Orbitofrontal Cortex and Its Contribution to Decision-Making

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prefrontal cortex, reward, neurophysiology, neuroeconomics, choice behavior

Abstract

Damage to orbitofrontal cortex (OFC) produces an unusual pattern of deficits. Patients have intact cognitive abilities but are impaired in making everyday decisions. Here we review anatomical, neuropsychological, and neurophysiological evidence to determine the neuronal mechanisms that might underlie these impairments. We suggest that OFC plays a key role in processing reward: It integrates multiple sources of information regarding the reward outcome to derive a value signal. In effect, OFC calculates how rewarding a reward is. This value signal can then be held in working memory where it can be used by lateral prefrontal cortex to plan and organize behavior toward obtaining the outcome, and by medial prefrontal cortex to evaluate the overall action in terms of its success and the effort that was required. Thus, acting together, these prefrontal areas can ensure that our behavior is most efficiently directed towards satisfying our needs.

Contents

INTRODUCTION

The orbitofrontal cortex (OFC) is the region of the brain directly behind our forehead resting on top of our eye orbits. Its position in the skull, on top of the ridges created by the sphenoid bone, makes it particularly susceptible to damage from head trauma. Yet damage to OFC often appears to have remarkably little effect. Consider the case of Elliott, a happily married young man in his thirties (Damasio 1994, Eslinger & Damasio 1985). Elliott excelled in college and rose rapidly through the ranks of a building firm to become comptroller at the age of 32. People described him as a role model and a natural leader. Unfortunately, at the age of 35 doctors diagnosed Elliot with a brain tumor. The operation to remove the tumor was successful, but the surgery left Elliot with bilateral damage to his OFC. However, neuropsychological tests could find no evidence of brain damage. Tests of his intelligence, memory, reading and writing comprehension, verbal fluency, visuospatial abilities, and facial recognition revealed average to superior performance. He could talk intelligently and knowledgeably about current issues. Even tests designed specifically to tax frontal lobe processes, such as working memory, rule switching, and cognitive estimation, failed to reveal any deficits.

So was Elliot unaffected by the damage? Sadly, the answer is no. Within months of the operation, he had quit his job, lost a large sum of money to a scam artist, divorced his wife, lost contact with family and friends, and remarried a prostitute he had known for a month. He had trouble holding down a job; employers complained about his tardiness and disorganization. His second marriage ended in divorce six months later, and he moved in with his parents. In short, prior to his tumor Elliot had made a series of excellent life decisions, but within months of the operation he made a series of catastrophic ones. Even simple decisions were difficult because he would agonize over every possible consideration. For example, deciding where to dine would take hours as he considered the menu, the seating arrangement, and the atmosphere. He would even drive to each restaurant to see how busy it was.

Here then is the paradox of OFC: How can damage to this area leave so many of our cognitive abilities intact, yet devastate our

OFC: orbitofrontal cortex

ability to make the decisions that enable us to navigate everyday life? This chapter focuses on understanding the neuronal mechanisms that contribute to decision-making to help us make sense of the deficits seen in OFC patients. We begin with a brief overview of OFC anatomy and explore the deficits that occur after OFC damage. We then examine the functional properties of OFC neurons, first concentrating on their role in processing rewards and then exploring more specifically the hypothesis that OFC is responsible for calculating the value of a reward. We finish by proposing a model demonstrating how other brain areas might use the information from OFC to control decision-making.

Working memory: a memory system enabling the temporary maintenance and manipulation of a limited amount of information over short delays

PFC: prefrontal cortex

ANATOMICAL ORGANIZATION

Structural Anatomy

OFC is part of prefrontal cortex (PFC) and occupies the ventral part of the frontal lobe (**Figure 1**). Discrepancies in the early maps of human and monkey OFC organization have been resolved, and researchers now agree that

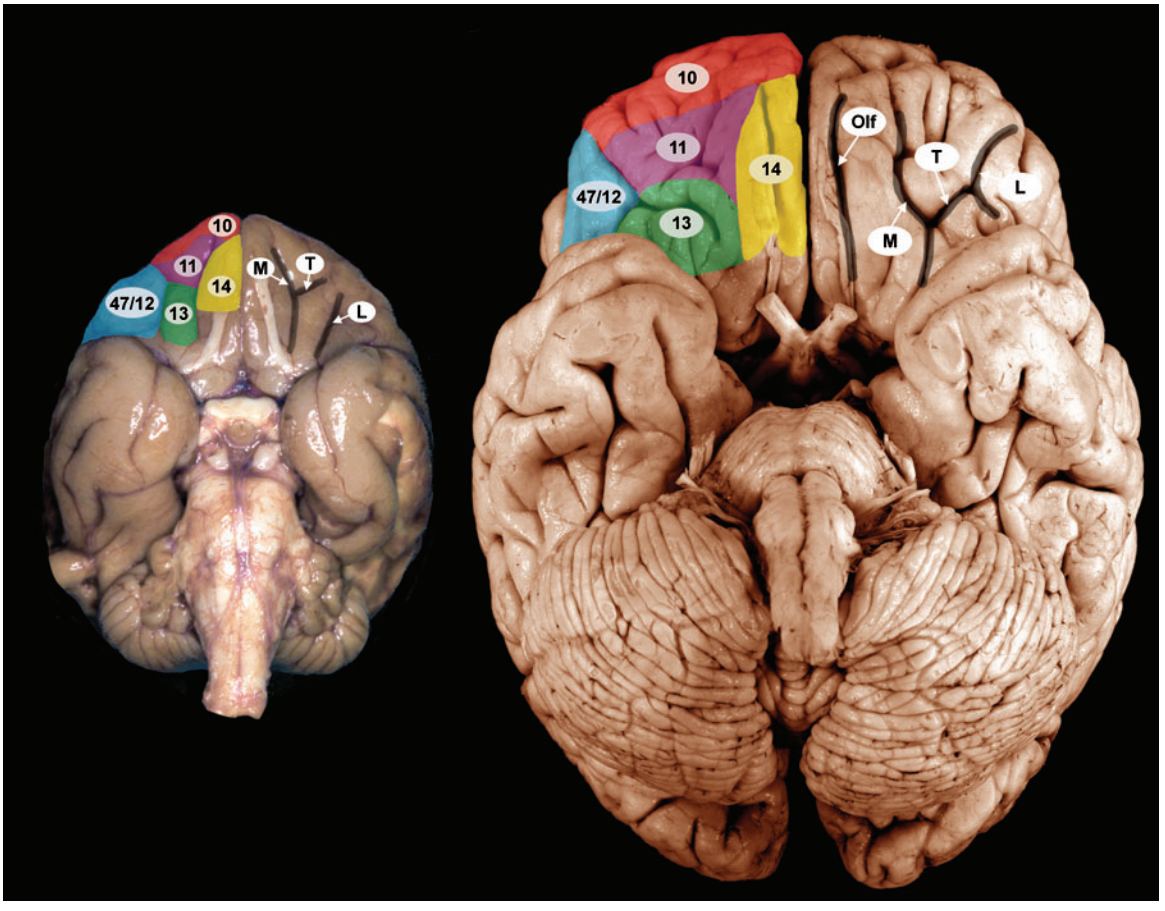

Figure 1

Ventral view of the macaque (*left*) and human (*right*) brains illustrating the major cytoarchitectonically distinct regions of OFC (Petrides & Pandya 1994) and the main sulci. Olf = olfactory sulcus, M = medial orbital sulcus, T = transverse orbital sulcus, L = lateral orbital sulcus. In the macaque brain preparation, the olfactory tubercle obscures the olfactory sulcus.

DLPFC: dorsolateral prefrontal cortex

VLPFC: ventrolateral prefrontal cortex

MPFC: medial prefrontal cortex

its basic structure and organization are similar across primates. It consists of five cytoarchitectonic subregions: frontal polar area 10, area 11 anteriorly, area 13 posteriorly, area 14 medially, and area 47/12 laterally (Carmichael & Price 1994, Petrides & Pandya 1994). Four sulci divide the surface into five gyri (Chiavaras & Petrides 2000). Running along the anterior-posterior axis are three parallel sulci. Most medially is the olfactory sulcus, followed by the medial orbital sulcus and lateral orbital sulcus. The transverse orbital sulcus connects the medial and lateral orbital sulci approximately halfway along their length.

