini *et al.*, 2002) and has been taken as evidence for VMF dysfunction in these populations. This line of research highlights the fact that studies of the neural bases of human decision-making have the potential to provide insights into the brain processes underlying self-defeating behaviors in a variety of pathological conditions. However, as has been pointed out by others, the IGT is a complex instrument that taps several component processes (Rogers *et al.*, 1999b; Busemeyer and Stout, 2002). These include (perhaps among others) stimulus–reinforcement learning, affective shifting, the ability to attend to, synthesize and remember complex reinforcement histories and to resolve the approach-avoidance conflicts that arise when a deck is associated with both reward and punishment. This raises two important, and related, questions: (i) is impairment on the IGT both sensitive to and specific for VMF dysfunction? and (ii) Can the abnormal performance of VMF subjects on this task be understood in terms of impairment of more fundamental cognitive processes?

In the present study, we first examined the specificity of impaired IGT performance by testing two groups with frontal damage involving either VMF or dorsolateral prefrontal (DLF) sectors. The existing evidence from human lesion studies using this task is conflicting both in regards to the role of DLF (Bechara *et al.*, 1998; Manes *et al.*, 2002; Clark *et al.*, 2003) and, indeed, the roles of the orbitofrontal and medial frontal cortices (Bechara *et al.*, 1997, 2000a; Manes *et al.*, 2002; Clark *et al.*, 2003). Second, we hypothesized that IGT performance may reflect impairment in different fundamental processes in these two groups of patients. We focused on reversal learning, a simple form of flexible stimulus–reinforcement learning that has been shown to be impaired following VMF damage in humans (Rolls *et al.*, 1994; Fellows and Farah, 2003) and other primates (Jones and Mishkin, 1972; Dias *et al.*, 1996). Reversal learning, an example of affective shifting, requires subjects to update stimulus–reinforcement associations as reinforcement contingencies change. Normal performance on the IGT appears to require reversal learning; cards are presented in a fixed order that induces an initial preference for the ultimately riskier decks that must then be overcome as losses begin to accrue.

Materials and Methods

Subjects

The study involved nine subjects with damage involving the ventromedial frontal lobe (VMF), 11 subjects with damage to dorsolateral frontal lobes (DLF) and two groups of age- and education-matched control subjects. Subjects with frontal damage were identified through the patient databases of the Hospital of the University of Pennsylvania and MossRehab. VMF damage was due to rupture of anterior communicating aneurysm in eight cases and to anterior cerebral artery infarct in one. DLF damage followed ischemic or hemorrhagic stroke in 10 cases and

resection of a low grade glioma with local radiotherapy in one. Four VMF subjects and five DLF subjects were taking psychoactive medications. These were most commonly anticonvulsants and/or antidepressants. One VMF subject was taking an acetylcholinesterase inhibitor and another both an acetylcholinesterase inhibitor and methylphenidate. One DLF subject was on low-dose lithium. Subjects were tested at least 6 months after brain injury had occurred.

Age- and education-matched control subjects were recruited by advertisement. Controls were not taking psychoactive medication and were free of significant current or past psychiatric or neurologic illness as determined by history and screening neurologic examination. Controls were excluded if they scored <28/30 on the mini-mental status examination (MMSE; Folstein *et al*., 1983). IQ was estimated by means of the National Adult Reading Test (NART). The main control group (CTL, $n = 17$) provided comparison data for all but the standard IGT. A second control group (CIG, $n = 14$) performed only the IGT, to avoid a possible learning confound in the control data. Groups did not differ significantly in age, education, or estimated IQ (ANOVA, all $P > 0.06$); demographic information is summarized in Table 1.

All subjects provided written, informed consent prior to participation in the study, in accordance with the declaration of Helsinki and were paid a nominal fee for their time. The study protocol was approved by the Institutional Review Boards of the University of Pennsylvania and MossRehab.

Figure 1 shows the extent and overlap of the lesions in the two frontal groups. The volume of damaged tissue was not significantly different in the two frontal groups (unpaired *t*-test on log-transformed data, $t = 0.7$, $P = 0.5$; Table 1). Subjects with frontal damage were administered a short neuropsychological battery for screening purposes. Results from the tasks with potential sensitivity to frontal damage, as well as a verbal memory task (recall of a list of five words after a 1 min delay) are provided in Table 2. The groups differed significantly only in their performance on the Trails B task, with VMF subjects making more errors (Mann–Whitney *U*-test, $P < 0.05$).

