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Characterization of the decision-making deficit of patients with ventromedial prefrontal cortex lesions

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Summary

On a gambling task that models real-life decisions, patients with bilateral lesions of the ventromedial prefrontal cortex (VM) opt for choices that yield high immediate gains in spite of higher future losses. In this study, we addressed three possibilities that may account for this behaviour: (i) hypersensitivity to reward; (ii) insensitivity to punishment; and (iii) insensitivity to future consequences, such that behaviour is always guided by immediate prospects. For this purpose, we designed a variant of the original gambling task in which the advantageous decks yielded high immediate punishment but even higher future reward. The disadvantageous decks yielded low immediate punishment but even lower future reward. We measured the skin conductance responses (SCRs) of subjects after they had received a reward or punishment. Patients with VM lesions opted for the disadvantageous decks in both the original and variant versions of the gambling task. The SCRs of VM lesion patients after they had received a reward or punishment were not significantly different from those of controls. In a second experiment, we investigated whether increasing the delayed punishment in the disadvantageous decks of the original task or decreasing the delayed reward in the disadvantageous decks of the variant task would shift the behaviour of VM lesion patients towards an advantageous strategy. Both manipulations failed to shift the behaviour of VM lesion patients away from the disadvantageous decks. These results suggest that patients with VM lesions are insensitive to future consequences, positive or negative, and are primarily guided by immediate prospects. This 'myopia for the future' in VM lesion patients persists in the face of severe adverse consequences, i.e. rising future punishment or declining future reward.

Keywords: reward; punishment; gambling task; decision-making; ventromedial prefrontal cortex

Abbreviations: SCR = skin conductance responses; VM = ventromedial prefrontal cortex; WCST = Wisconsin Card Sorting Test

Introduction

Over the years, we have studied numerous patients with bilateral lesions of the ventromedial prefrontal (VM) cortex. Such patients develop severe impairments in personal and social decision-making in spite of otherwise largely preserved intellectual ability. After the onset of their prefrontal cortex lesion, these patients begin to have difficulties learning from previous mistakes, as reflected by repeated engagement in decisions that lead to negative consequences. In general, these patients appear to have 'myopia' for the future in that they are oblivious to the consequences of their actions and are guided only by immediate prospects (Bechara *et al*., 1994). In contrast to this impairment in real-life decision-making, most of these patients retain normal intellect, memory and problem-solving ability in laboratory settings (Eslinger and Damasio, 1985; Damasio *et al*., 1990; Damasio, 1994; Bechara *et al*., 1998).

Several investigators have developed behavioural paradigms to study the neural mechanisms underlying the behaviour of patients with lesions in the prefrontal cortex. Rolls and colleagues have studied stimulus–reward learning and the ability to reverse and/or extinguish responses that have been rewarded previously (Rolls *et al*., 1994; Rolls, 2000). In this paradigm, subjects obtained a reward by touching a stimulus when it appeared on a video screen, but they had to withhold the response if a different stimulus appeared. After the subjects had learned the stimulus–reward association, the reward contingencies were reversed unexpectedly. Patients with orbital frontal lesions were unsuccessful in making the shift in behaviour, although they were able to report that the contingencies had changed. Based on these findings, Rolls has argued that the orbitofrontal cortex is critical for evaluating the associations of

environmental stimuli with reinforcement (Rolls, 2000). In our studies of VM lesion patients, we have found that this feature of disinhibited behaviour is seen in some cases. Specifically, a disinhibition deficit is seen in patients whose VM lesions include the basal forebrain or extend more laterally into the orbitofrontal cortex and/or dorsolaterally in areas of prefrontal cortex (Bechara *et al*., 1998). This is consistent with the findings of Rolls and colleagues (Rolls *et al*., 1994; Rolls, 2000), who studied patients with lesions in the orbital frontal area lateral to the damaged VM area in our patient group. Our studies reveal that patients with restricted VM lesions do not suffer simply this type of disinhibited behaviour (motor impulsivity), although they may suffer a more complex form of disinhibition (cognitive impulsivity) (Bechara *et al*., 2000).

Another hypothesis, the 'inhibition hypothesis', was proposed by Sahakian and colleagues to account for the social cognition deficits observed in patients with frontal lobe dysfunction (Plaisted and Sahakian, 1997; Rahman *et al*., 1999*a*, b). The hypothesis is based partly on work in non-human primates with the attentional set-shifting paradigm developed by Roberts and colleagues (Dias *et al*., 1996, 1997). The hypothesis proposes that the inability of the patient to suppress the response evoked by the stimulus present in the immediate environment prevents the patient from selecting an appropriate action plan. Thus, the behaviour becomes dominated by the immediate emotional impact of the stimulus at hand. This group showed that patients with either prefrontal cortex lesions (mesial lesions) or frontotemporal dementia do not suffer from complete loss of inhibitory control (Rahman *et al*., 1999*b*; Rogers *et al*., 1999). The patients make disadvantageous choices, but only after taking some time to deliberate. This view is consistent with our position that patients with VM lesions may suffer from a form of cognitive impulsiveness, but we have argued that impulsiveness alone is a construct that does not explain satisfactorily the decision-making deficit of VM lesion patients (Bechara *et al*., 2000).

Our work has been guided by the 'somatic marker hypothesis' (Damasio, 1994). This hypothesis proposes that the body states evoked by the experience of reward or punishment signal the potential occurrence of an outcome, so that these signals guide the behaviour in a manner that is advantageous to the organism in the long term. In order to detect and measure in the laboratory the decision-making impairment of VM lesion patients, we developed a gambling task which resembles the decisions made in real life in terms of reward, punishment and the uncertainty of outcomes (Bechara *et al*., 1994). The task involves four decks of cards, called A, B, C and D. Subjects must choose one card at a time from one of the four decks. For two decks (A and B), choosing a card is followed by a high gain of play money, but the selection of a card is followed at unpredictable points by a high penalty. For the other two decks (C and D), the immediate gain is smaller but the future loss is also smaller. After sampling and encountering losses in each deck, normal subjects begin to avoid the decks with high immediate gain (disadvantageous decks), and they also begin to produce anticipatory skin conductance responses (SCRs) before their selection of a disadvantageous response. By contrast, VM lesion patients continue to select more cards from the disadvantageous decks and they fail to produce any anticipatory SCRs (Bechara *et al*., 1996).

Based on our studies with the gambling task, in which VM lesion patients select options that bring a higher immediate reward at the expense of more severe delayed punishment, the purpose of this study was to answer two questions: (i) why do VM lesion patients fail to avoid the disadvantageous decks? and (ii) can performance on the gambling task be normalized in VM lesion patients if adverse future consequences are increased?

