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The Role of Ventromedial Prefrontal Cortex in Decision Making: Judgment under Uncertainty or Judgment Per Se?

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Ventromedial prefrontal cortex (VMF) is thought to be important in human decision making, but studies to date have focused on decision making under conditions of uncertainty, including risky or ambiguous decisions. Other lines of evidence suggest that this area of the brain represents quite basic information about the relative "economic" value of options, predicting a role for this region in value-based decision making even in the absence of uncertainty. We tested this prediction in human subjects with VMF damage. Preference judgment is a simple form of value-based decision making under certainty. We asked whether VMF damage in humans would lead to inconsistent preference judgments in a simple pairwise choice task. Twenty-one participants with focal damage to the frontal lobes were compared with 19 age- and education-matched control subjects. Subjects with VMF damage were significantly more inconsistent in their preferences than controls, whereas those with frontal damage that spared the VMF performed normally. These results argue that VMF plays a necessary role in certain as well as uncertain decision making in humans.

Keywords: executive functions, frontal lobes, human, lesion orbitofrontal cortex, reward

Introduction

A role for ventromedial prefrontal cortex (VMF) in human decision making was first posited on the basis of clinical case reports: damage to this region can lead to striking (and relatively isolated) changes in personality and behavior marked by poor judgment and impulsive choices. Efforts to study the poor decision making of patients with VMF damage in the laboratory have used a variety of gambling tasks, thereby focusing the research on how such individuals deal with uncertainty (Bechara et al. 1997; Rogers et al. 1999). This and subsequent work has established that VMF damage leads to difficulties in choosing between options with uncertain outcomes, whether in the form of risk or ambiguity (Bechara et al. 1999; Manes et al. 2002; Sanfey et al. 2003; Camille et al. 2004; Fellows and Farah 2005; Hsu et al. 2005). In the words of Bechara and colleagues, such experiments are meant to "simulate real-life decision making in the way [they] factor uncertainty, rewards, and penalties" (Bechara et al. 1997).

A separate body of work has investigated the functions of this region in animal models. There is growing evidence that orbitofrontal cortex (OFC), an area within VMF, is involved in flexibly encoding the relative value of stimuli. Single-unit recordings in nonhuman primates have identified OFC neurons that carry information about the relative, context-specific "economic," or reward value of stimuli (Tremblay and Schultz 1999; Rolls 2000; Wallis and Miller 2003; Roesch and Olson 2004; Padoa-Schioppa and Assad 2006). Functional magnetic resonance imaging (fMRI) studies of normal human subjects have found activation patterns in ventromedial and OFC that are broadly compatible with the view that these regions represent information about relative value whether in preference paradigms (Zysset et al. 2002; Arana et al. 2003; Cunningham et al. 2003; Paulus and Frank 2003; McClure et al. 2004; Johnson et al. 2005; Volz et al. 2006), reinforcement learning, or choice tasks (reviewed in O'Doherty 2004; Montague et al. 2006).

However, both single-unit and fMRI studies have found that many other areas of the brain, including midbrain nuclei, striatum, parietal cortex, and dorsolateral prefrontal cortex also represent reward or value information (Schultz 2000; Schultz et al. 2000; O'Doherty 2004; Sugrue et al. 2005; O'Doherty et al. 2006). Such findings alone cannot speak to the question of whether any or all of these regions play a necessary role in processes that rely on value information, whether reinforcement learning or decision making. The latter claim requires converging evidence from loss-of-function studies.

There is compelling evidence from loss-of-function studies that VMF plays a necessary role in at least some forms of reinforcement learning: lesions of OFC in several species, including humans, have been shown to impair performance on tasks that require the flexible updating of stimulus-reinforcement associations, as in reversal learning or extinction (Jones and Mishkin 1972; Fellows and Farah 2003; Pears et al. 2003; Hornak et al. 2004; Izquierdo et al. 2004). Although these deficits could reflect a fundamental difficulty in determining the relative value of stimuli in a reinforcement learning context, they could equally reflect a difficulty inhibiting overlearned responses or impairment in shifting behavior in response to punishment amongst other possibilities (Roberts 2006). As such, these data do not provide definitive support for the claim that VMF plays a central role in representing value.

