Advances in understanding ventromedial prefrontal function : The accountant joins the executive

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CME

Advances in understanding ventromedial prefrontal function

The accountant joins the executive

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Abstract—Studies of the brain basis of decision-making and economic behavior are providing a new perspective on the organization and functions of human prefrontal cortex. This line of inquiry has focused particularly on the ventral and medial portions of prefrontal cortex, arguably the most enigmatic regions of the "enigmatic frontal lobes." This review highlights recent advances in the cognitive neuroscience of decision making and neuroeconomics and discusses how these findings can inform clinical thinking about frontal lobe dysfunction.

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Orbitofrontal (OFC) and medial prefrontal cortex (PFC) are common sites of damage due to aneurysm rupture, traumatic brain injury, or tumor and are preferentially affected in frontotemporal dementia.[1] The potentially devastating effects of such damage on behavior have been recognized clinically as far back as Harlow's famous description of Phineas Gage.[2] However, a clear understanding of the functions of this area of the brain has proved elusive. In the last few years, experimental methods and heuristic frameworks borrowed from, on the one hand, economics and decision science[3] and, on the other, studies of reinforcement learning in animals,[4] have begun to provide more specific descriptions of the processes subserved by this region of the frontal lobes.[5]

The ventromedial frontal lobes encode value. Studies of patients with damage to the ventromedial frontal lobes (VMFs; figure) have made an important contribution to recent advances in this area.[6] Converging evidence suggests that VMF is involved in representing the current relative value of stimuli: what a potential choice is "worth" to the chooser at that moment compared with other available choices.[7] This value information guides decision making, both by determining the goals toward which behavior is directed and by providing a context from which to judge decision outcomes. Thus, VMF can be seen as serving an evaluative or 'accounting' role in support of the execution of complex behavior.[8] This is sophisticated accounting, incorporating information about factors such as risk, delay, and ambiguity. It also seems to be more than a numbers game: Value assessment may be reflected in (or affected by) emotional and autonomic responses to potential choices, biased by the outcomes of previous decisions, and even influenced by the outcome of "the road not taken."

Viewing the behavioral difficulties of patients with VMF damage in the light of decision-making and economic behavior has proved to be fruitful from both theoretical and practical perspectives. This work provides new ways of conceptualizing certain forms of "frontal" behavior and new tools for measuring these behaviors in both the laboratory and the clinic.[9,10] This review will highlight some of the recent cognitive neuroscience work in this area and discuss the potential clinical relevance of these findings.

An accountant with good connections. VMF is well positioned to serve as an interface between emotional–motivational information (such as reward or punishment) and information about the environment. The orbitofrontal portion of this area receives sensory input from taste, olfaction, and the ventral visual stream.[7,11,12] It is interconnected with limbic structures such as the amygdala and hypothalamus, and, in contrast to dorsolateral PFC, is an important

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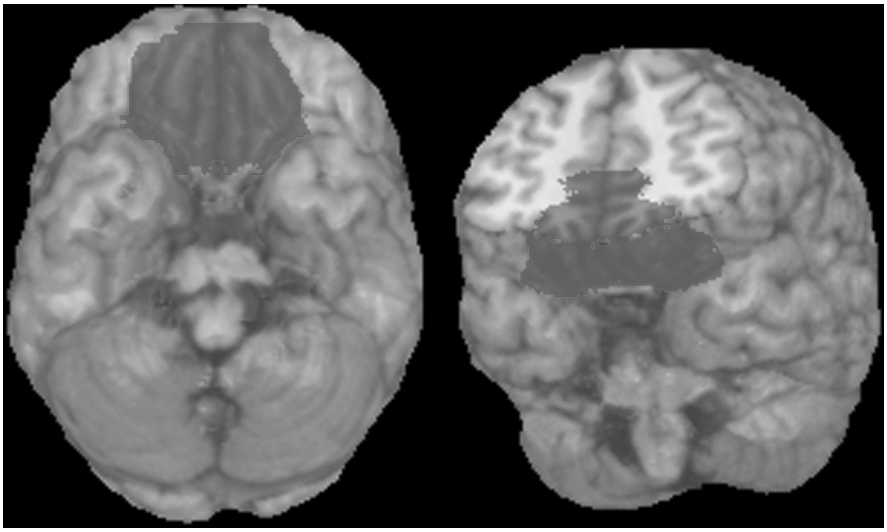