To answer the first question, we considered three possibilities that may account for the behaviour of VM lesion patients. One was hypersensitivity to reward, i.e. the prospect of a large immediate gain outweighs any prospect of future loss. Another was insensitivity to punishment, i.e. the prospect of a large loss cannot override any prospect of gain. The third was insensitivity to future consequences, positive or negative, so that the subject is oblivious to the future and is guided by immediate prospects. We approached the question in two ways. First, we designed a variant of the original gambling task with decks E, F, G and H, in which we reversed the order of reward and punishment, i.e. the punishment became immediate and the reward became delayed. In the variant task (EFGH), we set the advantageous decks (E and G) to be those with high immediate punishment but higher future reward. The disadvantageous decks (F and H) were those with low immediate punishment but lower future reward. Secondly, we measured subjects' SCRs after receiving reward or punishment during the original (ABCD) and variant (EFGH) versions of the gambling task. We reasoned that hypersensitivity to reward would be associated with the generation of reward SCRs with magnitude higher than normal. On the other hand, insensitivity to punishment would be associated with lower than normal punishment SCRs. From these combined behavioural and psychophysiological approaches, we made several predictions. First, in the variant task, preference for the decks with high immediate punishment (good decks) combined with abnormally low punishment SCRs would be consistent with insensitivity to punishment as the explanation. Secondly, preference for the decks with high delayed reward (good decks) combined with abnormally high reward SCRs would be consistent with hypersensitivity to reward as the explanation. Thirdly, preference for the decks with low immediate punishment (bad decks) combined with normal reward and punishment SCRs would be consistent with insensitivity to the future as the explanation. Based on the real-life behaviour of VM lesion patients, we hypothesized that insensitivity to future consequences would provide the best account of their decision-making deficit.

To address the second question, we developed

Table 1 *Demographic data of subjects participating in the original gambling task with decks ABCD*

	Controls	VM lesion patients
Total no. of subjects	20	10
Gender (male, female)	8, 12	5, 5
Age (years; mean ± SD)	42.5 ± 11.6	44.1 ± 14.5
Age range (years)	22–68	18–65
Education (years; mean ± SD)	13.9 ± 2.2	12.1 ± 3.5

Table 2 *Demographic data of subjects participating in the variant gambling task with decks EFGH*

	Controls	VM lesion patients
Total no. of subjects	20	10
Gender (male, female)	8, 12	5, 5
Age (years; mean ± SD	42.1 ± 11.6	44.1 ± 14.5
Age range (years)	22–68	18–65
Education (years; mean ± SD)	14.3 ± 1.2	12.1 ± 3.5

Four of the 20 controls were from the previous control group tested with the original task ABCD. The remaining 16 controls were new subjects. All the VM lesion patients were from the previous group tested with the original task ABCD.

Table 3 *Demographic data of subjects participating in the computer gambling task with progressive punishment schedules in decks A′B′C′D′*

	Controls	VM lesion patients
Total no. of subjects	17	8
Gender (male, female)	8, 9	4, 4
Age (years; mean ± SD)	39.4 ± 3.6	44.0 ± 4.9
Age range	21–63	18–63
Education (years; mean ± SD)	14.0 ± 0.5	12.0 ± 1.4

All 17 controls were new and had never been tested on the original or variant versions of the gambling task. Seven of the eight VM lesion patients were from the previous groups tested with the original and variant versions of the gambling task. One VM lesion patient from this group was new and inexperienced in the gambling task.

computerized versions of the above two tasks (original and variant). For the original version, we set the schedules of reward and punishment in such a way that the future punishment would increase progressively as subjects selected more cards from the disadvantageous decks A′ and B′. For the variant version, the schedules were set in such a way that the future reward would decrease progressively in the disadvantageous decks F′ and H′. We also measured the subjects' SCRs during the computerized tasks. Based on the real-life behaviour of VM lesion patients, we hypothesized that their decision-making impairment would not improve in spite of rising adverse future consequences.

Methods

Subjects

Normal controls were recruited by local advertisement and were paid for their participation. Patients with VM lesions were selected from the Patient Registry of the University of Iowa's Division of Behavioural Neurology & Cognitive Neuroscience. All VM lesion patients had undergone basic neuropsychological (Tranel, 1996) and neuroanatomical (Damasio and Damasio, 1989; Damasio and Frank, 1992; Damasio, 1995*b*) characterization. All subjects provided informed consent to participation in the study, which was approved by the appropriate human subject committees at the University of Iowa.

The selection criterion for normal subjects was the absence of a history of mental retardation, learning disability, neurological disorder, psychiatric disorder, substance abuse or any systemic disease capable of affecting the CNS. The selection of VM lesion patients conformed to the above criteria for normal controls (except the neurological disease) with the following additional criteria: (i) a stable and chronic lesion (onset was at least 3 months before the experiments); and (ii) bilateral involvement of the VM cortices.

The number, gender, age, age range and years of education of controls and VM lesion patients who participated in the study with the original gambling task (ABCD) are presented in Table 1. Similar information on controls and VM lesion patients who participated in the variant task (EFGH) are presented in Table 2. These two experiments were carried out at separate times. It was not possible to contact all of the same control subjects who were tested on the ABCD task; thus, only four control subjects participated in both experiments. The remaining subjects were different control subjects. Because of the rarity of VM lesion patients and because of the accessibility of these patients through the Registry, the number of VM lesion patients was smaller than the number of controls. We tested the same patients on both tasks.

Because of the steep learning curve of control subjects when re-tested on similar versions of the gambling task (Bechara *et al*., 2000), we did not re-test control subjects who had a prior exposure to the gambling task. Therefore, in the computerized version of the gambling task with increased delayed punishment (A′B′C′D′), a new group of normal controls participated in the experiment. The demographic data for these control subjects are shown in Table 3. By contrast, VM lesion patients do not improve their performance on the gambling task when tested repeatedly (Bechara *et al*., 2000). Because of the rarity of these patients, we re-tested seven of the patients who had participated in the previous experiments (the eighth VM lesion patient was new). The demographic data on these VM lesion patients are also shown in Table 3. Table 4 shows the demographic data for the controls and VM lesion patients who participated in the computerized version of the gambling task with changes in delayed reward (E′F′G′H′). Some of the controls and VM lesion patients were not accessible for this experiment.

Table 4 *Demographic data of subjects participating in the computer gambling task with progressive reward schedules in decks E′F′G′H′*

	Controls	VM lesion patients
Total no. of subjects	14	6
Gender (male, female)	7, 7	3, 3
Age (years; mean ± SD)	37.3 ± 12.7	40.0 ± 13.0
Age range (years)	21–58	18–53
Education (years; mean ± SD)	14.0 ± 1.9	12.3 ± 3.4

Eight of the 14 controls were from the previous group tested with the computer gambling task with decks A′B′C′D′. The remaining six were new. All six VM lesion patients were from the previous group tested with the computer gambling task with decks A′B′C′D.