Lesions

Lesions were traced from MR or CT images onto the standard Montreal Neurological Institute brain using MRIcro software (Rorden and Brett, 2000) by a neurologist experienced in imaging interpretation. All DLF lesions were unilateral (five right, six left). VMF damage was either definitely or probably bilateral in all cases, although asymmetrically so in many (see Fig. 1). The uncertainty is due to the presence of aneurysm clip-related artefact on the imaging, which variably obscured portions of the postero-medial ventral frontal lobes in eight of nine VMF subjects.

Tasks

A computerized version of the IGT was used, identical in design to the original task as described in Bechara *et al* (2000b) (except that there were no sound effects). Task instructions were taken from the same source. Subjects chose from four decks of cards and after each choice were given feedback about how much play money they had won and lost. Two decks conceal large wins, but intermittent even larger losses, while the other two provide small wins, but smaller losses, and so are more advantageous overall. The main dependent measure was the total number of cards chosen from the more advantageous (low risk) decks over the 100 trials of the task.

To test the role of reversal learning in IGT performance, a variant of the task was designed to eliminate the need to overcome an initial preference for the high-risk decks. This tendency develops in all players because in the first several turns of the original game, all cards conceal only wins and the riskier decks have higher wins. In our 'shuffled' variant task, the same cards were used, but the order was changed (i.e. cards 1–8 from each deck were moved to the bottom of their respective decks, so that each deck now began at card 9; in addition, in deck B the original cards Nos 11 and 14 were switched) so that the losses associated with the high risk decks were experienced on the first few trials, eliminating the need for reversal learning. As in the IGT, subjects played for 100 trials and the total number of choices from the advantageous decks was the dependent measure.

A simple reversal learning task was also administered. This computerized, card-based task involved two decks, one associated with a $50 play money win, the other with a $50 loss. When initial learning had successfully occurred, these contingencies were reversed. The total number of errors during the reversal phase comprised the dependent measure. The task is described in more detail elsewhere (Fellows and Farah, 2003).

Tasks were administered in the same order, intermixed with unrelated material. Subjects with frontal injury were tested in two sessions, generally separated by several weeks (mean delay = 58.4 days). The IGT was administered in the first session, along with the other tasks reported here and the shuffled variant was administered in the second session. In nine cases (six DLF, three VMF), two sessions were not feasible due to travel constraints and the shuffled task was instead administered at the end of the single testing session. All VMF subjects who were available for a third session ($n = 6$) were administered the IGT a second time, during a third session, to test for learning effects.

Statistical Analysis

The main dependent measure for the IGT and its variants was the total number of cards chosen from the advantageous decks over the course of

Table 1
Subject characteristics; see text for details [mean (SD)]

Group	Age (years)	Education (years)	NART IQ	Frontal lesion volume (cm^3)
VMF ($n = 9$)	57.1 (11.8)	13.3 (2.5)	115 (9)	26 (33)
DLF ($n = 11$)	63.0 (10.9)	15.9 (2.7)	119 (11)	18 (15)
CTL ($n = 17$)	55.4 (14.6)	15.8 (2.8)	122 (11)	
CIG ($n = 14$)	59.1 (12)	14.9 (2.3)	124 (6)	

Table 2
Results of selected neuropsychological screening tests [mean (SD)]

Group	Digit span forward	'F' fluency	Trails B errors	Verbal recall
VMF	5.3 (0.8)	9.9 (5.0)	2.7 (2.0)*	3.4 (1.5)
DLF	5.6 (1.1)	9.5 (5.5)	0.8 (1.0)	3.6 (1.0)