Overview of Connections

The connections of OFC exhibit three prominent features:

1. Within frontal cortex it is unique in receiving information from all sensory modalities (Carmichael & Price 1995b, Cavada et al. 2000, Romanski et al. 1999). Area 47/12 receives highly processed visual information from areas such as inferior temporal cortex, auditory information from secondary and tertiary auditory areas, somatosensory input from secondary somatosensory cortex and parietal cortex, and inputs from polysensory areas such as the superior temporal cortex. Primary olfactory and gustatory cortex both project to posterior area 13.
2. OFC has only weak motor connections. Some connections exist between area 47/12 and the supplementary eye fields, and between area 13 and the ventral premotor cortex (Carmichael & Price 1995b). In comparison, the medial wall of PFC densely connects with cingulate motor areas, whereas dorsal and lateral PFC densely connect with premotor cortex (Chiba et al. 2001, Lu et al. 1994). OFC may influence behavior through a subcortical route because it strongly connects with the nucleus accumbens (Haber et al. 1995).
3. OFC extensively connects with the limbic system, including the amygdala, cingulate gyrus, and the hippocampus (Carmichael & Price 1995a). It can also influence the autonomic nervous system through its connections with the hypothalamus and other brainstem structures, such as the periaqueductal gray matter (Ongur et al. 1998).

In summary, the connections of OFC are compatible with a structure that integrates sensory and reward information.

Other PFC Areas

Throughout this review we frequently compare and contrast the functions of OFC with other major PFC subregions. Using the nomenclature of Petrides & Pandya (1994), dorsolateral PFC (DLPFC) consists of areas 9, 46, and 9/46. Ventrolateral PFC (VLPFC) consists of areas 47/12 and 45. Medial PFC (MPFC) consists of area 32 and the anteriormost portions of area 24. MPFC is often considered part of anterior cingulate cortex. The anterior cingulate cortex is a large area that extends posteriorly to about midway along the cingulate gyrus. The region we discuss is the anterior-most portion of the anterior cingulate cortex. Although the nomenclature of this region is controversial, for brevity we simply refer to it as MPFC. Clear differences exist in the pattern of connections of these different PFC regions. The lateral regions of DLPFC and VLPFC connect predominately with sensory and motor areas (Carmichael & Price 1995b, Lu et al. 1994), whereas MPFC connects predominately with motor and reward areas (Carmichael & Price 1995a, Chiba et al. 2001).

NEUROPSYCHOLOGY OF OFC

Having familiarized ourselves with the anatomical organization of OFC, let us now return to patients with OFC damage. Recall

that such patients often show intact performance on a wide range of neuropsychological tests, including those designed to detect frontal lobe dysfunction. Indeed their brain damage was so difficult to detect that they often had trouble obtaining insurance payments or disability benefits (Damasio 1994). In the early 1990s two tests were developed that were sensitive to OFC damage in humans. The first of these derived from research into the effects of lesions of OFC in monkeys and tested patients' ability to switch stimulus-reward associations. The second led to an influential theory called the somatic marker hypothesis, which described how OFC might use autonomic signals to guide decision-making.

Stimulus-Reward Learning and Flexible Behavior

One of the earliest deficits associated with OFC lesions in monkeys was a failure to perform stimulus-reward reversals (Mishkin 1964). A monkey learns that choosing one of two objects will lead to a reward. Then the contingencies reverse and the monkey must learn that to get a reward he now has to choose the previously unrewarded object. Monkeys with lesions of OFC were impaired at the task. Following the reversal, they were unable to inhibit responding to the previously rewarded object, a behavior called perseveration. The monkeys seemed to have difficulty modifying their behavior even when it was no longer successful in obtaining reward. Later studies revealed that the deficit was specific to OFC (monkeys with lesions of lateral PFC were unimpaired) and depended on serotonergic innervation (Clarke et al. 2004, 2006; Dias et al. 1996).

The task was adapted to test humans, and investigators found that frontal lobe damage impaired performance (Rolls et al. 1994). In addition, the extent of the patient's impairment on the task correlated with the extent to which his/her day-to-day behavior had changed. Thus, the same deficit that underlies the inability to reverse stimulus-reward associations might also underlie the patient's poor decisions. One possibility is that the patient is unable to modify his/her behavior in response to negative feedback. For example, scam artists might initially work to gain our trust, but we realize their intentions before we are taken advantage of and modify our behavior accordingly. In contrast, Elliott may have been unable to modify his initial trust and so was swindled by the fraudster. Only patients with OFC damage have problems with reversal learning: Patients with damage to DLPFC are unimpaired (Fellows & Farah 2003), consistent with the previous findings in monkeys.

Somatic marker: a bodily state or central representation of the bodily state corresponding to the consequences of choosing a particular course of action

Perseveration: the tendency to continue or repeat a previously rewarded act or activity even when no longer appropriate

Somatic Marker Hypothesis and Decision-Making

Another neuropsychological test that aims to mimic patients' day-to-day impairments is the Iowa gambling task (Bechara et al. 1994). In this task, there are four decks of cards, and the subject must choose from these decks one card at a time. Each card wins the subject a small amount of money, but some of the choices also lose money. The aim of the game is to win as much money as possible. Unbeknownst to the subject, two of the decks are risky: They are associated with large gains but also large and frequent losses. In the long term, choosing from these decks is a losing strategy. In contrast, the other two decks are associated with small gains but small and infrequent losses, so choosing from these decks will win money overall. Control subjects initially favor the decks associated with the largest gains but, after encountering losses, gradually realize that this choice will lose them money, and they alter their choices accordingly. Patients with OFC damage likewise initially favor the decks associated with larger gains, but unlike control subjects, they continue to favor these decks until they have lost all their money. The deficit was specific to patients with damage to OFC: Lesions of DLPFC did not affect performance (Bechara et al. 1998).

OFC patients also had unusual autonomic responses during the performance of the task

SCR: skin conductance response

Outcome: the consequence of an action; can be either positive (reward) or negative (punishment)

(Bechara et al. 1997). During learning, control subjects showed a marked increase in their skin conductance responses (SCRs) immediately before making a selection from one of the risky decks. This anticipatory SCR was missing in OFC patients. However, there was not a general disruption of autonomic processing. OFC patients continued to show an SCR to the delivery of the monetary reward or punishment. Nor was there a general failure of learning to affect the autonomic nervous system. OFC patients developed normal SCRs during conditioning to a loud noise (Bechara et al. 1999).

From these results, Damasio (1994) developed a theory of how autonomic responses might facilitate decision-making called the somatic marker hypothesis. He argued that bodily states corresponding to the emotions produced while evaluating different courses of action (so called somatic markers) help to facilitate normal decision-making. The role of OFC is to store associations between patterns of environmental inputs and the somatic states that those inputs produce. When making a decision, OFC activates the somatic states, which can then bias decision-making. Damage to OFC destroys patients' ability to activate the somatic states, and so all choice outcomes become emotionally equivalent. In this state, the patient must rely on a cognitive appraisal of a decision. Consequently, the myriad of variables needed to assess a choice can easily overwhelm the decision-making process. In effect, the patient loses the ability to make a decision by gut feeling.

These ideas embody many of the concepts from the James-Lange theory of emotions, which argued that changes in our autonomic state gave experiences an emotional quality (James 1884, Lange 1922). Accordingly, many of the criticisms leveled at the James-Lange theory (Cannon 1927) might apply to the somatic marker hypothesis. For example, patients with autonomic failure due to peripheral denervation of autonomic neurons do not have deficits in everyday decision-making and perform normally on the Iowa gambling task (Heims et al. 2004). To circumvent such criticisms, Damasio proposed that somatic markers did not necessarily have to operate through the peripheral autonomic nervous system but might operate through an "as-if" central representation. In effect, OFC might use somatosensory cortex to simulate the emotion that a particular course of action would produce. Unfortunately no direct evidence yet demonstrates that somatosensory cortex is involved in decision-making. Although it is involved in recognizing emotion (Adolphs et al. 2000), we do not know how patients with damage to somatosensory cortex would perform on the gambling task. Furthermore, centrally mediated responses to emotional stimuli, such as the P300 orienting response, show enhancement, not reduction, in OFC patients (Rule et al. 2002). It is difficult to reconcile this enhanced orienting response with an inability to activate a central representation of somatic states.