Therefore, some of the subjects who participated in the E′F′G′H′ task were not the same as those who participated in the A′B′C′D′ task (Table 4).

Behavioural tasks

The following gambling tasks were administered manually. Below is information on how each task was assembled and administered.

Original task (ABCD)

Assembly and administration of the task. To assemble the task, four custom-made decks of cards were used (the cards used in the task were not real cards). Each deck had 40 cards: 20 of the cards had a black face and the remaining 20 had a red face. The backs of the cards all looked the same, like a real deck of cards. Using the score sheet shown in Fig. 1, it was possible to construct the red and black card sequence in each deck. Each square (on the score sheet) which contained the figure '0' or a negative number represented a red card, and each square which did not have anything in it represented a black card. Facsimile US dollar bills were used for reward and punishment; they had the denominations $5, $20, $50 and $100.

The four decks were laid out on a table in front of the subject, and the labels (A, B, C and D) were placed at the top end of each deck (relative to the subject). During administration of the task, one simply wrote on the score sheet the number of the *n*th card selected by the subject. For example, if the first card selection was from deck B, we wrote '1' in the first box for deck B. If the second card selection was also from deck B, we wrote '2' in the next box. If the subject now picked the third card from deck A, we wrote '3' in the first box for deck A, and so on. The task was stopped after the subject had picked 100 cards. However, the subjects were not told in advance how many cards they were going to pick.

The number (+100) next to decks A and B in Fig. 1 means that subjects always earned $100 if they picked a card from deck A or B. The number (+50) next to decks C and D means that subjects earned $50 every time they selected deck C or D. When a box on the score sheet (which corresponds to a card in the deck) that had a negative number in it was reached, the subject was told: 'You won $50 or $100, but you lost *X* dollars' (*X* being the amount indicated by the negative number). Subjects then had to pay back this amount. When boxes that had '0' in them were reached, there was no money loss. Subjects were told 'You won $100 or $50'. Empty boxes were like '0' boxes, for which subjects only won money.

When a given deck ran out of cards, the subject was instructed to stop picking from that deck and to continue choosing from the remaining decks. The colours of the cards did not serve any specific function. Using real decks of cards proved to be too distracting, as the subjects attempted to construct all sorts of strategies from the different categories of cards in a real deck. In order to reduce the distraction, we used decks of cards with only two colours: red and black.

Instructions before administering the task. The following instructions were given orally before administering the task, and we ensured that the subject understood all the instructions before administering the task.

> In front of you, there are four decks of cards A, B, C and D (*all the decks were face-down, i.e. the black and red colours were hidden, and the subject saw four identical decks of cards*).
> I want you to select one card at a time from any deck you choose. I want you to show it to me like this (*showing the colour to the examiner was demonstrated*), and then to place it in front of you like this (*the card was placed with the black or red colour facing up, directly in front of the deck from which the card was picked*).
> I will give you some money each time you select a card. I will not tell you now how much money you will get. You will find out as we go along.
> Every so often, however, you will have to pay me some money too. I will not tell you now when these payoffs will occur or how much they will cost you. You will find out as we go along.
> You are absolutely free to switch from one deck to the other at any time, and as often as you wish.
> The goal of the game is to win as much money as possible, or avoid losing money as much as possible.
> You won't know when the game will end. You must keep on playing until I tell you to stop.
> It is important to know that the colours of the cards are irrelevant in this game and that there is no way for you to figure out when you lose money. All I can say is that some decks are worse than others. You may find all of them bad, but some are worse than others. No matter how much you find yourself losing, you can still win if you stay away from the worst decks. Please treat the play money in this game as real money, and any decision on

Original Task (ABCD)

Deck	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40
A (+100)			-150		-300		-200		-250	-350		-350		-250	-200		-300	-150				-300		-350		-200	-250	-150			-350	-200	-250				-150	-300		
B (+100)	0	0		0		0			-125		0	0		-125		0	0				-125		0	0		0		0			0	-125		0		0		0		
C (+50)			-50		-50		-50		-50	-50		-25	-75				-25	-75		-50				-50	-25	-50			-75	-50				-25	-25		-75		-50	-75
D (+50)	0		0			0	0			-250	0	0			0				0	-250		0			0	0	0		-250			0		0	-250	0			0	

Variant Task (EFGH)

Deck	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40
E (-100)	0		1250	0		0		0			1250			0		0	0			0	1250		0		0		0	0			0		1250	0		0	0			
F (-50)				25	50			75	25	75	50		25			25	75			75				25	75	50			75	25				50	50		25		75	50
G (-100)		350		250		300	200		150				350		250		200	150		300		300		350		150	200	250			150	200	350				200	350		
H (-50)	0		0			0	0	250			0	0			0				0	250					0	0	0		0	250			0	250		0		0	0	

Fig. 1 Score-cards from the original and variant versions of the gambling task. The top part of the figure represents a score-card from the original gambling task. The negative numbers inside each box indicate the amount of money lost when the card corresponding to that box was turned. The empty boxes correspond to cards with money gain, without loss. The boxes with '0' inside them are like the empty boxes, i.e. they correspond to cards with gain, without loss. The bottom part represents a score-card from the variant version of the task. The positive numbers inside each box indicate the amount of money gained when the card corresponding to that box is turned. The empty boxes correspond to cards with money loss, without gain. The boxes with '0' inside them are like the empty boxes, i.e. they correspond to cards with loss, without gain. All numbers in the bottom section are positive.

what to do with it should be made as if you were using your own money.

I will give you now this loan of $2000 of play money. At the end, I will collect back the loan and see how much you won or lost.

Variant task (EFGH)

Assembly and administration of the task. The assembly of this task was almost identical to that of the previous task except for the order of the cards and the payment schedule. On the score-sheet shown in Fig. 1, each box with a '0' or another number in it represented a black card, and each empty box represented a red card. The number (–100) next to decks E and G in Fig. 1 means that subjects had to pay $100 every time they selected a card from one of these decks. The number (–50) next to decks F and H means that subjects had to pay $50 every time they selected from one of these decks. When a box on the score-sheet (which corresponds to a card in the deck) that had a number in it was reached, the subject was told: 'You must pay $50 or $100, but you won *X* dollars' [*X* being the amount indicated by the number]. When boxes that had '0' in them were reached, there was no money gain. Empty boxes were like '0' boxes, for which the subjects only had to pay money.