Figure. The region within the frontal lobe designated as ventromedial frontal (VMF) is shown in dark gray on a three-dimensional reconstruction of the standard Montreal Neurological Institute brain. This region encompasses the medial portion of orbitofrontal cortex (shown in the view of the base of the brain in the left panel) and the adjacent ventral part of the medial wall of prefrontal cortex (visible in coronal section through the frontal lobes in the right panel). Three-dimensional volume renderings were done using MRIcro software (www.sph.sc.edu/comd/rorden/mricro.html).

source of corticostriatal input to nucleus accumbens, which in turn modulates the activity of midbrain dopaminergic neurons and is itself an important node in the network that processes reinforcement.[13] OFC is thus in a position to link a stimulus to its "economic" or motivational value. In turn, OFC is highly interconnected with the adjacent ventral areas of medial PFC and directly or indirectly with other areas of PFC.[12] These corticostriatal and corticocortical pathways provide routes by which the evaluative information represented in VMF might influence both simple and higher-order goal-oriented behavior.

VMF damage affects value-based learning. There has long been a gap between the vivid clinical descriptions of the effects of VMF damage and the ability to successfully measure these changes in the laboratory. Recent progress in closing this gap was triggered, in part, by the observation that patients with VMF damage could show marked impairments in decision making[14] and by the development of an experimental task to measure these decision-making deficits in the laboratory.[9] Now known as the Iowa gambling task, this card game requires participants to select between decks with high initial pay-offs, but eventual higher losses, and decks with small pay-offs, but overall smaller losses. Most healthy subjects learn to prefer the safer decks, but those with VMF damage persist in choosing from the disadvantageous decks despite mounting losses. The Iowa gambling task had its conceptual origins in studies of reinforcement learning in animals, but it prompted investigators to begin asking larger questions about how economic information important to decision making such as expectancies, risk, and uncertainty might be represented in the brain.

These questions are being increasingly addressed using theoretical frameworks and experimental tasks first developed in behavioral economics and decision psychology—work that will be reviewed below. Ironically, the Iowa gambling task does not fit easily within these frameworks.[15] Instead, patients with VMF damage may be impaired on this task because of a more basic difficulty in adjusting behavior in response to feedback. Studies of simple forms of reinforcement learning in both rats and nonhuman primates have established that OFC lesions lead to a particular form of perseveration: Lesioned animals continue to choose a previously rewarded stimulus after it ceases to be rewarded (extinction) or after pre-existing reward and punishment associations are switched (reversal learning).[16-19] Humans with VMF damage also have difficulty with these forms of value- or feedback-driven learning.[20-22] The Iowa gambling task includes a requirement for reversal learning, in that the ultimately disadvantageous decks initially hold the highest rewards. When this reversal requirement is eliminated, patients with VMF damage perform as well as healthy controls.[23]

Thus, VMF damage impairs the adjustment of behavior when the pay-offs attached to choices are changing. The Iowa gambling task is one example of such a situation. It has been speculated that similar perseverative "approach" behaviors despite negative feedback may have a parallel in some of the intrusive, socially inappropriate behavior such patients can exhibit.[24] The degree of impairment on laboratory reversal learning tasks is correlated with overall functional impairment in everyday life[20] and with a measure of social/emotional behavioral change post injury,[25] providing indirect support for this possibility.