Another difficulty with interpreting the results from the gambling task is that it is unclear precisely which psychological mechanisms the task taxes. For example, the original formulation of the task requires a reversal of a stimulus-reward contingency. The reward contingencies cause subjects to respond initially to the high-reward decks, but they must then switch to the lower-reward decks to win money in the long term. To address this confound, Fellows & Farah (2005) developed a "shuffled" version of the gambling task, which used reward contingencies that did not initially bias the subject toward any of the decks. Patients with OFC damage were not impaired on this version of the task. Furthermore, there was a positive correlation between the size of impairment that the patients displayed on a stimulus-reward reversal task and the size of their impairment on the original Iowa gambling task. The results suggest that the deficits on the gambling task might have arisen from the problems that OFC patients have in reversing stimulus-reward

associations. However, despite these concerns, the somatic marker hypothesis remains the only theory to attempt to explain both the autonomic changes observed in OFC patients as well as their decision-making impairments.

Summary

The 1990s saw the development of two theories to account for deficits seen in humans with OFC damage: stimulus-reward inflexibility and the somatic marker hypothesis. However, one difficulty with interpreting the neuropsychological literature is determining which mechanisms underlie the deficits. There is not necessarily a straightforward link between the process performed by a region and the behavioral deficit that damage to that region produces (if one removes the capacitor from a radio, the radio will howl, but that does not mean the function of the capacitor is to inhibit howling). To understand what the underlying mechanisms might be, we turn to the neurophysiological literature. A caveat, however, is that any properties we observe in OFC neurons must be capable of explaining the neuropsychological impairments that follow OFC damage.

NEURONAL MECHANISMS WITHIN OFC

Specialization of OFC for Reward Processing

The first neurophysiological studies of OFC noted the frequency of neurons that showed selective responses to the delivery of food and liquid rewards (Rosenkilde et al. 1981). They also supported the notion that OFC was important for stimulus-reward reversals. In a stimulus-reward reversal task, neurons showed differential activity to two visual stimuli, one of which predicted the delivery of fruit juice and the other of which predicted the delivery of saline (Thorpe et al. 1983). Such neurons were not simply encoding the visual properties of the stimulus; when the reward contingencies reversed, the neuronal selectivity would also reverse. Thus, the neurons appeared to be encoding the reward predicted by the stimulus and expected by the monkey.

Later studies began to challenge the notion that these properties were unique to OFC. Reward-selective neurons, that is, neurons that show different firing rates depending on the expected reward outcome, were found in many different brain areas. For example, many studies demonstrated that reward-selective neurons were also in DLPFC (Amemori & Sawaguchi 2006, Hikosaka & Watanabe 2000, Kobayashi et al. 2002, Leon & Shadlen 1999, Watanabe 1996), and DLPFC neurons showed similar responses to OFC neurons during the performance of stimulus-reward reversal tasks (Wallis & Miller 2003). Particularly challenging was a study by Roesch & Olson (2003), which examined the influence of reward expectation on neurons throughout the frontal lobe. The prevalence and strength of reward selectivity were weakest in PFC and strongest in motor areas such as premotor cortex. Reward-selective neurons were also found in posterior cortex, such as perirhinal cortex (Liu & Richmond 2000), parietal cortex (Musallam et al. 2004, Platt & Glimcher 1999), and even primary visual cortex (Shuler & Bear 2006). However, we must be careful in interpreting these results. A neuron is not necessarily encoding a reward just because its firing rate correlates with some parameters of that reward. Many behavioral and cognitive measures also correlate with expected reward and may equally be driving the neuron's response. For example, an animal's muscles will often tense when it expects a large reward, and its behavior will be quicker and more accurate (Roesch & Olson 2003). Another argument is that animals pay more attention to cues that predict reward (Maunsell 2004) and enter a state of higher autonomic arousal. Any of these processes may be driving neuronal firing rates.

Which Aspect of Reward is OFC Encoding?

Hedonic value: the amount of pleasure or pain associated with an outcome (how much we like something)

Incentive value: the degree of desirability of an outcome (how much we want something)

Given that reward has multiple behavioral and cognitive correlates, how are we to determine which aspect of reward OFC neurons encode? Because we know that OFC damage impairs decision-making, a sensible place to begin is by concentrating on those aspects of reward that drive our choices and decisions. However, multiple aspects of a reward can drive our behavior. For example, rewards have a hedonic value (how much we like something) and an incentive value (how much we want something) (Robinson & Berridge 1993). For now, we refer to these multiple aspects simply as value, but we return later to look at which factors make one reward more valuable than another. The first question we must address, however, is whether OFC neurons are encoding value or are, in fact, encoding one of the correlates of value.

One approach is to compare the neuronal response to rewards and punishment. The rationale is that punishers should have many of the same behavioral and cognitive sequelae that rewards do. For example, punishment motivates behavior, focuses attention, and produces arousal. However, in terms of its value punishment is clearly different from reward. We try to obtain reward and avoid punishment. Thus, neurons encoding value should show a difference in activity between rewards and punishments. In contrast, neurons encoding some sequelae of the reward should show a similar response to both rewards and punishers. Using this rationale, Roesch & Olson (2004) compared neuronal responses in OFC and premotor cortex when an animal made choices based on the size of either a reward or a punishment. OFC neurons tended to fire more strongly to choices predicting larger rewards and showed a decreased firing rate when choices predicted larger punishments. In contrast, neurons in premotor cortex showed stronger responses to choices indicating larger punishments or rewards. From these results, they concluded that OFC was encoding the value of a choice, whereas the reward-selective responses in premotor cortex were actually indicative of the increased motor readiness an animal exhibits when it is making an important choice (that is, one associated with large amounts of reward or punishment).

A second approach has been to compare the neuronal latency at which reward selectivity appears across various brain regions. The rationale in this case is that brain areas extracting the value of a choice should display reward selectivity before those areas responsible for using the value information to control behavior and cognition. To investigate this idea, we trained monkeys to choose between different pictures associated with delivery of different amounts of fruit juice (Wallis & Miller 2003). Pictures appeared on the left and right of a screen, and monkeys were required to make a saccade to the picture they wanted to choose. Monkeys soon learned to maximize their reward by selecting pictures associated with larger rewards. We recorded simultaneously from DLPFC and OFC and found neurons in both areas that encoded the size of reward. **Figure 2** illustrates the time-course of this encoding across the DLPFC and OFC populations of neurons. The measure of selectivity is derived from the receiver operating characteristic (ROC) of each neuron's firing rate. The ROC is the probability that an independent observer could correctly identify the payoff given the firing rate of the neuron. No selectivity equates to an ROC value of 0.5 (in practice it is slightly higher than this because we rectify the ROC value during its calculation. Small fluctuations due to noise push the value to about 0.52). Maximal selectivity equates to a value of 1.0. Both populations begin to encode the expected payoff at about the same time, but selectivity reaches its peak value in OFC ~60 ms before it does in DLPFC. In addition, OFC neurons tended to encode the reward alone, whereas DLPFC neurons encoded a combination of the reward and the upcoming motor response (**Figure 3**). We recently replicated

