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Social and Emotional Decision-making Following Frontal Lobe Injury

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Abstract

Neuropsychological, psychophysiological and functional imaging research has begun to offer insights into the everyday difficulties in decision-making experienced by some patients with frontal lobe damage. It is widely accepted that the ventral prefrontal cortex plays a pivotal role in social and emotional decision-making. This article will review experimental findings using the Iowa Gambling Task and the Cambridge Gamble Task that explore the brain mechanisms of decision-making. Convergent evidence from the two tasks confirms the importance of ventral PFC, but also highlights the relevance of lesion laterality, lesion aetiology, and the contribution of other brain regions (including the dorsal prefrontal cortex and amygdala) to decision-making abilities. The extent to which disrupted decision-making can be separated from the broader domain of executive function is discussed.

Introduction

Damage to the prefrontal cortex (PFC) in humans is associated with everyday difficulties in social functioning, emotional experience and the organization of behavior. Formal neuropsychological testing in groups of patients with PFC damage has revealed deficits in domains including decision-making, planning, cognitive flexibility, verbal fluency and working memory (see Stuss and Levine, 2002 for review). Considerable research efforts have been directed towards differentiating these processes within PFC. In this article, we will focus primarily on decision-making and its association with the ventral region of PFC. The discussion of decision-making will be focussed on two laboratory tasks that have received particular attention: the Iowa Gambling Task (Bechara *et al*., 1994) and the Cambridge Gamble Task (Rogers *et al*., 1999a). Whilst we accept the contribution of other paradigms to this field (including delayed-reward tasks and other tests from the behavioral economics literature), this article will compare and contrast data from these two established tasks that have been used by multiple research laboratories. We will examine the relationship between ventral PFC and decision-making deficits in light of recent findings addressing neuropsychological *specificity*. Specificity applies firstly at the neuroanatomical level: to what extent are deficits in decision-making selectively associated with the ventral region distinct from other sectors of prefrontal cortex? Secondly, specificity also applies at the cognitive level: to what extent are deficits in decision-making dissociable from the wider domains of executive function?

Firstly, it is useful to describe our neuroanatomical terminology. The PFC is the cortical region in the frontal lobe anterior to the primary and association motor cortices. Within the PFC there are several functional zones, including the dorsolateral, dorsomedial and orbitofrontal cortices. In this review, we are interested in the ventral aspects of PFC, including the orbitofrontal cortex. The orbitofrontal cortex covers the ventral surface of the frontal lobe above the orbits—the bones that form the eye sockets—hence the term orbitofrontal. It is, itself, an anatomically heterogeneous structure, and receives direct inputs from the dorsomedial thalamus, temporal cortex, ventral tegmental area, olfactory system, and amygdala. Its outputs project to several brain regions, including the cingulate cortex, hippocampal formation, temporal cortex, lateral hypothalamus, and amygdala, as well as reciprocal connections with other regions of PFC (Rolls, 1999). Several anatomical terms have been used to refer to brain regions that include, or are adjacent to, the orbitofrontal cortex. Bechara refers to ventromedial PFC, constituting areas 25, lower 24 & 32, and the medial aspects of 10, 11 and 12 (Bechara, 2002). Where researchers refer to orbitofrontal damage (Rogers *et al.*, 1999a; Manes *et al*., 2002), this includes the lateral orbital surface (BA 11/47, 12) that is spared in the ventromedial cases. Further studies have highlighted the role of a ventrolateral region in the inferior frontal gyrus (BA 44, 45) (Aron *et al*., 2003), that is superior to the orbitofrontal cortex but may show some functional overlap. In this review, the term ventral PFC is used to subsume these more discrete areas of

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orbitofrontal cortex (BA 10, 11, 12, 13, 47), ventromedial PFC (25, medial 10, 11, 12, lower 24, 32) and the inferior frontal gyrus (BA 44, 45).