Instructions before administering the task. The instructions were identical to those of the previous task, except for appropriate changes pertaining to the names of the decks and what happened after selecting a card.

Computer task with progressive changes in delayed punishment (A′B′C′D′)

Structure of the task. This task was analogous to the original task (ABCD). The only difference was a change in the frequency or magnitude of delayed punishment relative to immediate reward. The change was such that the discrepancy between reward and punishment in the disadvantageous decks (A′ and B′) was larger in the negative direction, i.e. towards larger loss. By contrast, this discrepancy between reward and punishment in the advantageous decks (C′ and D′) was larger in the positive direction, i.e. towards larger gain.

In the computerized version of the gambling task, the subject saw four decks of cards on a computer screen. The decks were' labelled A′, B′, C′ and D′ at the top end of each deck. Using a mouse, the subject could click on a card from any of the four decks. The computer tracked the sequence of the cards selected from the various decks. Every time the subject clicked on a deck to pick a card, the computer generated a distinct sound (similar to that of a Casino slot machine). The face of the card appeared on top of the deck (the colour was red or black), and a message was displayed on the screen indicating the amount of money the subject had won or lost. On the top of the computer screen was a green bar that changed according to the amount of money won or lost after each selection. A gain was indicated by a proportionate increase in the length of the green bar, and a loss was indicated by a proportionate decrease in the length of the bar. Once the money had been added or subtracted, the face of the card disappeared and the subject could select another card.

The inter-trial interval between two consecutive card selections could be set by the examiner at the beginning of the task. The total number of card selections (trials) in the experiment was also set at the beginning. In the present experiment, we set the inter-trial interval at 6 s. The total number of trials was set at 100 card selections. The experiment shut off automatically when the 100 selection trials had been completed.

Each deck of cards was programmed to have 60 cards (instead of 40 cards in the original version): 30 of the cards had a black face and 30 had a red face. The sequence of red and black cards in each deck was consistent with the original task, i.e. black cards yielded only reward and red cards usually yielded punishment (except when there was a '0' and no penalty in deck B′ or D′). The negative consequences in the disadvantageous decks (A′ and B′) were amplified in two ways. (i) In deck A′, the frequency of delayed punishment was increased by 10% in every block of 10 cards, but the magnitude of an individual delayed punishment remained the same. (ii) In deck B′, the magnitude of an individual delayed punishment, relative to an immediate reward, was increased in every block of 10 cards by an amount equal to the increase in deck A′. However, the frequency of delayed punishment in deck B′ remained the same. There were parallel increases in the frequency and magnitude of delayed punishment in decks C′ and D′. However, the net difference between reward and punishment in each block of 10 cards was set up in such a way that this difference in decks A′ and B′ increased in the negative direction across each block (i.e. towards larger loss). On the other hand, this difference in decks C′ and D′ increased in the positive direction across each block (i.e. towards larger gain).

Instructions before administering the task. Initial studies indicated that subjects playing the computer task believed that the computer was generating the reward and punishment schedules, and that they could not win no matter what they did. To circumvent this problem, we expanded our task instructions to include the following:

> In front of you on the screen, there are four decks of cards: A′, B′, C′ and D′.
> I want you to select one card at a time, by clicking on the card, from any deck you choose.
> Each time you select a card, the computer will tell you that you won some money. I don't know how much money you will win. You will find out as we go along. Every time you win, the green bar gets bigger.
> Every so often, however, when you click on a card, the computer tells you that you won some money, but then it says that you lost some money too. I don't know when you will lose, or how much you will lose. You will find out as we go along. Every time you lose, the green bar gets smaller.
> You are absolutely free to switch from one deck to the other at any time, and as often as you wish.
> The goal of the game is to win as much money as possible, and if you can't win, avoid losing money as much as possible.
> You won't know when the game will end. You must keep on playing until the computer stops.
> I am going to give you this $2000 credit, the green bar, to start the game. The red bar here is a reminder of how much money you borrowed to play the game, and how much money you have to pay back before we see how much you won or lost.
> It is important to know that just like in a real card game, the computer does not change the order of the cards after the game starts. You may not be able to figure out exactly when will you lose money, but the game is fair. The computer does not make you lose money at random, or make you lose money based on the last card you picked. Also, each deck contains an equal number of cards of each color, so the color of the cards does not tell you which decks are better in this game. So you must not try to figure out what the computer is doing. All I can say is that some decks are worse than the others. You may find all of them bad, but some are worse than the others. No matter how much you find yourself losing, you can still win if you stay away from the worst decks. Please treat the play money in this game as real money, and any

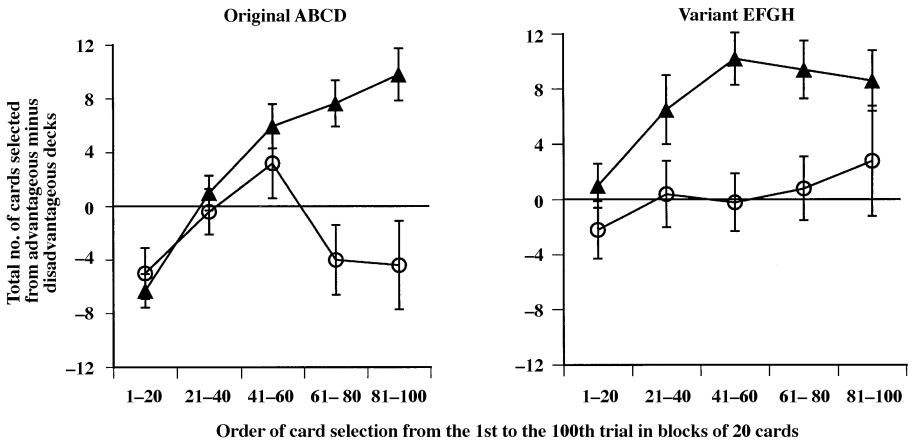

Fig. 2 Decision-making in the original (ABCD) and variant (EFGH) versions of the gambling task. Relative to normal controls (filled triangles), VM lesion patients (open circles) were impaired in their performance on both the original (ABCD) and variant (EFGH) versions of the gambling task. The figure shows net scores [(C + D) – (A+B) or (E + G) – (F + H)] of cards selected by each group across different blocks expressed as mean ± SEM. Positive net scores reflect advantageous performance whereas negative net scores reflect disadvantageous performance.

decision on what to do with it should be made as if you were using your own money.

Computer task with progressive changes in delayed reward (E′F′G′H′)

Structure of the task. This task was analogous to the variant task (EFGH). The only difference was a change in the frequency or magnitude of the delayed reward relative to immediate punishment. The change was such that the discrepancy between punishment and reward in the disadvantageous decks (F′ and H′) was larger in the negative direction, i.e. towards larger loss. By contrast, this discrepancy between punishment and reward in the advantageous decks (E′ and G′) was larger in the positive direction, i.e. towards larger gain.

