Functional magnetic resonance imaging of reward prediction

Brian Knutson and Jeffrey C. Cooper

Purpose of review

Technical and conceptual advances in functional magnetic resonance imaging now allow visualization of real-time changes in oxygenation of deep subcortical regions, leading to rapid advances in scientific characterization of the neural substrates that underlie reward prediction in humans.

Recent findings

Neuroimaging research over the past year has focused on determining the necessary neural substrates for reward prediction.

Summary

While the orbitofrontal cortex has long been implicated in modality-specific reward representation, the ventral striatum (particularly the nucleus accumbens) may play a role in modality-independent representations of predicted reward. On the other hand, the mesial prefrontal cortex appears to play a role in representing reward prediction error and the dorsal caudate in linking reward to behavior. Theoretically, future studies will need to establish the specificity of these responses to reward versus punishment and anticipation versus outcome. Clinically, current findings suggest that patients can predict reward without a prefrontal cortex, but should experience difficulty correcting their behavior when reward predictions are violated.

Keywords

accumbens, fMRI, prediction, prefrontal cortex, reward, review, striatum

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Psychology Department, Stanford University, Stanford, CA, USA

Correspondence to Brian Knutson, Bldg. 420, Jordan Hall, Stanford, CA 94305, USA
Tel: +1 650 724 2965; fax: +1 650 725 5699;
e-mail: knutson@psych.stanford.edu

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Abbreviations

fMRI	functional magnetic resonance imaging
MPFC	mesial prefrontal cortex
OFC	orbital frontal cortex
PET	positron emission tomography

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Introduction

The case of Phineas Gage, perhaps the most famous in neurology, also remains one of the most puzzling. After a tamping iron flew through Gage's left cheek and the top of his head, he not only suffered damage to the prefrontal cortex, but also a change in temperament. The account of Gage's physician, John Martyn Harlow, has been cited as evidence for involvement of the prefrontal cortex in emotion ('The…balance…between his intellectual faculties and animal propensities seems to have been destroyed.' [1]). However, with respect to emotion, Harlow's account raises more questions than it answers. Specifically, Harlow noted that Gage not only showed emotional deficits after the prefrontal damage ('…capricious and vacillating'), but also emotional excesses ('…impatient of restraint or advice when it conflicts with his desires') [2].

Over a century and a half after Gage's accident, advances in brain-imaging techniques may shed new light on the role of the prefrontal cortex in emotion in general and reward processing in particular. Rewarding stimuli can be broadly defined as those that an organism will work to acquire. Thus, reward value does not critically depend upon the sensory modality of the stimulus and can even change dynamically for the same stimulus. Historically, comparative studies using electrical stimulation of the brain point towards subcortical rather than cortical regions as necessary substrates for eliciting reward-related behavior [3,4]. More recently, electrophysiological recordings suggest that midbrain dopamine neurons of monkeys initially fire in response to unexpected rewards but subsequently track reward cues [5]. Further, voltammetric recordings in the ventral striatum of rats demonstrate dopamine release in response to both natural and pharmacological reward cues [6]. Together, these comparative findings implicate subcortical dopamine release not just during reward consumption, but also during reward prediction.

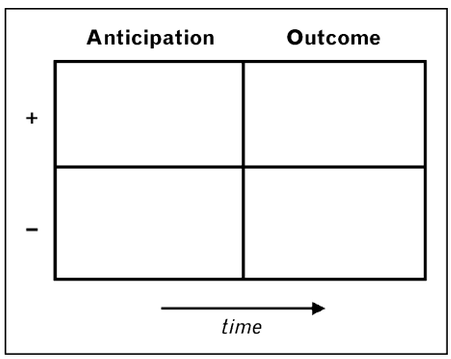
Parallel with improvements in comparative methods, techniques for imaging the human brain are also showing startling improvements in spatiotemporal resolution. Positron emission tomography (PET) imaging allows visualization of general metabolic and specific neurochemical changes in subcortical regions. For instance, a recent PET study extended earlier work [7], controlling for motor confounds, to show that both rewarding and probabilistic features of a monetarily rewarded video game could elicit striatal dopamine release [8•]. However, current PET protocols ($\sim$8 mm^3 every