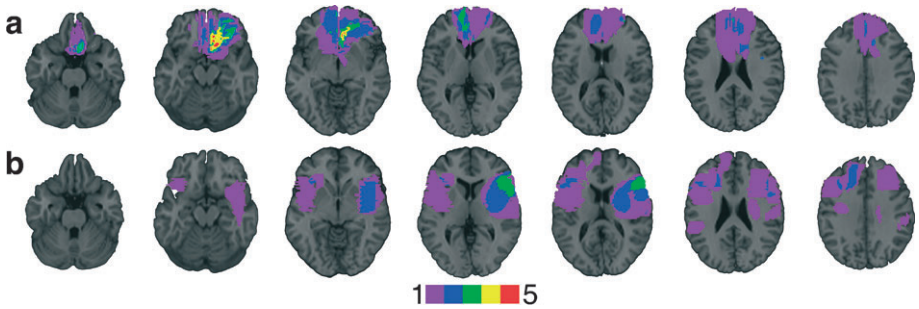

Figure 1. Location and degree of overlap of brain lesions. The top row (*a*) shows the lesions of the nine subjects with ventromedial frontal damage, the bottom row (*b*) those of the 11 subjects with dorsolateral frontal damage. Lesions are projected on the same seven axial slices of the standard MNI brain, oriented according to radiologic convention. Areas damaged in only one subject are shown in purple; warmer colors denote the degree to which lesions involve the same structures in up to five individuals, as indicated in the legend.

the 100 trials. This is the most common measure used in the IGT literature, and the one for which at least preliminary normative data are available (Bechara *et al.*, 1998). Also in keeping with the existing literature, the data are presented graphically in terms of the choices from the advantageous decks per block of 20 trials, to provide information about how the pattern of choices might change with experience. The data were approximately normally distributed (Kolmogorov–Smirnov Normality test, all $P > 0.99$). Analysis of variance was used to examine the effect of group membership on performance and unpaired *t*-tests were used for comparing VMF and DLF groups individually against the performance of the control subjects. Significance levels were set at $P < 0.05$, two-tailed.

Results

Iowa Gambling Task

Iowa gambling task performance for all three groups is shown in Figure 2. As in the original reports, control subjects tended to choose more cards from the advantageous, low risk decks than from the disadvantageous, high risk decks. The total number of choices from the advantageous decks over 100 trials was submitted to ANOVA, which indicated a significant effect of group [$F(2,31) = 7.4$, $P < 0.01$]. *Post hoc* Neuman–Keuls tests indicated that both VMF and DLF performance was significantly worse than that of the control group, while the performance of the two frontal groups did not differ. When the data were analyzed by blocks of 20 trials, there was a significant effect of group [$F(2,31) = 7.4$, $P < 0.01$] and a trend toward an effect of block [$F(4,124) = 1.9$, $P = 0.12$], with no significant interaction [$F(8,124) = 1.3$, $P = 0.26$]. When the effect of block was examined individually for each group, controls picked more often from the advantageous decks as the task progressed [repeated measures ANOVA, effect of block $F(4,48) = 2.8$, $P < 0.05$], while the frontally-damaged groups did not (both $P > 0.27$).

Bechara *et al.* (1998) have provided normative criteria for this task: based on data from nine VMF subjects, 10 dorsal frontal subjects and 19 control subjects, they defined normal performance as the choice of >50 cards from the advantageous decks. All control subjects in the present study also met this criterion. However, only three of nine VMF subjects in the present study are below this standard, while 5 of 11 DLF subjects chose <50 advantageous cards overall (see Fig. 4).

Laterality Effects

There have been recent efforts to clarify the role of lesion laterality in IGT performance. Tranel *et al.* (2002) have argued, based on a small sample of subjects with unilateral VMF damage, that right VMF damage is crucial for poor IGT performance, with unilateral left VMF subjects performing similar to controls. A recent study of a large group of patients with unilateral frontal lobe damage found that right DLF damage resulted in the most impaired performance on this task, although patients with left DLF damage were also impaired (Clark *et al.*, 2003).

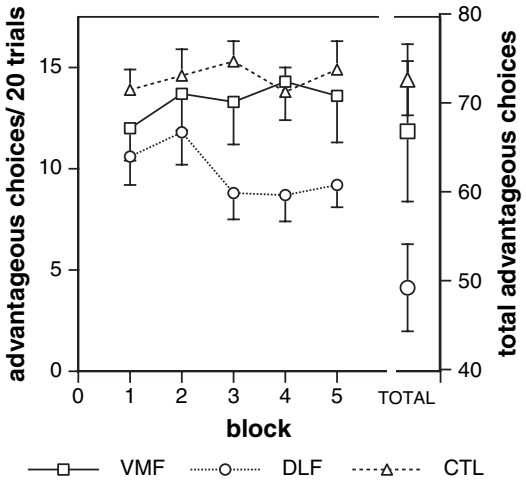

Figure 3. Mean performance on the shuffled version of the IGT for all three groups. This task uses the same cards as the original task (Fig. 2), but changes the card order so that the losses associated with each deck are experienced in the first few choices, eliminating the reversal learning component of the task. Performance of the VMF group was not significantly different from control performance without the reversal learning requirement, whereas the DLF group continued to show impairment. Number of choices from the advantageous decks per block of 20 trials are shown on the left; totals are shown on the right. Error bars indicate the standard error of the mean.