Studies of decision making in humans with VMF damage have the potential to test this claim directly. As reviewed in the opening paragraph, existing work is consistent with a necessary role for this area in human decision making, but leaves open whether this is specific to relatively complex decisions involving uncertainty, or reflects a general difficulty in assessing the relative value of options. If the latter hypothesis is true, then VMF damage should lead to impaired value-based decision making even under conditions of certainty.

Preference judgments are an example of decision making under conditions of certainty. Any deviation from routine or habit-bound behavior requires choosing between options, and any nonarbitrary choice requires determining and comparing the value of these options. There is some evidence from animal work that VMF is involved in this process: VMF ablation in macaques leads to abnormal food preferences. Such animals

show an increased willingness to eat meat (avoided by intact animals) and are more erratic in establishing relative preferences when offered novel foods (Baylis and Gaffan 1991). On the other hand, another study found that such damage did not affect relative preference for familiar foods (Izquierdo et al. 2004). One recent study of multiattribute decision making under certainty in humans found that VMF damage influenced the process of information acquisition prior to making a decision. However, the study was not designed to determine whether the resulting decision was abnormal (Fellows 2006).

The present study examined the effect of VMF damage on human decision making under certainty. Control groups included both age-matched normal subjects (control, CTL) and patients with frontal damage that spared the VMF (dorsal and/or lateral frontal, D/LF) (Fig. 1, Tables 1 and 2). We evaluated the consistency of the choices these individuals made in a simple preference judgment paradigm using a variety of stimuli. As in the experimental economics literature (Tversky 1969) and the animal literature (Baylis and Gaffan 1991; Izquierdo et al. 2004), the number of failures to maintain transitivity of preferences (i.e., erratic choices) constituted the dependent measure. A control task requiring pairwise perceptual judgments was also administered.

Materials and Methods

Subjects

Subjects with frontal lobe damage were identified through the patient databases of the Center for Cognitive Neuroscience at the University of Pennsylvania and McGill University, both databases of individuals with focal brain injury. Subjects were eligible for the study if they had damage principally involving the frontal lobes anterior to the precentral sulcus and of at least 6 months duration. Individual lesions were traced from the most recent clinical computerized tomography (in 8 cases) or magnetic resonance imaging (13 cases) onto the standard Montreal Neurological Institute brain by a neurologist with experience in image analysis, using MRIcro software. Subjects were divided into 2 groups, a priori: the VMF group if damage principally involved orbitofrontal and/or the ventral portion of the medial wall of the frontal lobe (following the boundaries laid out in Stuss and Levine 2002) and a group with frontal lobe damage that spared the VMF region (D/LF). The areas of the brain damaged in each patient group are shown as overlap images in Figure 1. As can be seen in the figure, the D/LF group was primarily composed of subjects with damage to the inferior and/or middle frontal gyri. In 4 cases, patients assigned to the D/LF group had damage that extended caudally to include portions of the insula and adjacent subcortical structures.

Lesions were secondary to rupture of anterior communicating artery aneurysms in 7 of 10 VMF subjects and to ischemic stroke in 3. Lesions in the D/LF group were due to ischemic or hemorrhagic stroke in 8 cases and to resection of low-grade astrocytoma in 3, 2 of whom also received local radiation therapy. VMF damage was bilateral in most cases, although often asymmetrically so. All D/LF subjects had unilateral damage (7 right, 4 left). Three VMF and 4 D/LF subjects were taking 1 or more psychoactive medications. These were most commonly anticonvulsants or antidepressants. One VMF subject was taking methylphenidate and an acetylcholinesterase inhibitor, and another was taking an acetylcholinesterase inhibitor alone, in both cases as off-label treatment for their injury-related cognitive complaints.