The neuropsychological assessment of decision-making

The Iowa Gambling Task and the Cambridge Gamble Task aim to characterize abnormalities in social and emotional decision-making using a standardized laboratory procedure. Both tasks are routinely administered in a computerized form and take 10–20 minutes to complete. The Iowa Gambling Task examines the subject's ability to learn the profile of wins and losses that characterize four decks of playing cards. Two ('risky') decks are associated with high immediate gains but large occasional losses that result in net loss over time. The other two ('safe') decks produce smaller wins but negligible losses such that there is net profit over repeated choosing. A series of studies from Bechara, Damasio and colleagues showed that patients with lesions to the ventromedial PFC persisted in selecting cards from the risky decks on this task, whereas healthy controls developed a preference towards the safe decks. The ventromedial PFC was proposed to regulate the retrieval of somatic states associated with the various decision-making alternatives (the somatic marker hypothesis, see below). A series of recent studies have investigated Iowa Gambling Task performance in neuropsychiatric groups including subjects with substance dependence (Bechara and Damasio, 2002), bipolar disorder (Clark *et al*., 2001) and psychopathy (Mitchell *et al*., 2002) in order to test hypotheses of ventromedial PFC dysfunction in these disorders (see Clark *et al*., 2004).

One weakness of the Iowa Gambling Task is that the reliance on learning and the development of preference can lead to difficulties in isolating the cause of task impairment. Case-control differences may emerge because of either a failure to learn the win-lose contingencies of the four decks or a straightforward preference for high risk. The Cambridge Gamble Task was developed in order to assess decision-making and risk-taking behavior outside of a learning context: relevant information is presented to subjects 'up front' and there is no need to learn or retrieve information over consecutive trials. On each trial, the subject is presented with an arrangement of red and blue boxes (there are 10 boxes in total), and must guess whether a token is hidden under a red or blue box. This is a relatively simple probabilistic judgment where the subject should choose the box color that is in the majority. After making this judgment, subjects are required to gamble some of their points on their confidence in this judgment. Healthy subjects moderate their betting according to the ratio of red:blue boxes (i.e., they place higher bets at a 9:1 ratio than a 6:4 ratio). Four studies to date have used the Cambridge Gamble Task in groups with preferential damage to the ventral PFC. Patients with subarachnoid haemorrhage of the anterior communicating artery (Mavaddat *et al*., 2000), frontal variant Fronto-Temporal Dementia (Rahman *et al*., 1999), and large prefrontal lesions including the orbitofrontal cortex (Manes *et al*., 2002) all showed significantly increased betting behavior, indicative of increased risk preference. In each of these studies, probabilistic judgment (the proportion of choices of the likely box color) was similar to matched controls, although the latency to make this judgment was generally slower in the patients. In the fourth study, patients with orbitofrontal cortex lesions (due to a range of aetiologies) showed decreased betting behavior in the presence of impaired (and slower) probabilistic judgment (Rogers *et al*., 1999a). It is likely that in cases with severely impaired decision-making, risk behavior may be reduced as a compensatory effect, but the consensus from these studies is that ventral PFC damage is associated with increased risk-taking compared to healthy controls. This is further supported by a recent study by Sanfey and colleagues (Sanfey *et al*., 2003) using a novel task where the subjects were presented with pairs of decisions that were matched for expected value (unlike the Iowa Gambling Task) but differed in the distribution of wins and losses. Control subjects and patients with dorsal prefrontal lesions displayed preference for the secure, low variance decks, whilst a subgroup of ventromedial PFC patients showed the reverse preference for high-variance, 'high-risk' decks.

Decision-making and somatic markers

Decision-making situations are characterized primarily by a series of different options from which a single response must be selected. Economic models of decision-making propose that following separation of the alternatives, a cost-benefit analysis is run on each option. The option with the superior cost-benefit ratio is selected for action. From a psychological perspective, a formal, rational method of calculating costs and benefits is rather inefficient. The procedure would be very time-consuming and given that both attention and working memory have capacity limitations, it would also be prone to error and distraction. It is increasingly accepted that humans do not adhere perfectly to utility models (see Hastie, 2001 for introduction), and that emotional and motivational factors have roles in guiding decision-making. The somatic marker hypothesis proposed that during decision-making, emotional and visceral representations associated with an option (from prior experience) are re-activated to bias decision-making covertly (Damasio, 1994). Options previously associated with reward are highlighted, and those associated with negative outcomes are suppressed. This process reduces the number of available options and reduces deliberation time. A rational analysis could then be applied to the restricted range of alternatives, or in more trivial scenarios, analysis of costs and benefits could be bypassed altogether.