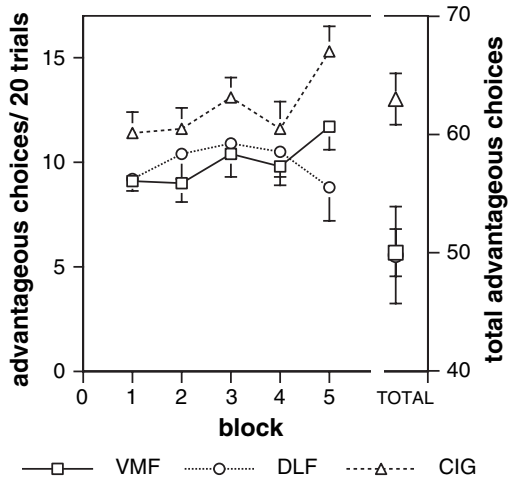

Figure 2. Mean performance on the IGT for all three groups. The number of choices from the two advantageous decks per block of 20 trials are shown on the left; totals over 100 trials are shown on the right. Error bars indicate the standard error of the mean. The control group made significantly more advantageous choices than either frontal group.

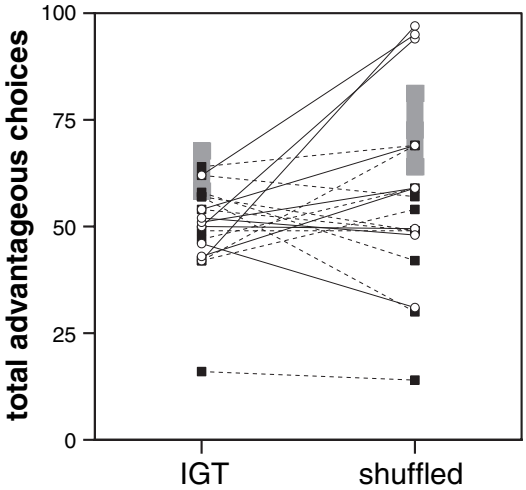

Figure 4. Choices from the advantageous decks in the IGT and shuffled variant for individual subjects with frontal damage. Open circles and unbroken lines show the performance of VMF subjects, filled squares and dotted lines the performance of DLF subjects. The grey bars indicate the 95% confidence interval around the mean for these measures in each control group.

The VMF group in the present study has too few subjects with strictly lateralized damage to allow meaningful statistical analysis of laterality effects, although the lesion overlap indicates that left orbitofrontal cortex was involved in more subjects than any other VMF area (Fig. 1). It is worth noting that the 3 VMF subjects who chose >50 cards from the risky decks (i.e. 'abnormal' performance, by the standard of Bechara *et al.*, 1998) had predominantly left hemisphere damage. In contrast to the findings of Clark *et al.* (2003), laterality effects were not evident in the smaller group of DLF subjects we studied. The mean ± SD number of choices from the advantageous decks in the right DLF group ($n = 5$) was 48.0 ± 19, and in the left DLF group ($n = 6$) was 51.3 ± 9 (unpaired *t*-test, $t = -0.4$, $P = 0.7$).

Shuffled Version of the IGT

Figure 3 shows the performance of the two frontal groups, and the second group of controls, on the shuffled variant of the IGT. Card order was changed so that participants would experience the losses associated with each deck in the first few choices, preventing the formation of an initial preference for the overall disadvantageous, riskier decks. The task was otherwise identical to the IGT. We reasoned that if an underlying reversal learning impairment was contributing to the poor performance of VMF subjects on the original task, than they should benefit from this manipulation. Normal controls developed a preference for the advantageous decks within the first 20 trials and continued to choose more often from the better decks throughout the game. Overall, the performance of the VMF group was indistinguishable from controls. ANOVA of the total number of advantageous choices showed a significant effect of group [$F(2,34) = 5.5$, $P < 0.01$]. *Post hoc* Neuman–Keuls tests showed that DLF performance was significantly worse than both CTL and VMF groups, while the latter groups did not differ. Figure 4 summarizes the performance of individual subjects on the two tasks.