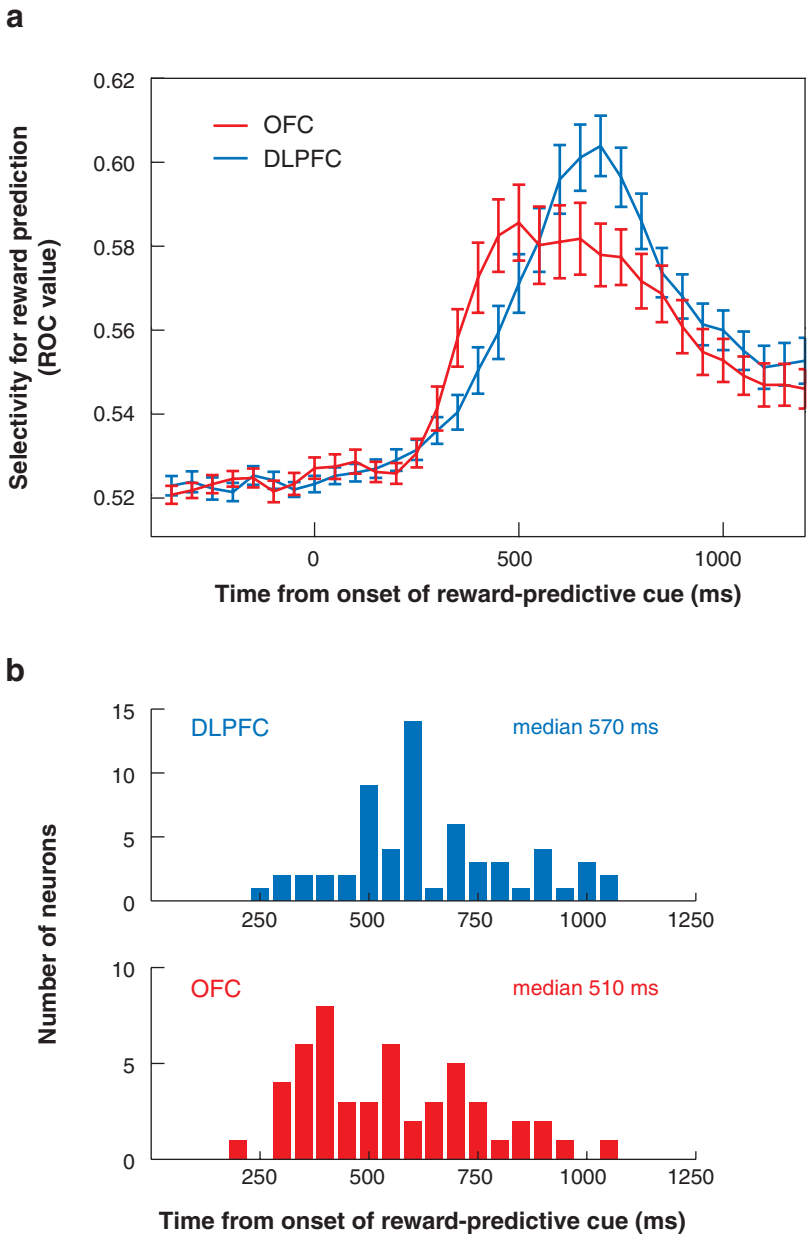

Figure 2

(*a*) Time-course of mean selectivity for encoding an expected reward across the DLPFC (*blue*) and OFC (*red*) population of neurons. Error bars indicate the standard error of the mean. (*b*) Distribution of peak selectivity across the population of DLPFC and OFC neurons. The OFC population reaches its peak selectivity ~60 ms before the DLPFC population (Wilcoxon's rank-sum test, $P < 0.05$).

these findings, using a very different behavioral paradigm designed to investigate the interaction of reward information with spatial working memory (Kennerley & Wallis 2006). In this paradigm, OFC neurons encoded the value of a reward-predictive cue 110 ms before DLPFC neurons did. From these results, we have concluded that OFC encodes the value of a choice outcome and then passes this information to DLPFC, which uses the information to control behavior. Our results are consistent with previous neurophysiological studies because reward-selective neurons were in both DLPFC and OFC. However,

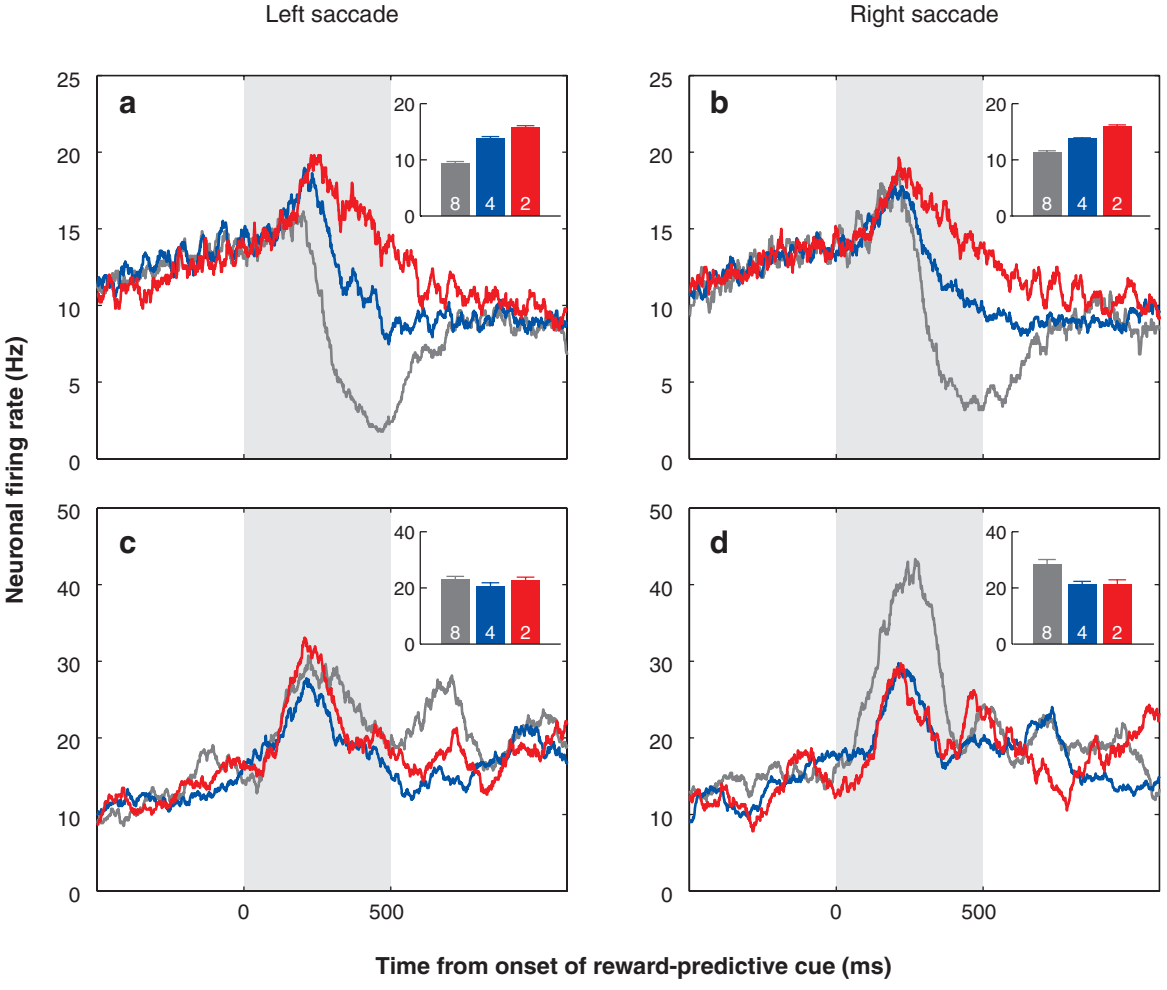

Figure 3

Spike histograms from two single neurons encoding the expected reward and/or the monkey's response (a left or right saccade). Inset bar graphs indicate the mean neuronal firing rate (± standard error) during the presentation of the reward-predictive cue (the first 500 ms). Gray indicates that the cue predicted the delivery of eight drops of juice, blue four drops, and red two drops. (*a*, *b*) OFC neuron encoding the predicted reward in a parametric fashion irrespective of saccade direction. This neuron showed a depression in its firing rate that was greatest for eight drops of juice, less for four drops, and least of all for two drops. Its firing rate, however, was the same irrespective of whether the monkey would make a left or right saccade to earn the reward. Significantly more OFC neurons (28%) showed this pattern of selectivity compared with DLPFC neurons (13%, chi-squared = 9.8, P < 0.005). (*c*, *d*) A DLPFC neuron that showed a complex pattern of selectivity that encoded a combination of the reward and the upcoming saccade. During the cue epoch, the neuron discriminated between the different expected reward amounts only when the monkey would make a rightward saccade (showing a high firing rate when eight drops of juice were expected). In contrast, during the subsequent period the same neuron was reward-selective only when the monkey would make a leftward saccade. Significantly more DLPFC neurons (43%) encoded a combination of the reward and response compared with OFC neurons (19%, chi-squared = 19, P < 0.00,005).

they are also consistent with the neuropsychological literature, suggesting a preeminent role for the OFC in reward processing, because our results suggest that OFC is the source of reward signals to DLPFC.