The appearance and operation of this task were very similar to those of the previous task. The only differences were in the schedules of punishment and reward. Each deck of cards was programmed to have 60 cards. The sequence of red and black cards in each deck was consistent with the variant task EFGH, i.e. red cards yielded only punishment and black cards usually yielded reward (except when there is was a '0' and no reward in deck E′ or H′). The negative consequences in the disadvantageous decks (F′ and H′) were amplified in two ways. (i) In deck F′, the frequency of delayed reward was decreased by 6% in every block of 10 cards (i.e. 30% across five blocks), but the magnitude of an individual reward remained the same. (ii) In deck H′, the magnitude of an individual delayed reward relative to immediate punishment decreased in each block of 10 cards by an amount that was equivalent to that in deck F′. However, the frequency of delayed reward remained the same in deck H′. There were parallel changes in the frequency (deck G′) and magnitude (deck E′) of delayed reward. However, the changes were such that the net difference between the immediate punishment and future reward in decks F′ and H′ increased in the negative direction across each block (i.e. towards larger loss). By contrast, this net difference in decks E′ and G′ increased in the positive direction across each block (i.e. towards larger gain).

Instructions before administering the task. To perform the task, subjects were given verbal instructions similar to those given in the previous computer task except for appropriate changes.

SCR recording during the gambling task

A computerized method for collecting and analysing SCR data has been described previously (Bechara *et al*., 1999). In the present study, we measured punishment SCRs and reward SCRs. Punishment SCRs were generated after turning a card for which there was a reward immediately followed by a penalty (in the original ABCD or computer A′B′C′D′ task), or a card with only an immediate penalty not followed by a reward (in the variant EFGH or computer E′F′G′H′ task). Reward SCRs were generated after turning a card for which there was a reward not followed by a penalty (in the original ABCD or computer A′B′C′D′ task), or a card with an immediate penalty followed immediately by a reward (in the variant EFGH or computer E′F′G′H′ task).

The time windows for the punishment and reward SCRs were the 5 s intervals immediately after the click of a card. We measured the area under the curve in the 5 s time window after selecting a card as described previously (Bechara *et al*., 1999). Since the time interval was always 5 s, we divided each area under the curve measurement by 5. The area

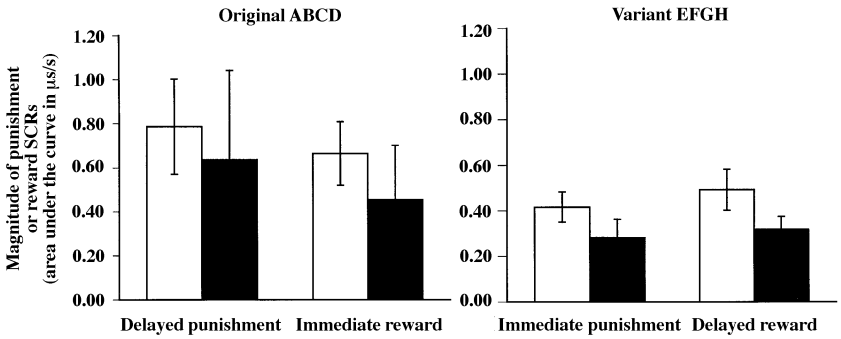

Fig. 3 Punishment (delayed or immediate) and reward (immediate or delayed) SCRs of controls (open squares) and patients with VM lesions (filled squares) measured during performance of the original (ABCD) or variant (EFGH) versions of the gambling task. SCRs are presented as the mean ± standard error of the mean of the average area under the curve of responses generated after selecting cards for which there was a penalty (punishment SCRs) or reward (reward SCRs) from all the decks. The magnitudes of the punishment and reward SCRs from the different groups were not significantly different.

measurements per second (μS/s) from the punishment or reward SCRs from all decks of the original task ABCD were averaged. Similarly, the punishment or reward SCRs from all decks of the variant task EFGH were averaged. Similar measurements were obtained from the computer tasks A′B′C′D′ and E′F′G′H′.

Results

Anatomy

Details of the anatomy of the lesions in a larger group of VM lesion patients were included in a review (Bechara *et al*., 2000). All the VM lesion patients in the present study had bilateral damage in the ventromedial sector of the frontal lobes due to meningioma resection or stroke. All the VM lesion patients had lesions confined to the ventral and low mesial sectors of the frontal lobe in both the right and left hemispheres.

Demographics

Table 1 indicates that the two groups tested in this study (controls and VM lesion patients) were similar in terms of gender, age, age range and years of education. The same holds true for the demographic data presented in Tables 2, 3 and 4. Although there were slight differences between the groups, none of the differences between the control and VM groups were statistically significant.

Behavioural performance on original (ABCD) and variant (EFGH) tasks

As shown in Fig. 2, we subdivided the 100 card selections into five blocks of 20 cards each. In the original (ABCD) task, we counted the number of selections from decks A and B (disadvantageous) and the number of selections from decks C and D (advantageous) for each block of 20 cards. We then derived the net score for that block ((C + D) – (A + B)); net scores below zero indicate that the subjects were selecting disadvantageously, whereas net scores above zero indicate that subjects were selecting advantageously.

We derived a similar net score for the variant task ((E + G) – (F + H)). Figure 2 depicts the net scores as a function of group and block from both the original (ABCD) and the variant (EFGH) task.

In the original task, as the task progressed, normal controls gradually shifted their preference towards the good decks (C and D) and away from the bad decks (A and B), as reflected by the shift in the net scores towards positive. By contrast, the VM lesion patients failed to demonstrate this shift in behaviour. By and large, they selected more cards from the disadvantageous decks. A 2 (group) × 5 (block) ANOVA (analysis of variance) on the net scores from the original task revealed a significant main effect of group [$F(1,28) = 19.0$, $P < 0.001$], suggesting that the controls made significantly more advantageous choices than the VM lesion patients. The ANOVA also revealed a significant main effect of block [$F(4,112) = 10.0$, $P < 0.001$] and an interaction of group with block [$F(4,112) = 9.1$, $P < 0.001$].

In the variant task there were similar findings. Normal controls increased their preference for the good decks (E and G). By contrast, the VM lesion patients did not make a significant shift in the advantageous direction. A 2 (group) × 5 (block) ANOVA on the net scores from the variant task revealed a significant main effect of group [$F(1,28) = 9.9$, $P < 0.004$], suggesting that VM lesion patients were impaired relative to controls in terms of making advantageous selections. This ANOVA also revealed a significant main effect of block [$F(4,112) = 2.8$, $P < 0.03$], but no interaction of group with block [$F(4,112) = 0.8$, $P > 0.1$].