VMF damage affects value-based decision making. It remains unclear whether the reversal learning impairment observed following VMF damage reflects a specific difficulty in flexibly shifting behavior in response to feedback in general, negative feedback in particular, or is simply one example of a more general deficit in determining the value of potential choices. Converging evidence from nonhuman primate neurophysiology and functional imaging

studies in normal human subjects lends support to the more general hypothesis that VMF represents the current value of choices.[5,8] Single-unit recordings have shown that macaque OFC neurons respond to the expectation of reward and to reward delivery. Further, these responses discriminate between different kinds of reward, responding selectively to the most preferred reward among those available in a given session.[26,27] Patterns of activity in human OFC consistent with this hypothesis have been observed in several functional imaging studies.[7]

Economic (or reward) value is, in many ways, a curious property of a stimulus: It is not a fixed feature, but rather a highly context-sensitive construct that depends on factors intrinsic to the organism (such as satiety) and on external factors (such as the values of other, currently available options). In many real-life situations, value cannot be determined with absolute certainty. Value estimates can be adjusted to account for uncertainty: known uncertainty (as in the likelihood of a coin toss coming up "heads," formally termed "risk") and unknown uncertainty (where the probability of a given outcome cannot be precisely determined: "ambiguity"). Economists and psychologists have been particularly interested in these forms of decision making under uncertainty, because actual choice behavior demonstrates that even the value of money is not a fixed property. For example, given a choice between a sure $10 or a one-in-four chance to win $100, many subjects will choose the sure thing, despite the fact that the expected value of the gamble ($100 \times 0.25 = 25$) is much higher. People therefore choose "irrationally," in effect assigning a cost to risk. This cost is also mutable and context sensitive: For example, individuals are typically risk averse in settings where they stand to gain, but risk seeking when avoiding losses.[28] Similar phenomena can be observed in decision making under conditions of ambiguity.[29]

Risky choices. Functional neuroimaging studies in healthy human subjects have shown that whereas activity in nucleus accumbens varies with the magnitude of anticipated monetary reward,[30,31] activity in medial PFC reflects both the magnitude and the probability of an anticipated reward (or lack thereof). In formal economic terms, this is the expected value of an outcome.[31,32] Thus, regions within PFC can be viewed as "interpreting" a potential reward within the context of its likelihood of occurrence.[33]

Are these prefrontal regions involved in making choices based on expected value? Several studies in patients with VMF lesions argue that this region is necessary for normal decision making in the settings of risk and ambiguity: In contrast to healthy subjects, patients with VMF damage are less ambiguity and risk averse in experimental gambling tasks.[34-36] Interestingly, these effects are not necessarily negative. In some of these paradigms, the normal tendency to avoid risk leads to suboptimal (in economic terms, "irrational") choices. In these highly constrained experimental settings (if not in real life), the reduction in risk aversion following VMF damage paradoxically results in more rational economic behavior and better financial outcomes.[36]

The value of time. Delay is another factor that influences the subjective determination of value and is frequently encountered in everyday decision making. Indeed, it is a feature of those particularly difficult decisions that require passing up immediate gratification (that piece of chocolate cake) in favor of longer-term goals (a healthy body weight). Even the value of money decays with delay: Studies of choice behavior show that $10 that will be provided in 6 months is worth less than $10 that will be provided right now, a phenomenon termed "temporal discounting." This subjective cost of delay varies across individuals (and across rewards) and has been proposed as a factor underlying some forms of impulsivity.[37] For example, heroin addicts show steeper temporal discounting (i.e., delay carries a higher cost) than nonaddicted control subjects.[38]

The brain basis of this phenomenon has yet to be studied in detail, and the findings to date are not entirely consistent. One fMRI study reported more activation in medial PFC and OFC (as well as in nucleus accumbens) for immediate compared with delayed monetary reward. In contrast, decisions concerning delayed reward recruited dorsolateral prefrontal and parietal areas typically activated by difficult cognitive tasks.[39] Another study, using a very different paradigm, reported effects of delay in the insula and striatum.[40]

One interpretation of these findings is that the more immediate rewards are represented in limbic regions, reflecting the enhanced emotional weight of such choices compared with the distant, "cooler" options that are evaluated in a more "rational" way. This leads to the prediction that patients with VMF damage would be less influenced by the "emotional" attraction of the immediate reward and so behave more rationally (analogous to their more rational [less risk-averse] performance in the laboratory tests of risky decision making discussed above). Consistent with this prediction, OFC lesions in rats increase the choices of larger but delayed rewards.[41] However, the authors of that study suggest a different interpretation: that OFC damage reduces the aversive effects of delay, thereby making the delayed option more attractive. Neither of these views is supported by a study showing that VMF damage in humans does not have any systematic effect on temporal discounting, at least as measured by one standard task involving hypothetical choices.[42] Differences in time scale and the use of hypothetical rather than experienced delays in the latter study may explain the discrepancy between rat and human findings. Alternatively, the role of OFC in integrating value and delay may be more nuanced: A recent electrophysiologic study of temporal discounting in the rat found that both immediate and delayed re-

wards are tracked in OFC, albeit by different neuronal populations.[43]