Age-matched control subjects were drawn from a pool of older normal volunteers recruited from the local Philadelphia community by advertisement. Normal controls (CTL; n = 19) had no history of neurological or psychiatric disease, closed head injury, or substance abuse and were not taking psychoactive medication. Controls passed a screening neurological examination and scored at least 28/30 on the Folstein mini-mental state examination. All participants provided written informed consent, in accordance with the principles set out in the Declaration of Helsinki and the stipulations of the local Institutional Review Boards.

Background information about the participants is provided in Table 1. Analysis of variance (ANOVA) revealed no significant difference between the groups with regard to age, education, IQ estimated by the American version of the national adult reading test, or score on the Beck depression inventory (all $P > 0.1$). Scores on a clinical apathy rating scale (which primarily evaluates the amotivational aspect of apathy [Starkstein et al. 1992]) did differ across the 3 groups ($F_{2,34} = 5.5$, $P < 0.01$). Post hoc pairwise comparisons with Neuman–Keuls tests indicated that controls had lower scores than either frontal group, although the frontal groups did not differ significantly from each other.

Subjects with frontal lobe damage were administered a short neuropsychological battery for screening purposes. These included standard tests of attention, verbal memory, and verbal fluency. We also included an experimental reversal learning task that we have previously found to be sensitive to VMF damage (Fellows and Farah 2003). This simple computerized task requires subjects to choose between 2 decks of cards, one of which results in a $50 play money win, the other in a $50 play money loss. Once subjects demonstrate learning of the initial contingencies, they are reversed without warning. If the new contingencies are successfully learned, additional reversals occur, for a total of 40 trials. Errors (choices from the currently punishing deck) during the reversal phase constitute the dependent measure. Screening data were incomplete for 2 subjects in each group. Selected results from this