In summary, neurons sensitive to reward parameters are widespread in the brain, which is not surprising. Obtaining rewards is critical to our survival, and so rewards drive many of our behavioral and cognitive processes. Thus we must be careful to differentiate between neurons that are directly responsible for encoding the value of a reward and those that encode a cognitive process that rewards happen to affect. Two different approaches both point to the importance of OFC within the frontal lobe for encoding a reward's value. OFC neurons respond quickly to rewards and differentiate between rewards and punishments.

However, OFC is not critical for much simple reward processing. For example, an animal with bilateral OFC removal is still motivated to work for reward (Izquierdo et al. 2004, Pears et al. 2003), can learn that a neutral stimulus predicts food (Pickens et al. 2003), and can make choices between rewarded and unrewarded alternatives (Izquierdo et al. 2004, Rudebeck et al. 2007). In real life, however, most of our choices are not so simple. We often have to consider multiple parameters of an outcome and weigh its pros and cons. We may or may not experience a physically identical outcome as rewarding, depending on our needs and the context in which it occurs. In all, considerable processing may be required to determine that a reward is actually rewarding. In the following section, we explore some of these processes and examine the evidence for their dependency on OFC.

Complexity of Reward Processing: Calculating a Reward's Value

Rewards involve integration and trade-off. Many of us could live in a larger house if we were prepared to accept a longer commute to the workplace. Our decisions about residence location depend on a trade-off between these two factors. Many of our everyday decisions are similarly complex often requiring us to weigh the pros and cons of several variables. A recent study by Padoa-Schioppa and Assad (2006) shows that OFC neurons integrate multiple sensory features of a reward to determine its value. Monkeys made choices between different volumes of different types of juice reward. To make its choice effectively, the monkey needed to consider both variables. For example, a thirsty monkey might prefer the taste of fruit juice to water. If so, then if the choice is between equal volumes of both, he will obviously choose the juice. However, increasing the volume of water available can compensate for its less desirable taste. If the volume of water is sufficiently large, relative to the juice volume, then the monkey will pick the water. At some point, the volume of water will compensate for its less desirable taste exactly, and the monkey will be indifferent between the two choices. This measures the monkey's value of one reward's taste relative to the other. For example, if the monkey is equally likely to choose four drops of water or one drop of fruit juice, we know that the monkey considers the taste of juice four times more valuable than water.

The firing rates of OFC neurons were more likely to vary systematically with the value of the drinks, rather than with the drinks' physical properties, such as their taste or volume. To see how the authors determined that the neurons were encoding the value of the drinks, we return to the juice and water example. A neuron that was encoding the value of the chosen reward might show a higher firing rate when the monkey was choosing one drop of juice compared with when he was choosing one drop of water. However, the neuron's firing rate would be the same when the monkey was choosing one drop of juice compared with when he was choosing four drops of water. We cannot explain this pattern of neuronal activity on the basis of the drinks' volume because equal

volumes of the drinks produce different neuronal firing rates. Nor can we explain it solely by the drinks' taste because certain volumes of the drinks produce equal levels of neuronal firing. However, we can explain it in terms of the monkey's valuation: When his valuation of the two drinks is the same (such as when there are four drops of water or one drop of juice), the neuronal firing rate is also equivalent.

Although the authors focused on gustatory stimuli, these processes could easily apply to high-level decision-making. Indeed, patients with OFC damage have difficulty integrating multiple attributes pertaining to a decision (Fellows & Farah 2005). For example, patients were poor at integrating the factors that might go into choosing an apartment (size, location, etc.). Anatomically, OFC is ideal for the multimodal integration of the parameters necessary to evaluate an outcome because it receives inputs from all sensory modalities. OFC neurons in the monkey respond to visual, olfactory, and gustatory aspects of rewards (Rolls & Baylis 1994). Neuroimaging reveals that human OFC is activated by pleasant and unpleasant smells, sights, sounds, and touches (Rolls et al. 2003, Royet et al. 2000), as well as more abstract rewards and punishments, such as receiving or losing money (Breiter et al. 2001, O'Doherty et al. 2001).

Reward is relative. Unlike physical properties, such as luminance or pitch, reward is difficult to measure in absolute terms. The value of a reward depends on other potential rewards. For example, you might be delighted to receive a $1000 pay raise until you find out that all your coworkers received $5000. In an analogous laboratory situation, investigators explored the ability of subjects to experience regret by having them rate their emotional experience during a task where they had to choose between two spinners (Camille et al. 2004). Depending on where the spinner landed, the subject might win or lose money. Critically, however, in some conditions the subject saw what would have happened had they chosen the alternate spinner. For control subjects, this simple manipulation could evoke regret by turning an otherwise positive experience (winning money) into a negative experience (if the subject would have won more money by choosing the alternative spinner). Patients with OFC damage showed a different pattern of emotional experience during this task. They still reacted positively or negatively to winning or losing money, but the outcome of the alternative spinner did not affect their emotional experience and they did not experience regret. Their deficit seemed to be in representing or simulating what would have happened had they chosen the alternative. Some evidence also indicates that OFC neurons encode rewards in a relative manner (Tremblay & Schultz 1999). For example, if a monkey prefers raisins over cabbage and oranges over both raisins and cabbage, then an OFC neuron might respond to raisins if the monkey's choice is limited to raisins and cabbage, but to oranges if the choice is between oranges and raisins.

Rewards must satisfy a need. Something is valuable only in the sense that it meets some need. We might pay $40 for a good steak, but if we were extremely thirsty, we would prefer to spend the money on water. Our needs are often complex, encompassing physiological, cognitive, emotional, and social factors, but in all cases, these needs affect how valuable a reward is. It also means that the exact same physical stimulus might be rewarding (a cold beer on a hot summer night) or aversive (that same beer the morning after) depending on our motivational state. Indeed, some evidence has shown that neuronal activity in OFC reflects our physiological needs. For example, some OFC neurons initially respond when a thirsty monkey tastes fruit juice, but the neuronal response declines as the animal drinks more juice and becomes sated (Rolls et al. 1989). This contrasts with gustatory cortex, where neuronal responses to gustatory stimuli remain constant irrespective of the animal's motivational state (Yaxley et al.

1988). Neuroimaging studies have shown similar results in human OFC (Gottfried et al. 2003).

Associations can make neutral events rewarding. Primary reinforcement, i.e., things we find intrinsically pleasant such as sweet tastes or orgasms, does not drive all our behavior. Instead, we direct much of our behavior toward secondary reinforcers, which would be otherwise neutral if it were not for their association with primary reinforcers. A good example in humans is money. Money is simply paper, with no intrinsic rewarding properties. Yet by its association with primary reinforcement (the good things in life that money can buy), the sight of a large sum of money has the same effect on people as does primary reinforcement. It is a positive and arousing emotional experience, and people will work for money just as they might work for food.