No regrets. As anyone who has sold a stock just before its share price skyrocketed can attest, the perceived value of missed opportunities can also be an important factor in the construction of subjective value. When the outcomes of unchosen options (hold!) are known, and turn out to be better than the chosen option (sell!), the result is the emotional state of regret. Avoidance of regret can be a powerful factor in human decision making.[44,45] A recent study suggests that intact VMF is required for the normal experience of regret.[46] Patients with VMF lesions reported normal levels of disappointment when the outcome of a chosen gamble was a loss rather than a win. However, unlike normal subjects, their emotional state was not influenced by learning the outcome of the gamble they did not choose; they did not compare "what was" with "what might have been." Normal subjects reported more sadness after a loss (and had larger skin conductance responses), when the unchosen option would have resulted in a win. Those with VMF damage did not show either of these phenomena. A functional imaging study in healthy subjects using the same paradigm found that degree of regret correlated with activity within VMF as well as in dorsal anterior cingulate and hippocampus.[47]

Avoidance of regret is partly what pushes some consumers to exhaustively search for the best available option, despite the fact that many options may be good enough. Those who pursue this so-called "maximizing" strategy invest more time and effort in decision making but are frequently less satisfied with the outcome.[48] In laboratory consumer decision-making tasks, patients with VMF damage appear to employ maximizing strategies less often than normal subjects, consistent with the hypothesis that such damage reduces the influence of regret on decision making.[49] The latter experiment also demonstrates that VMF damage can affect decision making even in the absence of risk or ambiguity, as would be predicted if this area plays a general role in representing the relative value of choices.

From behavioral "bench" to bedside. How can these basic science findings be related to the clinic? The primary contribution is at the conceptual level, by providing a more specific framework for describing and measuring the effects of VMF damage on behavior. For example, the "impulsive" choices of such patients may not reflect risk seeking, but rather a relative failure to be risk averse. More generally, these patients may simply have a degraded ability to compare the value of decision options. This deficit may be particularly evident in decisions that involve subtle or abstract factors such as risk, ambiguity, or regret or in situations where reinforcement contingencies are changing rapidly. This impairment may result in a higher frequency of disadvantageous choices or at least choices that differ from those the patient might have made prior to their brain injury. In other decision settings or in different patients, such a deficit might lead to disinterest in choosing at all or to apparently random or capricious choices, phenomena that may underlie the apathy that is a frequent clinical correlate of VMF damage.

More practically, the laboratory tasks developed in these basic studies may prove to be valuable clinical tools for measuring VMF-mediated abilities. Reversal learning or risky decision tasks may detect deficits in these patients, who often perform relatively well on traditional tests of executive function.[10] These tasks may also provide information relevant to the formal assessment of such patients' competency to make medical or financial decisions in real life. In the not-so-distant future, assessment of economic behaviors such as risk tolerance may be as useful to neurologists localizing frontal dysfunction as it is to financial advisors planning an investment portfolio.

Most definitions of frontal executive function include those "top down" processes that permit the flexible pursuit of particular goals, especially under conditions of complexity.[50] The work reviewed here argues that the VMF sector of PFC provides a missing component to this frontal executive paradigm. This region appears to be particularly important in the context-sensitive evaluative processes that lead to the choice of the goal to be pursued. This "accounting" function can be viewed as linking the context-specific affective/motivational value of a goal to the higher-order cognitive processes required to obtain it. The cross-disciplinary research in cognitive neuroscience and neuroeconomics reviewed here had its origins in studies of neurologic patients and is already providing new ways to describe and measure prefrontal function and dysfunction. Future studies in this rapidly growing field of research are likely to continue to generate new insights into the brain basis of the regulation of complex human behavior.

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