This result is consistent with the hypothesis that a reversal learning deficit underlies the abnormal performance of VMF subjects on the IGT. Additional support for this conclusion comes from a comparison of the improvement demonstrated by frontal subjects on the shuffled variant and a direct measure of their reversal learning ability.

A measure of the effect of the shuffled variant manipulation was derived by subtracting the total number of advantageous choices in the shuffled version from the total advantageous choices in the original version of the IGT (mean ± SD change in advantageous choices: VMF = 16.9 ± 23.1; DLF = –0.6 ± 14.6). We then examined the relationship between this index and the degree of impairment on a much simpler reversal learning task. VMF damage was associated with selective impairment in reversal learning measured by this simple task [mean ± SD errors in reversal: CTL = 5.3 ± 0.9; DLF 5.9 ± 1.4; VMF 10.1 ± 3.6; ANOVA $F(2,31) = 17.5$, $P < 0.0001$; for details, see Fellows and Farah (2003)]. There was a strong correlation between the degree of improvement on the shuffled version of the IGT and reversal learning impairment measured by the simpler reversal learning task ($r = 0.53$, $P < 0.05$). Thus, the worst performers on the simple reversal learning task benefitted the most from the shuffling of the cards, providing further support for the assertion that impaired reversal learning contributes to the poor performance of VMF subjects on the IGT.

Although the IGT and the shuffled variant were administered on separate days (with a few exceptions; see Materials and Methods), we were concerned that non-specific familiarity effects might occur across the two tasks, given their similarity. It has been reported that VMF subjects do not show systematic improvements on repeat testing with the IGT (Bechara *et al.*, 2000a) and we confirmed this in our study population. The total number of choices from the advantageous decks did not differ significantly on the second administration of the IGT in the six of nine VMF subjects who were available for this assessment [ANOVA, $F(1,5) = 2$, $P = 0.22$]. Given the small sample size we cannot entirely exclude a contribution of non-specific learning. However, if such familiarity effects were contributing importantly to these data, we would expect an even greater improvement on the second iteration of the IGT than on its shuffled variant, since it represented the third exposure of these subjects to some form of the task. In fact, we found the contrary: the subgroup of six VMF subjects who performed the IGT twice, as well as the shuffled variant, showed a detectable improvement in performance on the shuffled compared to the original IGT, choosing an average of 20 more cards from the advantageous decks (one group *t*-test, $P < 0.05$, one tailed), while choosing only 8.8 more advantageous cards on average on the second, compared to the first iteration of the IGT [a value not significantly >0 (one group *t*-test, $P > 0.1$ one-tailed)]. The improvement in performance of the VMF group on the shuffled variant is particularly striking in light of the persistantly impaired performance of the DLF group, despite the fact that the DLF subjects were more highly educated, less impaired on other tests of executive function (Tables 1 and 2), and more likely to have performed the two tasks within the same testing session.

Discussion

This study sought to clarify the effects of VMF and DLF damage on IGT performance and to determine how impairment in the more fundamental process of reversal learning might be contributing to the performance of this complex task. As the literature using this task grows, its interpretation is becoming increasingly complex. This work addresses two main issues concerning the role of the VMF in decision-making, as measured by the IGT. The first concerns the empirical findings themselves, the second the interpretation of these findings; we will discuss these in turn.

In keeping with the original reports, but in contrast to the study of Manes *et al.* (2002), we found that VMF damage was associated with impaired performance on the IGT compared to controls. However, most of the VMF subjects we studied did not demonstrate the markedly disadvantageous pattern of choices reported by Bechara *et al.* (1994, 1997). The differences between these studies may relate to the degree of VMF damage: the original work was in subjects with relatively extensive bilateral lesions, while Manes and colleagues found no effect of small, unilateral lesions restricted to orbitofrontal cortex. The lesions of the participants in the present study are probably midway between these two extremes, on average. Furthermore, the VMF subjects who participated in the original studies of Bechara *et al.* were included only if they had both VMF damage and clinical evidence of impaired decision-making. This approach likely introduced selection bias, which may explain the relatively severe IGT impairment in these subjects. The present study, and that of Manes *et al.* (2002) recruited subjects only on the basis of lesion location, and are therefore more likely to give

a true estimate of the range of IGT performance that can follow VMF damage.