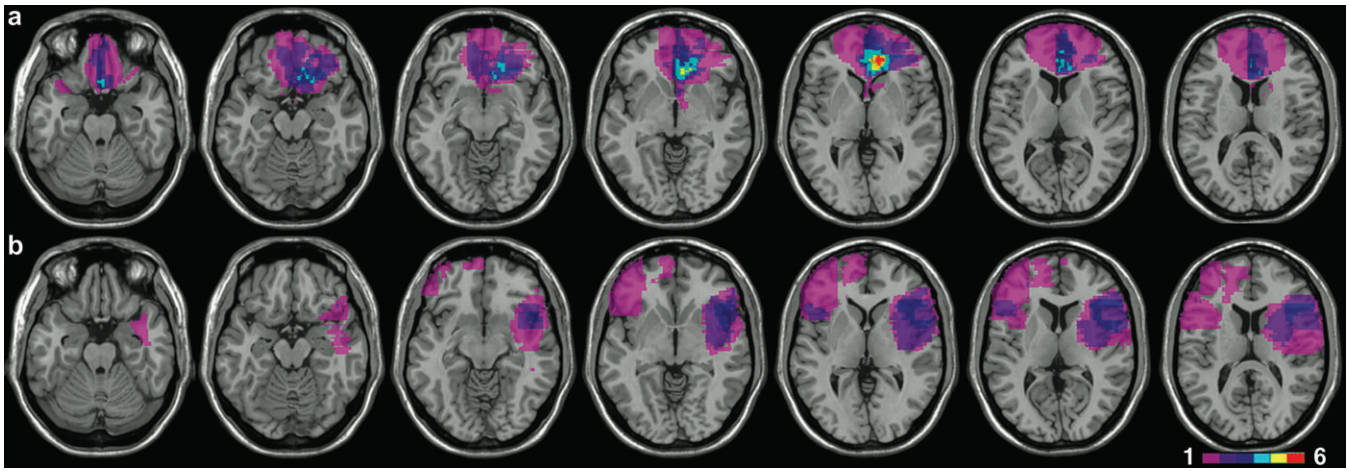

Figure 1. Location and overlap of brain lesions. Panel (*a*) shows the lesions of the 10 subjects with ventromedial frontal damage, and panel (*b*) those of the 11 D/LF subjects. Lesions are projected on the same 7 axial slices of the standard Montreal Neurological Institute brain, oriented according to radiological convention (i.e., left is right). Areas damaged in one subject are shown in pink; brighter shades denote the degree to which lesions involve the same structures in 2 or more individuals, as indicated in the legend.

Table 1
Background information [mean (standard deviation)]

Group	Age (year)	Education (year)	IQ estimate	Sex (M/F)	Beck depression inventory score	Apathy score	Lesion volume (cc)
CTL (n = 19)	58.7 (13.9)	14.3 (2.3)	123 (9)	8/11	6.8 (8.2)	8.7 (6.0)	—
D/LF (n = 11)	61.0 (9.6)	14.4 (3.5)	118 (13)	4/7	9.5 (4.5)	13.6 (2.1)[a]	28.1 (18.8)
VMF (n = 10)	58.4 (11.1)	12.8 (1.7)	114 (8)	6/4	10.9 (8.2)	14.8 (4.8)[a]	24.9 (35.1)

[a]Values that differ significantly from those of the CTL group. The 2 frontal groups did not differ significantly on any of these measures.

Table 2
Results of selected screening tasks [mean (standard deviation)]

Group	Digit span forward	Animal fluency (in 60 s)	F fluency (in 60 s)	Verbal recall (1 min delay; correct/5)	Errors in reversal learning
D/LF	4.0 (1.6)	15.4 (4.3)	9.9 (5.8)	4.3 (1.0)	6.1 (2.1)
VMF	4.8 (0.4)	17.2 (2.8)	10.8 (4.4)	3.7 (1.7)	8.9 (3.1)[a]

[a]Values that differ significantly between the 2 groups.

screening battery are provided in Table 2. The 2 patient groups differed significantly only in reversal learning performance.

Tasks

A novel preference judgment task was developed that required subjects to choose between stimuli, presented 2 at a time. Three categories of stimuli were used: food, famous people, and colors. Eight names of food (e.g., pizza slice, carrot sticks), 6 photographs of people (e.g., Britney Spears, Shaquille O'Neal), and 6 color swatches (e.g., pink, yellow) were printed on index cards. Each category was examined separately and in the same order for all participants. Pairs of stimuli were presented, and the subject was asked to indicate which of the 2 they preferred, that is, "which of these 2 would you prefer, which do you like better?" Subjects were asked to make each judgment in isolation, without reference to their previous choices. No mention was made of any requirement for the choices to be internally consistent. All possible pairs were presented within each category, for a total of 58 trials. For example, in the "food" category, subjects would choose between carrot sticks and watermelon on one trial and between a donut and a chocolate bar on the next, continuing until they had indicated their preference between all possible pairs of the 8 food items in the set. Overall completion time for the food and color categories was measured by means of a stopwatch. Each participant chose from the same foods and colors, but compared different sets of people. This was necessary to ensure that the people were familiar to each subject. For the "people" section of the task, subjects first sorted a larger set of photographs into those they recognized and those they did not. The experimenter than drew 6 cards at random from the "recognized" group and used these as the stimuli for that subject.

The order of preferences within each stimulus category was established by examining the choices of each subject. Erratic choices were choices that deviated from the overall pattern of preferences. For example, if a subject chose A over B and B over C, they were expected to choose A over C. If they instead chose C over A, this was counted as an erratic choice. The optimal preference ordering for each subject was the order that minimized this "erratic choice" score.