2 min) cannot attain the spatiotemporal resolution of functional magnetic resonance imaging (fMRI; $\sim$4 mm^3 every 2 s). Since reward prediction changes on a second-to-second basis and presumably recruits small subcortical nuclei, fMRI methods have been increasingly applied to the study of human reward processing. Indeed, a literature search with the search items reward and fmri (excluding reviews, commentaries, and nonhuman studies) reveals a nearly linear increase in published studies starting at the millenium (2000, six studies; 2001, nine; 2002, 15; 2003, 21; 2004, 26).

Following PET research, initial fMRI studies localized brain areas that responded to presentation of both primary and secondary rewarding stimuli, after stabilization of learning [9–11]. Commonly activated 'reward circuitry' includes midbrain, ventral striatum (including the nucleus accumbens), medial amygdala, orbital frontal cortex (OFC), and mesial prefrontal cortex (MPFC) – all areas innervated by mesolimbic dopamine projections. These findings have been well-summarized by a spate of recent reviews [12•,13•,14,15••]. Soon afterwards, a second round of event-related fMRI studies indicated that different parts of this circuit are activated preferentially during reward anticipation (e.g. ventral striatum) versus outcome (e.g. MPFC) [16,17]. These findings raise further questions about the function of 'reward circuitry.' For instance, do these regions activate as a monolithic whole? If not, which aspect of reward most potently activates different regions, and when? What is the physiological basis of activation, and how do regions interact? Essentially, researchers have begun to ask questions about the dynamic function of putative reward circuitry.

Reward processing can be situated in a broader framework of incentive processing. Specifically, one can qualitatively distinguish between positive and negative incentives, as well as temporally distinguish incentive anticipation from outcomes [18] (Figure 1). Such a framework raises specific questions: does reward prediction carry a distinct neural signature? Is it similar to punishment prediction, or the response to reward outcomes? The framework can also accommodate additional variables, such as whether a behavioral response is required prior to or after anticipation in order to obtain an outcome, the length of the anticipatory period, the probability of the outcome, and so forth. fMRI studies in the recent past have primarily examined neural activation in responses to reward outcomes (upper-right quadrant, Figure 1), whereas fewer have focused on reward anticipation (upper-left quadrant, Figure 1), and a handful have examined reward learning, which could be conceptualized as the transfer of neural activation from reward outcomes to reward anticipation (i.e. upper-right to upper-left quadrant, Figure 1). In this review, we focus on recent studies of reward processing (the top quadrants), though some of these studies include punishing incentives as controls.

Figure 1. A simple framework for incentive processing



Recent findings (2004–2005)

Over the past year, investigators have used different designs affording varying amounts of temporal resolution. One implication of the above conceptual scheme for incentive processing is that enhanced temporal resolution should also increase specificity of findings.

Dynamic design

An emerging trend includes a growing number of fMRI studies that dynamically model aspects of incentive processing. Following monkey studies, many (but not all) of these studies focus on learning and posit the transfer of a neural signal from reward outcomes to reward-prediction cues. For instance, in a study involving a probabilistic task during which subjects learned to choose an option that afforded monetary gains and avoid another which incurred losses, investigators found that a model of short-term reward prediction maximally correlated with activation in the caudate/ventral striatum and lateral OFC, while a model of longer-term reward prediction correlated with activation in cortical regions including dorsolateral prefrontal cortex and inferior parietal cortex [19•]. A second study using a similar paradigm indicated that activation of the caudate/ventral striatum most closely correlated with behavioral indices of reward learning, independent of task difficulty [20]. In another probabilistic choice task focusing on learning which cues afforded monetary gain, the caudate showed more activation in early stages of learning [21•]. Finally, in a study that involved learning which cues yielded juice, subjects' ventral striatal activation tracked reward-cue prediction in both passive and active tasks (i.e. subjects selected the cue), while their dorsal striatal activation only tracked reward cues in the active task [22••]. One strength of this study involved comparison of two different models rather than simple correlation of brain activation with one model. Together, these studies point to the ventral striatum/rostral caudate as an important substrate for reward learning and, eventually, short-term prediction