Turning to the neuronal mechanisms that underlie this process, OFC neurons do respond to previously neutral stimuli that predict the delivery of food (Schoenbaum et al. 1998, Thorpe et al. 1983, Wallis & Miller 2003). However, this does not necessarily mean that such neurons are encoding secondary reinforcement. We must be careful to distinguish between cues that simply predict primary reinforcement and cues that are genuine secondary reinforcers. The difference is that secondary reinforcers, through their association with primary reinforcement, are now rewarding in their own right. We can demonstrate this by teaching animals new responses using solely secondary reinforcers as the reward (Mackintosh 1974). Lesions of OFC in monkeys disrupt the ability of secondary reinforcers to support new learning (Pears et al. 2003), which suggests that OFC is critical in mediating the rewarding effects of secondary reinforcement.

Summary. To summarize, OFC seems to be particularly involved in complex situations where significant processing is required to determine the value of the outcome. How far can we extend this idea? One proposal suggests that OFC encodes a "neuronal currency" by integrating all the relative parameters pertinent to a decision (Montague & Berns 2002). We explore this idea in the next section.

Neuroeconomics

To make sense of neuronal data, neurophysiologists must compare neuronal responses against a model of the behavioral or cognitive process that the neuron is putatively encoding. Traditionally neurophysiologists have used models derived from sensorimotor psychophysics or animal learning theory. Over the past decade, however, scholars have realized that to understand the neuronal mechanisms underlying decision-making, it might help to widen the fields from which we construct our behavioral models. Evolutionary biologists and economists have constructed detailed models of the parameters that animals and humans use to make everyday decisions. Neuroeconomics refers to the nascent field that attempts to relate these models to patterns of neuronal firing (Glimcher 2003, Sanfey et al. 2006, Schultz 2004).

These models emphasize the consideration of three basic parameters that one needs to consider when making a decision: the expected reward or payoff, the cost in terms of time and energy, and the probability of success (Kahneman & Tversky 2000, Stephens & Krebs 1986). Determining the value of a choice involves calculating the difference between the payoff and the cost and discounting it by the probability of success. One suggestion is that OFC integrates all these parameters to derive an abstract measure of the value of a choice (Montague & Berns 2002). This encoding scheme offers distinct computational advantages. When faced with two choices, A and B, one might imagine it would be simpler to compare them directly rather than going through an additional step of assigning them an abstract value.

Primary reinforcement: outcomes that have innate reinforcing qualities, such as the pleasure from a sweet taste or an orgasm

Secondary reinforcement: outcomes where the reinforcing qualities are learned through their association with primary reinforcers, such as money

Neuronal currency: an abstract signal encoded by neurons to indicate the value of a behavior

Neuroeconomics: the relation of neuronal activity to models derived from economics and behavioral ecology

The problem with this process is that as the number of available choices increases, the number of direct comparisons increases exponentially. Thus, choosing between A, B, and C would require three comparisons (AB, AC, and BC), and choosing between A, B, C, and D requires six comparisons (AB, AC, AD, BC, BD, and CD). The solution quickly suffers from combinatorial explosion as the number of choices increases. In contrast, valuing each choice along a common reference scale provides a linear solution to the problem.

An abstract representation provides important additional behavioral advantages, such as flexibility and a capacity to deal with novelty, both of which are hallmarks of prefrontal function. For example, suppose an animal encounters a new food type. To determine whether it is worth choosing relative to other potential food sources, the animal must determine the value of that food. If the animal relies on making direct comparisons, it can determine this only by iteratively comparing the new food with all previously encountered foods. If the animal calculates an abstract value, however, it has to perform only a single calculation. By assigning the new food a value on the common reference scale, it knows the value of this foodstuff relative to all other foods. Second, it is often unclear how to compare directly very different outcomes. How does a monkey decide between grooming a conspecific and eating a banana? Valuing the alternatives along a common reference scale can help. For example, although I have never needed to value my car in terms of bananas, I can readily do so by assigning each item an abstract, monetary value.

Thus, there are good theoretical grounds for expecting a neuronal system to encode the value of behavioral choices in an abstract manner, but is there empirical evidence for such a system and does it reside in OFC? As we have seen, some evidence demonstrates that OFC encodes payoff information, and it does so by calculating a value signal. This signal is abstract because a single sensory feature cannot explain it (Padoa-Schioppa & Assad 2006). But does OFC also encode the other factors relevant to a decision, cost, and probability of success?

Cost

Although an outcome may be highly desirable, we may not pursue it if the cost to obtain it is too great. For example, behavioral ecologists have specified several costs in obtaining food, such as search costs to find the food and handling costs to render the food consumable (Stephens & Krebs 1986). If these costs exceed the energy that the animal will derive from the food, then the animal does not attempt to obtain that food. Although there are many different types of cost, we can describe them largely in terms of either energy (effort) or time (delay).

A recent study by Roesch & Olson (2005) shows that OFC neurons encode time costs. Monkeys performed a cognitive task, and the final reward for correct performance was either large or small or occurred after either a short or a long delay. Confirming previous results, OFC neurons tended to fire more strongly when the monkey anticipated a large reward as opposed to a small one. However, they also tended to fire more strongly when the monkey anticipated reward after a short delay as opposed to after a long delay. Furthermore, the strength of an individual neuron's response to the delay manipulations correlated with its response to the manipulations of reward size. Thus, the value signal encoded by OFC neurons incorporates not only multiple sensory parameters of a reward but also temporal information.

A different picture emerges when considering effort. Studies by Rushworth and colleagues have implicated MPFC as responsible for effort-based decisions (Walton et al. 2002, 2003). Most recently, they have demonstrated a double dissociation between OFC and MPFC in the types of cost the two areas use to guide decisions (Rudebeck et al. 2007). Rats learned to make decisions on a T-maze. The two arms contained different amounts of

reward as well as either barriers of different heights that the rats had to clamber over (effort manipulation) or gates that would open only after the rat had been in the arm for a specific amount of time (delay manipulation). Lesions of MPFC biased rats toward choosing less effortful alternatives but did not affect decisions involving delays. In contrast, lesions of OFC biased rats toward choices with more immediate access to the reward but did not affect decisions involving effort. The impairments did not relate to changes in sensitivity to reward or motor abilities. If the arms were equal in terms of effort or delay, then the rats consistently chose the arm associated with largest reward. Thus, whereas ecological and economic models often lump together costs in terms of time and effort, the brain has not adopted this solution. OFC factors time costs into decisions, whereas MPFC factors effort costs. This functional dissociation is consistent with the stronger connections between MPFC and motor regions relative to OFC, which places it in a better position to evaluate effort (Carmichael & Price 1995b, Cavada et al. 2000, Chiba et al. 2001).

Probability of Success

A second parameter that we need to consider when assessing a choice alternative is the uncertainty in obtaining the outcome. However, this uncertainty could arise owing to sources of variation anywhere along our cognitive processing pathways. For example, we might not get the behavioral outcome we expected because we misinterpreted sensory information owing to perceptual ambiguity. A batter has a fraction of a second to determine what pitch has been thrown; failure to do so could result in a strike rather than a home run. Alternatively, perhaps the relationship between the sensory stimulus and the response is uncertain; a goalkeeper does his best to predict which direction a striker intends to shoot a penalty, but even so, he will often dive in the wrong direction. Sometimes our interpretation of the sensory situation is correct, and we make the correct response, but the outcome is inherently uncertain. The poker player is happy to put his money into a pot when dealt pocket aces, even though he may be outdrawn, because in the long run this is the most profitable course of action. Even our estimation of risk can itself vary. For example, some risks are certain (the probability that the roulette ball will land on black), whereas other risks are ambiguous (the probability that it will rain tomorrow). Finally, risk interacts with emotion. Uncertainty in a negative situation makes the situation even more unpleasant, whereas uncertainty in positive situations can be exciting and fun (as a visit to the casino can attest).

Given the different sources of variance that can affect the probability of a given outcome, it is perhaps not surprising that such manipulations activate diverse brain areas. Neuroimaging studies have revealed that multiple brain areas activate during decisions involving uncertainty, including OFC and MPFC (Hsu et al. 2005, Knutson et al. 2005), but also lateral PFC, parietal, cingulate, and insular cortex (Critchley et al. 2001, Kuhnen & Knutson 2005, Yoshida & Ishii 2006). Furthermore, some studies have begun to dissociate how different brain regions are involved in processing different types of risk. For example, different networks process certain versus ambiguous risks (Huettel et al. 2006). Neurophysiology studies show that neurons in a variety of regions, including MPFC (Amiez et al. 2006), parietal cortex (Platt & Glimcher 1999), and dopamine neurons (Fiorillo et al. 2003), combine information about the size of a payoff and its probability of occurrence to derive an expected value for a given action.