Two perceptual judgment tasks were included as control tasks. They followed the same form as the preference judgment tasks, with stimuli printed on index cards and presented in pairs. The line length task required subjects to judge which of 2 lines (in different orientations) was longer, and the "blueness" task required them to judge which of 2 color swatches (in various shades of purple) looked more blue. As in the preference judgment task, all possible pairs from a set of 8 lines of different lengths and of 6 shades of purple were presented. The number of errors constituted the dependent measure.

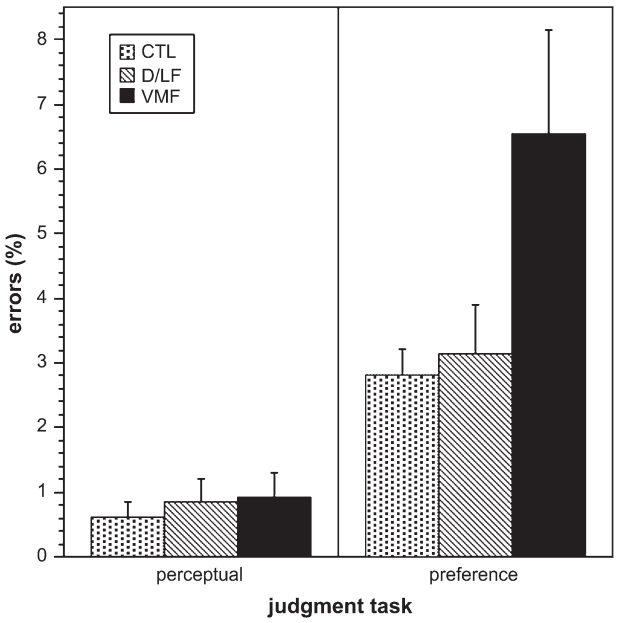

Figure 2. The mean percentage of errors in the perceptual judgment task (left panel) and of erratic choices in the preference judgment task (right panel) for all 3 groups of subjects. Error bars indicate standard errors of the mean.

Statistical Analysis

The main dependent measures were the total "erratic choice" score and the total perceptual error score, summed across categories. Repeated measures ANOVA was used to evaluate overall performance, and post hoc pairwise comparisons were made with Neuman–Keuls tests when the ANOVA indicated that significant differences were present. Significance was set at $P < 0.05$, 2 tailed.

Results

The areas of the brain damaged in each patient group are shown as overlap images in Figure 1. Mean lesion volumes were similar ($F_{1,19} = 0.07$, $P = 0.79$). Demographic information is shown in Table 1, and selected neuropsychological screening results are provided in Table 2. The performance of the 2 patient groups on tests of attention, recall, and verbal fluency did not differ. Subjects with VMF damage made more reversal learning errors than did the D/LF group ($F_{1,16} = 5.1$, $P < 0.05$).

As illustrated in Figure 2, there were significant differences between the groups in the consistency of their preference judgments, relative to their ability to make simple perceptual judgments. Repeated measures ANOVA revealed a main effect of task ($F_{1,37} = 48$, $P < 0.0001$) and an effect of lesion site (ANOVA, $F_{2,37} = 5.1$, $P = 0.01$). Crucially, there was a significant interaction between task and lesion site ($F_{2,37} = 4.5$, $P < 0.05$). Pairwise comparisons confirmed that subjects with VMF damage were significantly more inconsistent in their preference judgments than either the D/LF or CTL groups, whereas D/LF subjects did not differ from controls. There was no significant pairwise difference in performance of the perceptual judgment tasks.