The ventromedial PFC was proposed to mediate this retrieval of somatic markers during decision-making (Damasio, 1994). By recording autonomic responses during performance of the Iowa Gambling Task, Bechara *et al.* (1996) gained further insight into the somatic activation during decision-making. Over the course of the task, healthy

subjects gradually develop 'anticipatory' skin conductance responses (SCRs) in the 5 second period prior to making card choices. These responses are greater before decisions to the risky decks. Patients with ventromedial PFC lesions do not show anticipatory SCRs prior to their decisions (Bechara *et al*., 1996) but show normal autonomic responses to reward and punishment ('appraisal' SCRs). This failure to develop anticipatory responses to risky decks presumably relates to these patients' persistent selection from these decks. One explanation of the anticipatory SCRs is that they reflect accumulating awareness of the long-term negative consequences of the risky decks (Bechara *et al*., 1996) – that the risky choice might incur a large penalty. An alternative explanation is that the anticipatory responses are related to the higher immediate short-term benefits of the risky decks ($100 versus $50) (Tomb *et al*., 2002)—that the risky choice will probably produce a large reward. In a variant task where the safe decks produced greater magnitude wins and losses than the risky decks, healthy subjects showed relatively greater anticipatory SCRs to the safe decks, even though this was the advantageous strategy (Tomb *et al*., 2002). Tomb *et al*. (2002) conclude that the anticipatory SCR effect is unrelated to any long-term somatic marker mechanism. However, this account does not readily explain deficient performance in ventromedial PFC patients. If these patients fail to develop an anticipatory response to the decks with immediate short-term benefits, why do they prefer these decks throughout the task? The variant task overlooks the defining feature of the original Iowa Gambling Task: the immediate short-term rewards are in conflict with the advantageous long-term strategy. In the variant task, immediate and long-term benefits point to the same decks, and so the anticipatory effect observed in this condition may reflect a positive somatic signal. Overall, studies using autonomic measurement have been unable to resolve whether ventromedial PFC patients are impaired at the Iowa Gambling Task because they fail to process some component of the high-risk decks, or whether they have a fully-realised bias towards high-risk behavior.

Recent studies indicate that the appraisal SCRs are also associated with decision-making performance on the Iowa Gambling Task. Lesion evidence indicates that the amygdala may play a dissociable role from ventromedial PFC in the affective processing of decision outcomes. Patients with bilateral damage to amygdala show behavioral impairments on the Iowa Gambling Task, and show blunted autonomic responses during *both* the anticipatory and appraisal phases (Bechara *et al*., 1999). The appraisal responses may also contribute to ongoing decision-making: healthy subjects with low appraisal SCRs to the risky decks developed a less-pronounced preference for the safe decks than those with high appraisal SCRs to the risky decks (Suzuki *et al*., 2003). Patients with Huntington's disease, who are behaviorally impaired on the task, also show reduced appraisal SCRs following risky decisions and in response to loss (Campbell *et al*., 2004). Huntington's disease is characterized by selective pathology in the basal ganglia, which is likely to interact with the PFC and amygdala in the control of decision-making, as with other executive domains.

Neuroanatomical considerations

Despite the burgeoning use of decision-making tasks as cognitive 'assays' of ventral PFC function, the association between decision-making and ventral PFC remains based upon a handful of studies in small series of patients. In the 9 patients described in Bechara *et al*. (1998), it is clear from the MRI data that the lesions overlapped in the ventromedial PFC, but that in individual cases, damage extended into dorsomedial and lateral PFC, the temporal poles and the basal forebrain. Similarly, in the study by Rogers *et al*. (1999a) comparing a group of orbitofrontal lesions with a group of dorsolateral/dorsomedial lesions, there was evidence in several of the ventral patients that damage extended into the dorsal sector. Primarily, highly focal lesions to the ventral PFC are very rare, and collaborations between research groups must be fostered in order to test cases with specific pathology.

Lesion aetiology is a key consideration in reviewing lesion studies. Typical aetiologies in the frontal literature are tumor (usually resected), infarct, aneurysm, traumatic brain injury (TBI), penetrating head injury, and surgery for intractable epilepsy. Each of these has unique neuropathological considerations. Epilepsy and slowly developing tumors may be associated with abnormal brain development and/or functional reorganization in the years prior to testing. Ruptured aneurysms of the anterior communicating artery are a frequent cause of medial prefrontal damage, including bilateral damage. However, these aneurysms are frequently associated with additional damage to the basal forebrain, which is also supplied by this artery. There is limited discussion of lesion aetiology in the Iowa ventromedial cases, but at least some of these patients had ruptured aneurysms with damage extending into the basal forebrain (Bechara *et al*., 1998).