Integrating Multiple Decision Parameters

Thus, several different brain regions appear to encode the parameters underlying decisions. Is there any evidence that a single region integrates these parameters to derive an overall value for a decision? A recent study in our laboratory tested this question by recording

simultaneously from OFC, MPFC, DLPFC, and VLPFC while monkeys made decisions guided by the amount of reward, the probability of reward delivery, and the effort required to obtain the reward (Kennerley et al. 2005). Within OFC, DLPFC, and VLPFC, few neurons encoded these parameters (<10%). In MPFC, however, more than half the neurons encoded at least one of the parameters, and a quarter of the neurons encoded two or more of the parameters. Thus, MPFC neurons seem to encode a variety of information pertinent to decision-making. Lesion studies also suggest a role for MPFC in using behavioral outcomes to guide actions (Kennerley et al. 2006). In sum, MPFC may be a better candidate for encoding an abstract value signal than is OFC because it accounts for not just the value of the outcome, but also the effort involved in obtaining that outcome and the likelihood of the action being successful. It can then integrate this information to derive an overall value of the behavior.

A MODEL OF DECISION-MAKING WITHIN PFC

Nature of the OFC Reward Representation: Working Memory for Value

Having considered the type of information that OFC encodes, we now consider the nature of this encoding. Although OFC is a subregion of PFC, many of the current models of PFC function pay less attention to OFC compared with lateral PFC (Duncan 2001, Goldman-Rakic 1987, Koechlin et al. 2003, Miller & Cohen 2001, Petrides 1996, Shimamura 2000). In addition, there is a disconnection in the types of tasks used to test functions of different PFC subregions. For example, tests of lateral PFC function typically focus on some type of sensory working memory (Funahashi et al. 1989, Rao et al. 1997, Romo et al. 1999, Wilson et al. 1993). In contrast, tasks used to examine OFC functions test stimulus-reward associations held in long-term memory (Roesch & Olson 2004; Schoenbaum et al. 1998, 1999; Thorpe et al. 1983; Tremblay & Schultz 1999; Wallis & Miller 2003).

Yet when one records the activity of OFC neurons during the performance of working memory tasks, their activity can closely resemble that of lateral PFC neurons (Wallis et al. 2001). Thus, we suggest that OFC neurons operate in much the same way as do neurons in the rest of PFC: by holding information in working memory across short delays and using that information to bias activity in other areas in a behaviorally relevant manner (Miller & Cohen 2001, Shimamura 2000). The difference between these areas lies in the nature of the information encoded, an idea originally espoused by Goldman-Rakic (1987). Lateral PFC encodes sensory information, behavioral responses, and the context in which these occur. In contrast, OFC encodes the potential goals and outcomes toward which we can direct our behavior. It encodes this information as a value signal, ensuring that the outcomes that satisfy our needs receive behavioral priority. This value signal relates only to the outcome itself and not to the means to achieve that outcome.

What advantages does such a system confer over simpler mechanisms such as associative learning? Associative learning depends on trial-and-error, which has inherent drawbacks. First, to modify our behavior, we must experience the outcome. This is problematic particularly for learning about aversive outcomes, which may be physically harmful. Second, obtaining a particular outcome may require considerable planning and effort. A system that can encode the value of the outcome beforehand can avoid wasting time and energy on outcomes that are not sufficiently valuable. Thus, the OFC system may be particularly important for planning behavior toward distant rewards, compared with more low-level subcortical systems, which might be adequate for obtaining immediate rewards.

Third, in the real world we often do not have the opportunity to engage in trial-and-error learning: Choices are often one-time deals.

As an example, consider an experiment by Murray and colleagues (Izquierdo et al. 2004). In one task, they allowed monkeys to choose between different food items. The experimenters could manipulate the monkeys' choices: If the animals were fed one of the foods prior to testing, they were less likely to choose this food during testing, a phenomenon called "sensory-specific satiety." In a second version, they trained monkeys such that selecting particular objects would lead to the delivery of specific food items. During testing, the monkey chose between pairs of objects, but each object pair appeared only once. Again, the experimenters could manipulate the monkeys' choices by varying what the monkeys ate prior to testing.

Monkeys with OFC lesions showed normal patterns of sensory-specific satiety on the first version of the task, but not on the second. A key difference between the two tasks is that the monkeys can engage in trial-and-error learning in the first version of the task but not in the second, where they face each choice only once. Instead, they must rely on an internal representation of value to guide their choice. As an analogy, compare the processes that might take place if you were selecting a meal from an all-you-can-eat buffet or from a menu. In the first case, you are free to select foods, try them, and decide whether you want more. In the second, this is not an option. You can guide your choice only by using information about your current motivational state and the sensory properties of the food item to generate a representation of the expected consequences of choosing that food. Indeed a recent study showed OFC activation when subjects considered food items on a menu (Arana et al. 2003). This mechanism might also explain why OFC patients fail to experience regret (Camille et al. 2004): To experience regret we must generate a representation of the consequences of the alternative outcome.

Thus, we speculate that a major function of OFC neurons is to encode a value representation in working memory, which can be used to anticipate the future consequences of our behavior. However, this value representation might take one of two forms: either a hedonic representation (liking), which would indicate that a choice outcome would produce a pleasurable emotional experience, or an incentive representation (wanting), which would indicate that a choice outcome was desirable. To date, research dissociating these two systems has focused on subcortical and neurotransmitter systems rather than on cortical areas (Pecina & Berridge 2005, Wyvell & Berridge 2000). In the healthy individual, however, these two systems probably operate in a tight coupling. Only in unhealthy individuals, such as drug addicts, do we see people expending considerable effort to obtain an outcome that provides them with no pleasure. We do not know which system OFC uses, but it is also possible that the signals are integrated by the time they reach cortical areas so that rewards are valued by both their hedonic and incentive properties.

Interaction of OFC with Other PFC Regions

Although OFC encodes the value of an outcome, it encodes little information about the means to achieve the outcome. We suggest that lateral PFC and MPFC are crucial in this regard. Lateral PFC is responsible for the top-down control of cognitive processes that enable the construction of plans and organization of behavior necessary to obtain goals and outcomes. These processes are beyond the scope of this chapter, but several recent reviews have described them in detail (Duncan 2001, Miller & Cohen 2001, Shimamura 2000). In contrast, MPFC can use information from OFC as to the value of the outcome and evaluate the plans generated in lateral PFC (for example, in terms of probability of success or effort) to

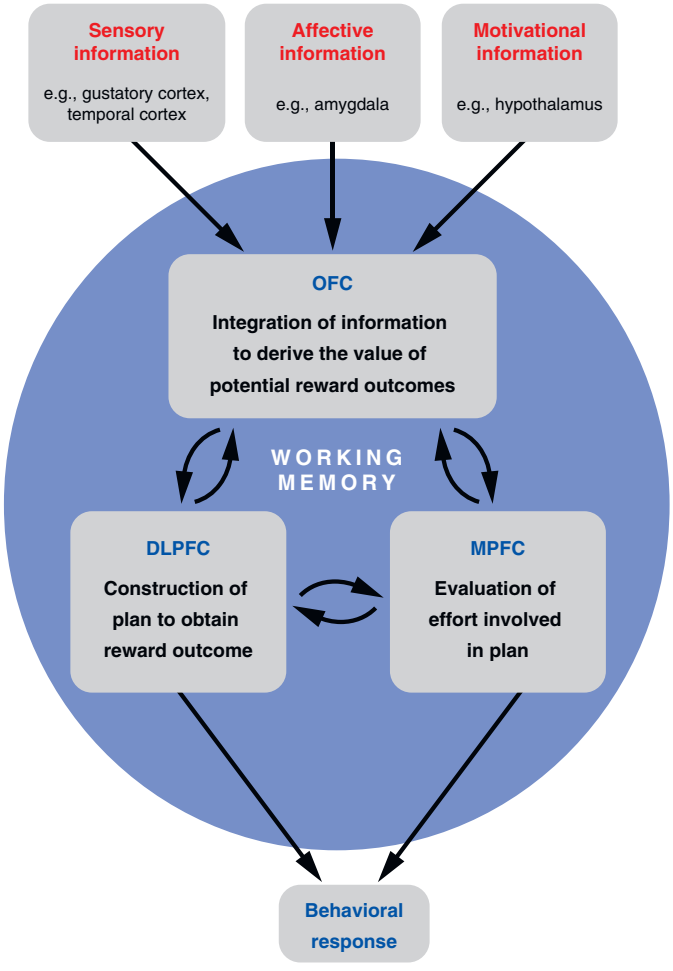

Figure 4

Model of the neuronal mechanisms underlying decision-making in PFC.

perform a cost-benefit analysis and generate an overall value for an action. Operating together these major PFC divisions can control behavior.