Punishment versus reward SCRs from original (ABCD) and variant (EFGH) tasks

Figure 3 shows that controls and VM lesion patients both generated SCRs after receiving punishment that was either

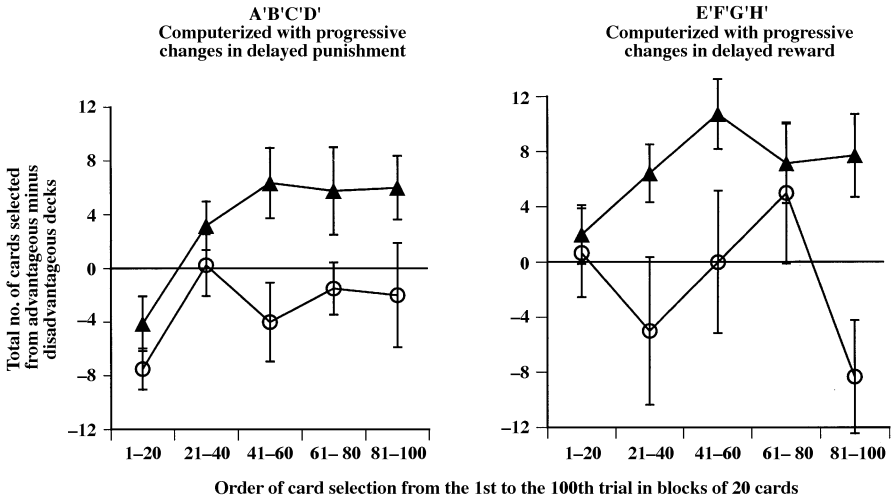

Fig. 4 Decision-making on computerized changes in delayed punishment (A′B′C′D′) and reward (E′F′G′H′). Despite introducing progressive increase in delayed punishment or progressive decrease in delayed reward, VM lesion patients failed to shift their behaviour away from these disadvantageous decks. Relative to normal controls (filled triangles), VM lesion patients (open circles) were impaired in their performance on the computer version of both the original (A′B′C′D′) and the variant (E′F′G′H′) gambling task. The figure shows net scores [(C′ + D′) – (A′ + B′) or (E′ + G′) – (F′ + H′)] of cards selected by each group across different blocks, expressed as mean ± SEM. Positive net scores reflect advantageous performance whereas negative net scores reflect disadvantageous performance.

delayed (in ABCD) or immediate (in EFGH). They also generated SCRs after receiving reward that was immediate (ABCD) or delayed (EFGH). Although the mean magnitudes of punishment and reward SCRs in VM lesion patients were somewhat lower than in controls, this difference was not significant. A 2 (group) × 2 (punishment versus reward) ANOVA on the SCRs from the original task did not yield any significant main effect or interaction. A similar ANOVA on the SCRs from the variant task also failed to reveal any significant main effect or interaction.

Behavioural performance on computer tasks (A′B′C′D′ and E′F′G′H′)

The data shown in Fig. 4 were graphed and analysed in the same way as those in Fig. 2. Figure 4 represents the net scores (total number of cards selected from advantageous minus disadvantageous decks) as a function of group and block from the computer tasks (A′B′C′D′ and E′F′G′H′).

The results from the computer tasks with progressive increase in delayed punishment (A′B′C′D′) or decrease in delayed reward (E′F′G′H′) in the disadvantageous decks mirrored those from the original (ABCD) and variant (EFGH) tasks. Normal controls shifted their preference gradually towards the good decks (C′ and D′) and away from the bad decks (A′ and B′). VM lesion patients failed to demonstrate a shift in behaviour. A 2 (group) × 5 (block) ANOVA on the net scores from the computer version of the original task revealed a significant main effect of group [$F(1,23) = 6.9$, $P < 0.015$], suggesting that controls made significantly more advantageous choices than VM lesion patients. This ANOVA also revealed a significant main effect of block [$F(4,92) = 3.5$, $P < 0.01$] but no interaction of group with block [$F(4,92) = 0.8$, $P > 0.1$].

Similar findings were obtained regarding the computer version of the variant task (E′F′G′H′). Normal controls increased their preference for the good decks (E′ and G′). By contrast, the VM lesion patients failed to demonstrate this shift away from the bad decks. A 2 (group) × 5 (block) ANOVA on the net scores from the computer version of the variant task revealed a significant main effect of group [$F(1,18) = 8.0$, $P < 0.01$), suggesting that VM lesion patients were impaired relative to controls in terms of making advantageous selections. This ANOVA did not reveal a significant main effect of block [$F(4,72) = 1.7$, $P > 0.1$] or an interaction of group with block [$F(4,72) = 2.1$, $P > 0.1$].

Punishment versus reward SCRs from computer tasks (A′B′C′D′ and E′F′G′H′)

The findings shown in Fig. 5 parallel those presented in Fig. 3. Figure 5 shows that controls and VM lesion patients both generated SCRs after receiving punishment that was either delayed (A′B′C′D′) or immediate (E′F′G′H′), or after receiving reward that was immediate (A′B′C′D′) or delayed (E′F′G′H′). The mean magnitude of punishment and reward SCRs in VM lesion patients were somewhat lower than those in controls in task A′B′C′D′; interestingly, the reverse was true for task E′F′G′H′. However, none of these differences was statistically significant. A 2 (group) × 2 (punishment versus reward) ANOVA on the SCRs from the computer version of the original task (A′B′C′D′) or the variant task (E′F′G′H′) did not yield any significant main effect or interaction.

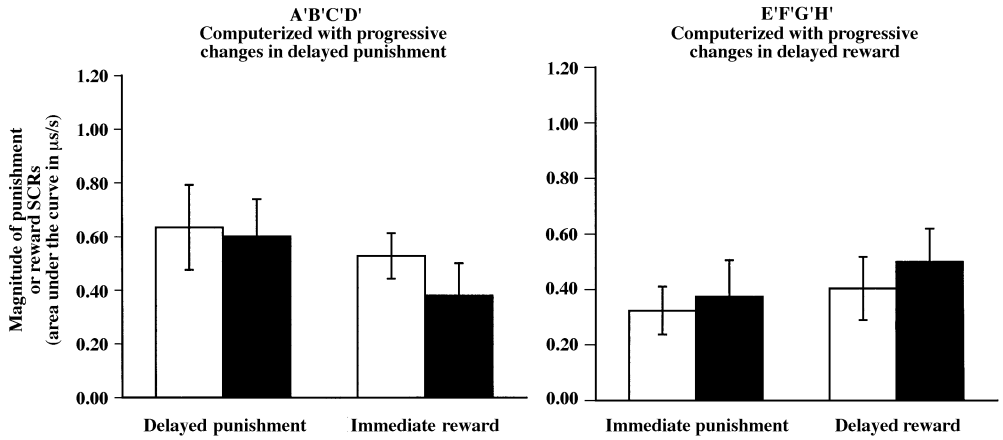

Fig. 5 Punishment (delayed or immediate) and reward (immediate or delayed) SCRs of controls (open squares) and patients with VM lesions (filled squares) measured during performance of the computer (A′B′C′D′ or E′F′G′H′) versions of the gambling task. SCRs are presented as the mean ± standard error of the meanof the average area under the curve of responses generated after selecting cards for which there was a penalty (punishment SCRs) or reward (reward SCRs) from all the decks. The magnitudes of punishment and reward SCRs from the different groups were not significantly different.