TBI is another common aetiology in bilateral cases. During TBI, powerful inertial forces can produce microscopic lesions (diffuse axonal injury) scattered throughout the brain, that often cannot be seen on CT and MRI scans (Meythaler *et al*., 2001). Since diagnosis is often by autopsy only, diffuse axonal injury is typically overlooked when there is evidence of a mass lesion in the brain. TBI assessment is further complicated by 'contrecoup' damage, where inertial forces convey damage to the brain opposite to the site of impact (and frequently to the frontal basal region). We have observed that patients with TBI without an obvious lesion in the frontal lobes on structural images, exhibit decision-making impairments consistent with frontal lobe injury, suggesting that the neuropathological complications of TBI per se can produce this profile (Torralva and Manes, unpub.#bs).

Laterality in decision-making

A further characteristic of the Iowa ventromedial PFC patients is that the original cases all had bilateral lesions.

Subsequent research has begun to investigate the effects of unilateral frontal lesions on decision-making. In a small series of patients with unilateral damage to the ventromedial PFC, (Tranel *et al*., 2002) showed that right-sided damage (n=4) was associated with impairment on the Iowa Gambling Task of a similar size to the effect seen in bilateral cases. This contrasted with intact task performance in 3 left-sided cases. In this study, disruptions of emotional and social functioning post-lesion were also only apparent in the right-sided cases.

Our own data in cases with unilateral focal lesions within the frontal lobes showed that a small group of patients with discrete lesions to left orbitofrontal cortex were not impaired on either the Iowa Gambling Task or the Cambridge Gamble Task, whereas a second group with large right-sided lesions including the ventral PFC were dramatically impaired on both measures (Manes *et al*., 2002). We have subsequently extended this case series to further separate the roles of lesion laterality and lesion size in decision-making (Clark *et al*., 2003). On the Iowa Gambling Task, the right frontal group (n=21) maintained a preference for the risky card decks throughout the task, and the extent of this deficit was correlated with the size of the lesion. Using a region of interest approach developed by Aron *et al*. (2003), the Iowa Gambling Task deficit in the right frontal group correlated with the volume of damage to the lateral PFC. The left frontal group (n=20) performed significantly better than the right frontals, showing only a subtle attenuation of the control profile. Performance in the left frontals was not associated with total lesion volume or any of the regional indices. The consensus across the studies in unilateral cases is that impairments on the Iowa Gambling Task are predominantly associated with right-sided damage. The cases in the Clark *et al*. (2003) study had damage predominantly affecting the dorsal and lateral PFC, and relatively little damage to the ventral PFC. On the Cambridge Gamble Task, there was limited evidence of impairment (e.g., increased betting) in these frontal cases, in contrast to previous studies in groups with ventral PFC pathology (Rahman *et al*., 1999; Mavaddat *et al*., 2000). We predict that the Cambridge Gamble Task is more selectively sensitive to ventral PFC damage than the Iowa Gambling Task, because of the negligible demands for learning and working memory in the Cambridge Gamble Task. In ongoing research, we are examining patients with focal (right-sided) lesions to ventral PFC to test this hypothesis.