Figure 4 summarizes these ideas in the form of a speculative model. Sensory, affective, and motivational information about an outcome enter OFC. For example, delivery of a juice reward might involve information about the juice's taste arriving from gustatory cortex, information that the taste is pleasant arriving from the amygdala, and information that the juice is thirst-quenching arriving from hypothalamus. OFC then uses this information to calculate the value of the outcome and determine how rewarding it is. This information passes to lateral PFC, which can use it to construct behavioral plans, to prioritize goals, and to generate expectancies about future events. In turn, MPFC can use information about the value of the outcome and the behavioral plan to determine whether an action is worth performing. These calculations take place in working memory, so the ongoing pattern of neuronal activity in each of these areas reflects these processes.

Application of the Model to the Current Empirical Evidence

How well does this model stand up to the current empirical evidence? Some studies suggest that OFC is not involved in working memory (Bechara et al. 1998, Hikosaka & Watanabe 2000), but they have focused on spatial working memory. Therefore, if a task was used that required subjects to hold the value of a reward or outcome in working memory, an involvement of OFC may be apparent.

How does the model relate to the deficits seen in OFC patients? Concerning the gambling task, Damasio originally argued that subjects performed the task with little knowledge of the contingencies underlying their successful performance (Bechara et al. 1997). The contents of working memory are, by definition, consciously accessible, so this finding would seem to preclude a role for working memory in the task. However, recent findings show that subjects are trying to track explicitly the experimental contingencies (Maia & McClelland 2004), which suggests that holding outcome information in working memory would be useful for performance. The model may also help explain some of the neuropsychiatric illnesses in which OFC dysfunction is implicated (see Clinical Implications).

Working memory for rewards might also be useful to solve stimulus-reward reversal tasks. Successfully performing these tasks involves gradually learning and unlearning stimulus-reward associations in long-term

memory. However, although these tasks can be learned using stimulus-reward associations, working memory might also contribute to the learning. Explicitly keeping track of a stimulus and its associated outcome might enable faster reversal. A role for working memory is most noticeable in trained monkeys, who are capable of performing reversals following a single error, a phenomenon thought to depend on the development of a reversal "learning set." Increasing the length of the intertrial interval impairs the development of a learning set, suggesting an involvement for working memory (Deets et al. 1970). Indeed, recent computational models of stimulus-reward reversals have incorporated neurons that encode the reward contingencies of the task in their ongoing pattern of neuronal activity (Daglish et al. 2001).

There is one class of deficits relating to OFC damage that does not fit with our model. OFC lesions in monkeys impair the learning of stimulus-response associations (Bussey et al. 2001, Parker & Gaffan 1998). How do we reconcile these results with the observations of a lack of neuronal activity in OFC relating to behavioral responses (Wallis & Miller 2003)? Closer examination of the deficits of OFC animals reveals that their problems stem not from learning stimulus-response associations per se, but rather from implementing strategies that speed learning (Bussey et al. 2001). Specifically, control monkeys adopt a "win-stay, lose-shift" strategy, which is absent in monkeys with OFC damage. Such a strategy conceivably requires the monkey to hold in working memory the outcome of its choice on the previous trial across the intertrial interval, which is compatible with our account of OFC function.

CONCLUSION

Damage to OFC produces a unique deficit, impairing everyday decision-making while leaving other cognitive capabilities intact. An extensive literature implicates the OFC in processing reward information, but in the laboratory situation, the experimenter usually endeavors to ensure that it is obvious whether a choice was rewarding. In real life, it is often not so clear cut. The ultimate outcome of our choice may not be apparent until some time distant from when we make the choice, or it may occur unpredictably. We may need to consider multiple variables, some of which will be more or less important to us depending on our present needs. Some choices could have negative consequences that we will need to offset against the positive. In short, in the real world, considerable processing is often required to determine just how rewarding a reward actually is. We suggest that this is the role of the OFC. Furthermore, we have proposed a mechanism by which this might take place. We suggest that the value of the

CLINICAL IMPLICATIONS

OFC dysfunction is associated with disorders involving compulsive behavior (Volkow & Fowler 2000) such as obsessive-compulsive disorder, substance abuse, eating disorders, obesity and pathological gambling. Subjects report feeling out of control of their behavior, an immense desire to engage in the compulsive behavior and a feeling of release once they do. This behavior is thought to depend on the nucleus accumbens, a region with which OFC heavily connects (Haber et al. 1995). For example, drugs of abuse are thought to sensitize the nucleus accumbens, which misdirects behavior towards drug acquisition (Everitt & Robbins 2005, Hyman & Malenka 2001, Robinson & Berridge 2003).

How might OFC influence this process? We have emphasized how OFC is important for planning and obtaining distant rewards and goals. Thus, one of its functions may be to provide top-down control to the nucleus accumbens, biasing behavior away from immediate rewards in the environment. This might be important when trying to quit a drug. For example, the recovering alcoholic must bring to working memory the long-term goal to remain sober in order to inhibit the habitual response to enter the liquor store. Disorders such as substance abuse and obesity might result from lack of top-down control, while disorders such as anorexia might arise from too much control.

expected outcome is held in working memory, in much the same way that sensorimotor and contextual information are held in working memory in the lateral PFC. MPFC can then use this information to determine whether a given action path is worthwhile, while lateral PFC can use the information to plan and coordinate behavior. In this way, these distinct PFC areas can act in concert to ensure that we get what we need.

SUMMARY POINTS

1. The anatomy of OFC suggests a region that integrates multiple sensory properties with affective information.
2. The functional properties of OFC are consistent with a direct role in reward processing rather than the performance of a function that merely correlates with reward.
3. OFC is responsible for calculating the value of a reward outcome, which includes assessing trade-offs, determining how well the outcome satisfies current needs, and comparing the outcome with other potential reward outcomes.
4. OFC conceivably operates in a fashion analogous to the rest of PFC, holding information about the value of reward outcomes in working memory. This would be useful for formulating action plans, as well as predicting and monitoring expected outcomes.
5. Lateral PFC could use the value signal to plan the most efficient behavior, whereas medial PFC may use the signal to perform a cost-benefit analysis of the plan.

FUTURE ISSUES TO BE RESOLVED

1. We need to specify more precisely the differences in function of OFC and MPFC. This will require experiments designed to detect double dissociations in the functions of the two areas, including direct comparison of lesions of the two structures, as well as the properties of neurons in both areas.
2. We need to understand how value information controls behavior: How does information pass between the different PFC areas, and how do subcortical structures, such as the nucleus accumbens, use the information?
3. We need to determine the nature of the value signal in OFC. Does it relate more to hedonic value, incentive value, or a combination of the two?
4. We need to understand the neuromodulation of PFC. For example, does reward information carried by dopamine neurons drive reward encoding in OFC or vice versa? How does the involvement of dopamine in spatial working memory relate to the capacity of dopamine neurons to encode rewards?

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