The identical pattern of results was found when the data were analyzed using nonparametric methods. The Kruskal–Wallis test showed a significant difference amongst the 3 groups in preference task errors ($H = 7.0$, $P < 0.05$) but no difference in perceptual judgment errors ($H = 0.6$, $P = 0.7$). Further, this effect appears to be mediated specifically by VMF damage: the 2 frontal groups did not differ in total lesion volume (Table 1), and

there was no consistent relationship between total lesion volume and preference task performance in the frontal group as a whole (Spearman rho = 0.26, $P = 0.25$) or in the D/LF group alone (rho = 0.02, $P = 0.95$). In contrast, the extent of VMF damage strongly predicted performance (rho = 0.79, $P < 0.05$). Within the VMF group, the etiology of the damage did not appear to affect performance: the proportion of subjects with damage due to aneurysm rupture compared with ischemic stroke did not differ in the subgroup classified as impaired, compared with the subgroup with intact performance (Fisher's exact test, $P = 0.48$).

Three different categories of stimuli were used in the preference task, with the intent of examining the domain generality of any deficits in preference judgments. All subjects had slightly more difficulty with the people preference judgments than with food or color judgments, but there was no significant interaction between judgment category and lesion group, arguing that the preference judgment impairment seen in VMF subjects was a general effect across the categories studied (ANOVA, effect of group $F_{2,37} = 5.3$, $P < 0.01$, effect of category $F_{2,37} = 5.2$, $P < 0.01$; group × category $F_{4,74} = 1.8$, $P = 0.14$). However, the relatively small number of trials within each category raises the possibility that subtle domain-specific effects may not have been detectable by the task. Future work with more sensitive preference judgment tasks will be required to provide a more definitive answer to this question.

There was no significant difference between the 3 groups in completion time for either task, although the perceptual tasks were completed more quickly overall. ANOVA (log-transformed data): effect of task $F_{1,34} = 79$, $P < 0.0001$, effect of group $F_{2,34} = 2.8$, $P = 0.08$, and group × task $F_{2,34} = 1.1$, $P = 0.33$. The trend toward a group difference was driven by a tendency for the D/LF group to respond more slowly on both tasks. Mean preference task completion time (standard deviation) in seconds was CTL 182 (41), VMF 181 (30), and D/LF 242 (105).

Both frontal groups performed a simple reversal learning task as part of the background screening assessment (Table 2). The VMF group was impaired on this task, whereas the D/LF group performed as well as control subjects. One parsimonious account of the VMF group's impairment on both reversal learning and preference judgment tasks is that both rely on the same fundamental evaluative process. However, closer examination of the data argues against such an account: There was no relationship between preference task performance and reversal learning performance, either within the frontal group as a whole (rho = 0.07, $P = 0.79$) or within the VMF group (rho = –0.02, $P = 0.96$). This lack of correlation raises the possibility that the 2 processes are influenced by damage to distinct regions of VMF, rather than relying on a shared requirement for the tracking of relative value. We have previously shown that reversal learning performance is predicted by the degree of damage to posteromedial OFC (Fellows and Farah 2003). In contrast, existing functional imaging studies suggest that preference judgments lead to activation within the ventral wall of the medial prefrontal cortex (PFC), rather than OFC. To further examine this question, we classified subjects as being impaired (erratic choice score exceeding the 99.9% confidence interval for control subjects) or intact on the preference judgment task. Most of the VMF subjects we studied had damage to both OFC and the ventral portion of medial PFC 5 of the 7 subjects with such combined damage were impaired on the preference task. Two of 2 subjects with damage including ventral medial PFC but sparing OFC were also impaired. In contrast, the single subject with OFC damage but spared ventral medial PFC was not impaired. These results are consistent with the hypothesis that it is ventral medial PFC, rather than OFC, that is necessary for making consistent preference judgments, although clearly this possibility requires independent confirmation in a larger sample.

Discussion

The present work tested the prediction that VMF damage leads to a general deficit in decision making per se. Such a fundamental deficit should be apparent in decision making under certainty as well as in settings of risk or ambiguity and in tasks that do not require trial-by-trial learning. We examined the ability of human subjects with VMF damage to make consistent preference judgments and found that such subjects were more inconsistent in making simple preference judgments than age- and IQ-matched control subjects.