Can the IGT performance of VMF subjects be understood at the level of simpler component processes? Converging evidence indicates that VMF (but not DLF) damage impairs reversal learning in both animals and humans (Rolls *et al.*, 1994; Dias *et al.*, 1996; Fellows and Farah, 2003). The card order in the IGT induces an initial preference for the risky decks that must then be overcome as losses begin to accrue, leading us to hypothesize that the impairment of subjects with VMF damage reflects an underlying impairment in reversal learning.

The present study provides two pieces of evidence that IGT performance reflects an underlying reversal learning impairment in these subjects. First is that the performance of VMF subjects improved to control levels when the card order was changed, eliminating the need for reversal learning. As further evidence that this manipulation changes the reversal learning demands of the IGT, we measured reversal learning abilities directly with a much simpler task. VMF (but not DLF) damage selectively impaired reversal learning in these subjects (Fellows and Farah, 2003), as it does in non-human primates with ventral prefrontal cortex lesions (Dias *et al.*, 1996). The degree of impairment on the simple reversal learning task correlated well with improved performance on the shuffled variant of the IGT, whereas potential confounders, such as total lesion volume, education, or estimated IQ did not predict improvement on the shuffled variant (all $P > 0.1$).

This finding allows IGT results to be linked to the literature on the neural bases of stimulus–reinforcement associative learning. Single-unit and lesion studies in several species have provided evidence that flexible stimulus–reinforcement associations are encoded within orbitofrontal cortex (reviewed in Rolls, 2000; Schoenbaum and Setlow, 2001), human functional imaging studies have found activations in orbital and medial prefrontal regions relating to various aspects of flexible reinforcement processing (Rogers *et al.*, 1999a; O'Doherty *et al.*, 2000, 2001) and lesion studies in humans and non-human primates have shown that reversal learning and extinction are specifically impaired when this prefrontal area is damaged (Jones and Mishkin, 1972; Rolls *et al.*, 1994; Dias *et al.*, 1996; Fellows and Farah, 2003). The performance of VMF subjects on the IGT may be interpreted as yet more evidence for a key role for this prefrontal area when circumstances require a reversal of stimulus–reinforcement associations. Interestingly, there is some preliminary, correlational evidence that impaired flexible stimulus–reinforcement learning may also underlie some of the changes in everyday behavior that can follow VMF damage (Rolls *et al.*, 1994; Fellows and Farah, 2003).

In agreement with recent reports (Manes *et al.*, 2002; Clark *et al.*, 2003), but in contrast to those of Bechara *et al.* (1998), we found that unilateral DLF damage led to impaired IGT performance of a similar magnitude to the effect of VMF damage. Given the literature available at the time the present study was launched, this was an unexpected finding and not one our study was designed to explore. Unlike VMF subjects, the performance of DLF subjects on the IGT does not seem to be due to reversal learning impairments. DLF subjects demonstrated persistant impairment on the shuffled variant of the IGT, as they did in the original task. Bechara *et al.* (1998) have shown that working memory deficits influence IGT performance, although the effect was less prominent in the group of subjects with dorsal frontal damage they studied. Further work will be required to establish the processes underlying impaired IGT performance in the DLF group we studied.

It is worth emphasizing that IGT performance can be impaired to a similar degree by either DLF or VMF dysfunction. This has implications for interpreting the results of studies using this task in other populations: isolated impairment on the IGT cannot be used to infer VMF dysfunction. Our findings indicate that impaired reversal learning will also manifest itself as impaired IGT performance, but impaired IGT performance is not necessarily due to a reversal learning deficit nor, by extension, to VMF dysfunction. A pattern consistent with such a relationship is evident in one study that administered both a reversal learning task and the IGT to a group of psychopaths, finding deficits in both (Mitchell *et al.*, 2002).

One of the central challenges of understanding the functions of the human prefrontal cortex is that impairment is most evident when experimental tasks are complex, but task complexity interferes with our ability to distinguish the different component processes that may be implicated. One method of resolving this difficulty is to identify common processes (and their underlying neural substrates) across different complex tasks (Duncan and Owen, 2000). A second approach, illustrated by the present study, is to measure the effects of aberrant processes at simpler levels and then trace the expression of such fundamental abnormalities under more complex conditions.

Notes

This research is supported by NIH grants R21 NS045074, R21-DA01586, R01-HD043078, R01-DA14129 and NSF grant no. 0226060. L.K.F. is supported by a Clinician–Scientist award from the Canadian Institutes of Health Research. We would like to thank Dr Marianna Stark for her help with subject recruitment and assessment.

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