Functional imaging of decision-making

Given the abundant difficulties with studying the effects of focal ventral PFC lesions in humans, functional imaging offers a valuable convergent methodology for testing hypotheses generated from neuropsychological data. The Iowa Gambling Task was adapted for PET imaging by Ernst and colleagues (2002). In the active task condition, subjects selected from the four card decks with the tracer injection timed to coincide approximately with choices 20–40. In a control condition, the subject selected cards from four decks (that were matched for wins and losses) in a specified order (A B C D A B C D…). The subtraction of the control from task condition therefore controlled for the sensorimotor aspects of the task, and isolated the volitional aspect of decision-making as well as the experience of outcome contingent upon the decision. This contrast revealed a distributed network of prefrontal and posterior cortical areas, including orbitofrontal cortex, anterior cingulate/medial PFC and dorsolateral PFC. These responses were lateralised mainly to the right hemisphere, in accordance with the lesion data discussed above. In a subsequent study using the same imaging protocol, cocaine users (who are reliably impaired at the Iowa Gambling Task) showed increased activation in the right orbitofrontal cortex and decreased activation in the right dorsolateral PFC (Bolla *et al*., 2003). In both studies, when task performance was correlated against regional cerebral blood flow, more discrete responses in right ventrolateral PFC (Ernst *et al*., 2003) and right orbitofrontal cortex (Bolla *et al*., 2003) were revealed. The interpretation of these data is unclear: on the one hand, they confirm that performance on the Iowa Gambling Task is particularly associated to a response in (right) ventral PFC. On the other hand, the distributed frontal and posterior response to the task against the control condition raises further questions about the anatomical specificity of Iowa Gambling Task deficits in neuropsychological studies.

The Cambridge Gamble Task was adapted for PET imaging by Rogers *et al*., (1999b), where the probabilistic decision and gamble stages were combined so that the subject could select the less likely option combined with a high-risk gamble, or the more likely option combined with a low-risk gamble. Thus, each decision represented a conflict between reward, punishment and uncertainty. In a sensorimotor control condition, the gambles were removed and the token was revealed at the start of each trial; subjects made a manual response to a color change on the screen. The contrast of the two conditions revealed a right-lateralized response in three distinct subregions of ventral PFC: medial (BA 11), lateral anterior (BA 10/11) and posterior (BA 47). There were no other responses in frontal cortex in this contrast. This supports an interpretation that by removing the learning and working memory demands in decision-making, the Cambridge Gamble Task may have superior anatomical sensitivity compared to the Iowa Gambling Task.

There is increasing neuroimaging evidence to suggest that within ventral PFC, the processing of reward, punishment and certainty may be anatomically dissociable (e.g., Elliott *et al*., 1999; O'Doherty *et al*., 2001). Using PET, for example, Arana *et al*. (2003) showed that the conflict between reward alone is sufficient to activate the medial orbitofrontal cortex. In this study, subjects were presented with restaurant menus constructed from individual food preference ratings. Medial orbitofrontal cortex and amygdala were activated simply by viewing high incentive menus compared to low incentive menus, but medial orbitofrontal cortex was selectively recruited when subjects had to choose which of two menus they would prefer. This is consistent with the dissociable

roles of the amygdala and medial orbitofrontal cortex in affective processing and decision-making suggested by the lesion study of Bechara *et al*. (1999). In brief, functional imaging studies support the notion that orbitofrontal cortex is concerned with resolving conflict between rewards, punishments and uncertainty. Adapted versions of the Iowa Gambling Task and Cambridge Gamble Task both activate this region, but with relatively greater specificity for the Cambridge Gamble Task. Lesions to the orbitofrontal cortex could slow down decision-making in a range of scenarios (Manes *et al*., 2002), but could alternatively create biases in decision-making towards particular types of information, for example, high reward irrespective of punishment, or immediate small rewards over larger delayed rewards.

Decision-making and executive functions

Executive function refers to a broad collection of cognitive processes including planning, inhibitory control, strategy development, cognitive flexibility and working memory. Frontal 'dysexecutive' syndrome is associated with damage to the more dorsal / dorsolateral aspects of PFC and has been shown in numerous case studies to dissociate from social and emotional deficits and the profile of 'acquired sociopathy' following damage to the ventral aspects of PFC (Malloy *et al*., 1993; Saint-Cyr *et al*., 2002). The relationship between executive functions and decision-making remains less clear. Executive processes such as working memory and inhibitory control may contribute indirectly to performance on decision-making *tasks*, or alternatively, may share resources directly with the decision-making process. For example, the Iowa Gambling Task places some demands on working memory in order to hold accumulating knowledge of the 4 decks across trials. Thus, it is plausible that working memory deficits may confound Iowa Gambling Task deficits. However, it is also possible that working memory is an integral part of any decision-making mechanism, in order to hold online the various options available for action.