This deficit was a specific effect of VMF damage; VMF subjects performed worse than the group with frontal damage that spared VMF, who in turn were not different from the control group. Furthermore, it was particular to preference judgments; VMF subjects were comparable to those with D/LF damage on basic tests of attention, memory, and verbal fluency and performed superficially similar perceptual judgments without difficulty. The latter observation is tempered by the fact that perceptual task performance was near ceiling in all groups. A more stringent test of perceptual decision making abilities following PFC damage would be of interest both to confirm the current findings and to investigate the role of lateral PFC in perceptual judgment suggested by recent neuroimaging work (Heekeren et al. 2004, 2006).

Interestingly, the impairment in preference judgments observed in the present study was not associated with a slowing of response times. VMF subjects were not equivocating, but rather made inconsistent decisions as quickly as control subjects. This pattern seems consistent with the classic anecdotal descriptions of the "whimsical" or "capricious" choices made by patients with VMF damage (Harlow 1848/1999; Ackerly 1950/2000), although not with the strikingly slow, obsessive decision making of the VMF patient EVR (Eslinger and Damasio 1985).

Although many functional imaging experiments have implicated medial PFC and OFC in various aspects of reward processing, only a few have specifically examined preference judgments. These have used varied imaging methods, study designs, and stimuli and have not yielded consistent findings, so are difficult to interpret as a group. A position emission tomography study implicated medial OFC (Arana et al. 2003), whereas 5 fMRI studies have reported activations in various regions of medial PFC (Zysset et al. 2002; Paulus and Frank 2003; McClure et al. 2004; Turk et al. 2004; Johnson et al. 2005). Nonetheless, the present study complements the general conclusions of this work, supporting a critical role for VMF in preference judgment.

Why would simple decisions, of the type studied here, require a specialized brain system? The essence of decision making is the weighing of the value of options, and value is not a simple, fixed feature of a stimulus. It is relative and context dependent, as when the attractiveness of a piece of pie depends on whether it is up against a slice of chocolate cake or a piece of fruit. It depends on changing factors intrinsic to the organism, such as satiety, as

when the cake's appeal is diminished after a rich meal. Finally, the value of different options may lie along different, incommensurate dimensions. Take a walk and enjoy the fresh air and exercise, or pull up a chair and savor the taste of that chocolate cake?

Although context-sensitive choices like these would seem to require the online determination of relative value, we speculate that there are (at least) 2 routes to making a preference judgment: one that relies on weighing the subjective relative value of currently available options and a second that relies on autobiographical knowledge of a person's "preference history." The latter, possibly more commonly employed route would require recalling the fact that a particular option is a favorite, rather than relying on an ongoing, dynamic assessment of relative value. A recent fMRI study by McClure et al. (2004) is consistent with such a dichotomy. That study implicated VMF only in the condition that emphasized dynamic relative value judgment. We cannot say which kind of evaluation was being performed by the subjects in the present study, although we attempted to choose stimuli that would require dynamic, rather than fact-based evaluation. It seems likely that knowledge about favorites is still accessible after VMF damage, particularly if that knowledge was acquired prior to the injury. Whether the development of new "favorites" requires intact relative evaluation, and so would be affected following VMF damage, is an open question that would be interesting to pursue in future work.

The finding that VMF damage leads to impaired decision making under certainty has implications for interpreting the existing decision making literature and for understanding some of the problems these patients can experience in everyday life. Although VMF damage may lead to difficulties in performing tasks that involve risk or ambiguity, this impairment is not restricted to such complex decision making. Rather, it may be an expression of more fundamental aspects of stimulus evaluation, detectable in much simpler decision making. Patients with such damage may be prone to erratic real-life decisions, running the gamut from ordering in a restaurant to high-stakes financial decisions. Presumably, lapses in the latter setting are more troublesome to patients and their families alike, which may explain why they have received more attention in the clinical literature. However, all may relate to a fundamental deficit in making consistent evaluations of the available choices.

Notes

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