Discussion

As in previous studies (for review, see e.g. Bechara *et al*., 2000), VM lesion patients preferred decks with high immediate reward to those with smaller reward, although the decks with small reward were more advantageous in the long term. VM lesion patients also preferred decks that had low immediate punishment to those with higher immediate punishment, although the decks with higher immediate punishment were more advantageous in the long run. VM lesion patients generated SCRs after receiving reward or punishment that were not significantly different from those of controls. This pattern of results is inconsistent with hypersensitivity to reward as an explanation, for two reasons. First, the large delayed rewards were in decks E and G, but VM lesion patients were not lured by the high reward in these decks. Secondly, the SCRs of VM lesion patients after receiving reward were not significantly different from those of normal subjects. The results are also inconsistent with the explanation involving insensitivity to punishment, also for two reasons. First, the high immediate punishments were in decks E and G. The VM lesion patients were reluctant to choose these decks because of the large immediate penalties. Secondly, the SCRs of VM lesion patients after receiving punishment were not significantly different from those of normal controls. Thus, a parsimonious explanation of the results supports our first hypothesis, that VM lesion patients are insensitive to future consequences, whatever they may be.

Increasing the delayed punishment or decreasing the delayed reward in the disadvantageous decks of either the original or the variant version of the gambling task failed to shift the behaviour of VM lesion patients away from the disadvantageous decks. Despite the progressive increase in frequency or magnitude of delayed punishment (decks A′ and B′) or the progressive decline in frequency or magnitude of delayed reward (decks F′ and H′), the VM lesion patients failed to benefit from these manipulations, and thus failed to demonstrate a shift in behaviour. These results support our second hypothesis, that the decision-making impairment in VM lesion patients may not be ameliorated by increasing the severity of future consequences. Together, the results reinforce the notion that VM lesion patients are oblivious to the future and are guided predominantly by immediate prospects. This 'myopia for the future' persists in the face of increasing adverse consequences.

This interpretation must be discussed in the light of other possible explanations of the behaviour of patients with VM lesions. Our results show that these patients develop an initial preference for the disadvantageous decks (those with higher immediate reward or lower immediate punishment), and then fail to shift their initial preference no matter what manipulation is employed. Could this behaviour be interpreted as being impulsive? Impulsiveness is a poorly defined term, but it is often linked to dysfunction of the prefrontal cortex (Jones and Mishkin, 1972; Miller, 1992; Fuster, 1997; Barrash *et al*., 2000) and it usually means the lack of response inhibition. We distinguish between two types of impulsive behaviour: motor impulsiveness and cognitive impulsiveness. Motor impulsiveness is usually studied in animals under the umbrella of 'response inhibition'. In these paradigms, after a habit of responding to a stimulus that predicts a reward has been established there is a sudden requirement to inhibit the previously rewarded response. Go/no go tasks, delayed alternation and reversal learning are prime examples of paradigms that measure this type of behaviour (Mishkin, 1964; Diamond, 1990; Fuster, 1990; Stuss, 1992; Dias *et al*., 1996). There is evidence that some patients with orbitofrontal lesions do suffer from this type of motor impulsiveness (Rolls *et al*., 1994; Rolls, 1999, 2000). However, in humans it has been proposed that motor impulsiveness can have several forms (Evenden, 1999). These include (i) impulsive

preparation, which involves making a response before all the necessary information has been obtained; and (ii) impulsive execution, which involves quick action without thinking. These types of impulsive behaviour can be tested using a variety of procedures, including the Matching Familiar Figures Test, the Proteus Mazes and the Tower of London (Evenden, 1999). Our VM lesion patients did not suffer from this form of motor impulsiveness (S. W. Anderson, personal communication).

There is some debate as to whether perseveration is actually an indication of impulsivity (Evenden, 1999). However, the question is: can perseveration explain the behaviour of VM lesion patients? We note that frontal lobe damage, especially damage to the dorsolateral sector of the prefrontal cortex, is associated with impairments on the Wisconsin Card Sorting Task (WCST). Patients with such damage persist with the original classification of cards despite being told they are wrong, i.e. they fail to suppress a previously correct response. Analogous deficits associated with damage to the lateral prefrontal cortex (Brodmann area 9) have been reported in monkeys by means of attentional shift tasks that are presumably analogous to the WCST (Dias *et al*., 1996, 1997). The perseveration on the WCST is certainly a deficit in impulse control, and it may be more complex than the motor impulsiveness described earlier. Irrespective of its nature, neuropsychological studies have shown that perseveration as measured by the WCST does not predict the behaviour of VM lesion patients (Anderson *et al*., 1991).

The other type of impulsive behaviour is cognitive impulsiveness, which can be seen as akin to an inability to delay gratification, and which is more complex than the other forms of impulsive behaviours. The term 'cognitive impulsiveness' has been used previously in human studies (Barratt, 1994), and it may be analogous to the term 'impulsive outcome', which refers to a failure to delay gratification and evaluate the outcome of a planned action (Evenden, 1999). On the basis of previous studies, we believe that VM lesion patients with more anterior lesions that spare the basal forebrain do not have motor impulsiveness, although those with lesions involving the basal forebrain may have the defect (Bechara *et al*., 1998). The absence of motor impulsiveness is supported by evidence showing, first, that when observing the behaviour of VM lesion patients during their performance of the gambling task, one finds that these patients frequently switch decks after they receive punishment. They switch decks just like normal controls, a performance that does not indicate lack of inhibition of a previously rewarded response (Bechara *et al*., 1994). Secondly, most VM lesion patients are unimpaired on delay task procedures that are considered sensitive to deficits in response inhibition (Bechara *et al*., 1998). On the other hand, it is possible that VM lesion patients have cognitive impulsiveness. That is, when the patients are presented with a deck of cards with a large immediate reward but with delayed costs, the patients seek the reward. These VM lesion patients seem unable to delay the gratification of the reward for too long, as indicated by their tendency to return quickly and more often to the decks that yield high immediate reward but an even larger future loss. Although the construct of cognitive impulsiveness can account for some of the behavioural impairments associated with prefrontal cortex damage, there is a need to explain the nature of the mechanism that triggers the inhibition of the response. In other words, what is the nature of the mechanism that decides when to suppress, or not to suppress, a certain response, such as the seeking of a large immediate reward? Indeed, there are situations in which the immediate reward outweighs the delayed punishment, and the response should not be suppressed. We have argued that the nature of this mechanism is a somatic state, i.e. an emotional signal that helps bias the selection of an advantageous response from among an array of possible options (Bechara *et al*., 2000). Rolls has argued that this evaluation takes place in the orbitofrontal cortex, independently of any incoming signals from the body (Rolls, 1999).