The issue of task independence can also be addressed in healthy subjects using dual-task methodology. Hinson *et al*. (2002) assessed Iowa Gambling Task performance whilst subjects performed working memory tasks, such as random number generation, between trials. With increased working memory load, there was attenuated preference for the safe decks, and blunted acquisition of anticipatory SCRs. It was concluded that working memory load interfered with the development of somatic markers, consistent with a degree of interaction between ventral and dorsal PFC in optimal decision-making. Bechara et al. (1998) investigated the independence of the Iowa Gambling Task and working memory, in patients with lesions in the ventromedial (VM) PFC (n=9) and the dorsolateral/ dorsomedial (DL/M) PFC (n=10). There was some evidence for a double dissociation: a subgroup of the VM patients with more anterior lesions were impaired on the Iowa Gambling Task but intact on working memory measures, whilst a subgroup of the DL/M group with right-sided damage displayed the reverse profile. Other subgroups displayed the remaining two possibilities: left DL/M patients were unimpaired in either domain, whilst posterior VM patients were impaired in both. This study demonstrated that a decision-making deficit could exist in the presence of intact working memory—but what about the contribution of other executive processes in that subgroup, like planning and inhibitory control? In the study by Manes et al. (2002), patients were administered a thorough neuropsychological assessment in addition to the decision-making tasks. In that study, patients with discrete dorsolateral PFC lesions (n=4), discrete dorsomedial PFC lesions (n=5), and large frontal lesions (n=5) all preferred the risky decks overall on the Iowa Gambling Task. These three groups were intact on a measure of working memory *span*, which only requires the rehearsal of information. All three groups were impaired on a measure of planning, the Tower of London task, which requires strategic choice between several alternative response sequences. These alternatives must be held temporarily in working memory, whilst other (subtly different) alternatives are considered. A similar process occurs during the Iowa Gambling Task, where competing profiles for the four card decks must develop in working memory and guide ongoing card selection. The DL and large lesion groups were also impaired on a self-ordered spatial working memory task which requires the manipulation of working memory and strategy implementation. These executive tasks differ from the Iowa Gambling Task in the respect that there is strategic choice towards a single goal (the correct solution is clearly defined), whereas in the Iowa Gambling Task, all options might generate a reward outcome, which must inform selection on subsequent trials. Critically, these executive processes are minimized in the Cambridge Gamble Task, because the information required to make the decision is presented explicitly on each trial. In the Manes *et al*. (2002) study, only the large lesion group (with damage including the ventral PFC) showed increased risk-taking relative to controls; the DL and DM groups were unaffected. There are clearly several potential mechanisms by which 'dorsal' executive processes could contribute to successful decision-making. It remains unclear from these few studies whether 'dorsal' executive processes are actually critical to successful decision-making, or whether the associations are attributable to low task purity.

Conclusions

Patients with frontal lobe injuries affecting the ventral aspect of PFC commonly present with everyday difficulties in making decisions about finances, relationships and employment, and these behavioral changes can be quantified using neuropsychological measures. We have reviewed recent research using two tasks, the Iowa Gambling Task and the Cambridge Gamble Task. Both tasks detect a profile of risky decision-making in cases with ventral PFC pathology. Lesion and neuroimaging studies using the Iowa Gambling Task indicate the contribution of more widespread frontal regions

including dorsolateral and medial PFC (Ernst *et al*., 2002; Manes *et al*., 2002), and Iowa Gambling Task performance can covary with executive demands (Hinson *et al*., 2002). The reduced demand for learning and working memory in the Cambridge Gamble Task appears to give rise to a more selective association with ventral PFC integrity. However, ventral PFC clearly does not regulate decision-making in isolation. Interactions with the amygdala have been emphasised (Bechara *et al*., 1999; Arana *et al*., 2003), and as well as interconnected regions of the basal ganglia (Stout *et al*., 2001; Saint-Cyr *et al*., 2002). These findings preclude the use of decision-making tasks as pure assays of ventral PFC dysfunction in neuropsychiatric disorders. The degree to which decision-making can be segregated conceptually from the broader domain of executive function remains unclear. The main obstacle to resolving this question lies with the tasks themselves. It is very difficult to design a decision-making assessment that does not involve an element of executive function in the form of working memory, cognitive flexibility, or inhibition of a tempting option. With this caveat, the double dissociation remains the cornerstone in neuropsychology for demonstrating process independence. Further investigation of patients with discrete lesions in the ventral PFC represents the most promising way to resolve these issues.

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