Most VM lesion patients who participated in this study were re-tested on all versions of the gambling task, whereas control subjects were not. We did not re-test controls because they reached a ceiling level of performance when they were repeatedly tested on the gambling task (Bechara *et al*., 2000). VM lesion patients do not usually improve their performance (Bechara *et al*., 2000), but even if there was some subtle improvement, the impairment was still present despite the advantage conferred by multiple exposures to the task.

The experimental strategies used to characterize the decision-making deficit in neurological patients provide parallels and direct implications for our understanding of the nature of several psychiatric disorders, especially addiction and psychopathy. For instance, addicts are similar to VM lesion patients in that, when faced with a choice that brings some immediate reward (i.e. taking a drug), at the risk of incurring a loss of reputation, job, home and family, they choose the immediate reward and ignore the future consequences. Using the gambling task, studies have shown behavioural impairments in people who are dependent on cocaine (Grant *et al*., 1997), opiates (Petry *et al*., 1998) or alcohol (Mazas *et al*., 2000). When similar decision-making tasks were used (e.g. tasks with betting strategies), there were similar impairments, linking decision-making in VM lesion patients to that in amphetamine and opiate addicts (Rogers *et al*., 1999). Although the decision-making deficit in addicts may be behaviourally similar to that in VM lesion patients, the pathophysiology of the deficit could be different. For instance, several authors have discussed the notion that drug-seeking behaviour is due in part to the augmented incentive motivational qualities of the drug and associated cues (i.e. hypersensitivity to reward) resulting from an abnormally functioning amygdala system (Grant *et al*., 1999; Jentsch and Taylor, 1999). This increase in the incentive value of substance-related cues may be due to changes in the reward set point, which lead to vulnerability to relapse (Leshner and Koob, 1999), or to abnormal strengthening of stimulus–drug reward contingencies (Di Chiara *et al*., 1999;

Everitt *et al*., 1999). Anatomically, the orbital prefrontal cortex projects primarily to the medial edge of the ventral striatum and to the core of the nucleus accumbens (Haber *et al*., 1995). Efferent projections from the ventral striatum are represented topographically in the ventral pallidum and non-topographically in the substantia nigra (Haber *et al*., 1995). In turn, the dopaminergic neurones from the ventral tegmental area and substantia nigra can influence an array of cortical and subcortical structures, including the VM cortex, the amygdala and the nucleus accumbens (Haber *et al*., 1995). Also, there are direct anatomical links between the VM cortex and the amygdala (Amaral and Price, 1984; Van Hoesen, 1985). Because of the close links between the amygdala system, the VM cortex and decision-making (Damasio, 1994, 1995*a*, 1996; Bechara *et al*., 1999), a dysfunction in any part of this neural system could affect the VM cortex and decision-making. Characterization of the decision-making deficit in addicts would allow better understanding of the nature of their decision-making deficit and the dysfunctional neural systems underlying the decision-making deficit.

Another relevant example is that the personality profile of VM lesion patients bears some striking similarities to psychopathic (or sociopathic) personality, to such an extent that we have used the term 'acquired sociopathy' to describe the condition of patients with VM damage (Damasio *et al*., 1990; Anderson *et al*., 1999; Barrash *et al*., 2000). This notion is supported by studies addressing the possibility that the psychopathic behaviour seen in cases in which no neurological history has been identified may be linked to the abnormal operation of the VM cortex (Damasio, 2000; Raine *et al*., 2000). Behavioural studies have indicated that dysfunction of the VM cortex may occur in at least a subgroup of psychopaths, the low-anxious psychopaths (Schmitt *et al*., 1999; Mazas *et al*., 2000). However, decision-making deficits similar to those in VM lesion patients have been revealed in neurological patients with bilateral amygdala lesions. The underlying cause of the deficit was poor somatic responsiveness to punishment and reward (Bechara *et al*., 1999). A similar decision-making deficit has been associated with lesions in the right insular/somatosensory cortices (Bechara *et al*., 1997), but the nature of this deficit has not been characterized so far. Thus, abnormal processing of reward and punishment in neural systems besides the VM cortex could affect VM function and precipitate deficits in decision-making. Several studies have addressed the notion that psychopathic behaviour is associated with insensitivity to punishment (Arnett *et al*., 1993), while others have argued that it is more associated with hypersensitivity to reward (Scerbo *et al*., 1990; Fonseca and Yule, 1995). Other authors have taken the middle ground, suggesting that insensitivity to punishment in psychopaths is revealed mostly in the presence of conflicts with reward, i.e. under conditions involving combinations of reward and punishment (Newman *et al*., 1985, 1992). Given the apparent heterogeneity of the behavioural mechanisms underlying psychopathic behaviours, characterization of the decision-making deficit in each subgroup and contrasting the outcome with that from neurological patients could provide better understanding of the dysfunctional neural systems involved in psychopathic behaviour.

Changing the schedules of reward and punishment did not improve the behaviour of VM lesion patients, despite increases in the severity of future consequences. This is an important finding because it suggests that it may be difficult for VM lesion patients to benefit from rehabilitation procedures focusing only on changes in behavioural strategies. Therefore, we began to look for other strategies that may improve decision-making in VM lesion patients, including pharmacological strategies. It is possible that because VM lesion patients suffer from focal brain damage, it may prove difficult to overcome the lost function in the lesioned area, and ameliorate their deficit via behavioural or pharmacological means. On the other hand, patients with head injuries in which the prefrontal damage may not be so severe could benefit from such combined behavioural and pharmacological strategies. Most importantly, because in the psychiatric conditions discussed above there is usually no gross brain damage, therapeutic strategies may prove effective in helping to reverse the decision-making impairment associated with these conditions.

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