independent of reward modality (i.e. money versus juice) and task difficulty. While dynamic studies complement static studies, static incentive paradigms also recruit mesolimbic pathways even after learning has stabilized. We turn next to recent findings involving these static tasks.

Block design

Only a handful of studies utilizing block designs focused on reward processing in the past year. One such study found that movement requirements produced additional activation in regions activated by monetary reward versus nonreward contingencies, including the putamen and amygdala [23]. A second study found that exposure to pictures of womens' own children and romantic partners versus familiar acquaintances elicited a broad swath of neural activation in regions including MPFC and striatum (i.e. including putamen, caudate, and ventral striatum) [24]. A third study of men and women reporting equivalently high levels of sexual arousal found robust ventral striatal as well as visual cortical activation in response to pictures of sexual versus nonsexual interactions [25•]. A fourth study focused not on pleasure but pain, comparing painful stimulation of the hand or foot to the absence of stimulation. However, pertinent to the current discussion, the only brain region to show deactivations during pain administration was bilateral nucleus accumbens [26••]. Historically, fewer block than event-related studies have obtained significant activations in small subcortical regions such as the rostral nucleus accumbens. At present, it is not clear whether these differences result from methodological issues such as low spatial resolution due to large smoothing kernels, uncontrolled psychological confounds involving expectation, or a physiological inability of these small structures to fire in a tonic versus phasic pattern.

Event-related design

A growing appreciation of the dynamic nature of reward processing has generated a recent proliferation of event-related studies on reward processing. Some of the most replicable paradigms utilize monetary incentives, perhaps because money confers experimental control (i.e. money is nearly universally valued, can serve as either a positive or negative incentive, and can be scaled in magnitude). Improving upon prior findings [9] with an event-related design, one study found that monetary gain versus loss feedback elicited more caudate activation than nominal feedback [27]. In a second study, choice between risky monetary gambles (i.e. those involving higher versus lower stakes) activated anterior cingulate, whereas gain versus loss outcomes across all stakes activated medial frontal gyrus and ventral striatum (including nucleus accumbens) [28]. In a third study, anticipation and choice of risky versus nonrisky gambles activated medial prefrontal gyrus, nucleus accumbens, caudate tail, and visual cortex (however, in this study, anticipated risk and reward covaried) [29•]. Two studies focused on motor demands as an alternative explanation for ventral striatal activation usually observed during reward processing. One study found that monetary gain requiring a motor response elicited greater subsequent activation of the caudate and ventral striatum than did a gain requiring no motor response [30]. However, the action requirement also elicited greater physiological arousal, making it unclear whether activation was related to motor demands or changes in affect. A second study found that when subjects were told that their button press determined monetary gain, dorsal caudate showed greater activation than after a noncontingent button press, implying that perception of contingency between reward outcomes and action activated the dorsal caudate [31•].

However, two additional studies indicated that ventral striatal activation could occur during reward anticipation in tasks that lacked significant anticipated motor demands. In one study utilizing passive monetary cues and reward outcomes, reward cues activated ventral striatum (including nucleus accumbens and globus pallidus), while reward outcomes activated MPFC [32•]. A second study involved a risky choice followed by an anticipatory delay and then outcome feedback. While risky choice activated anterior cingulate, parietal cortex, and supplementary motor area, anticipation of rewarding outcomes activated ventral striatum (including nucleus accumbens), even after choice but prior to outcome revelation [33•]. Finally, a study of choices between 'immediate' (a gift certificate after the scan) and 'delayed' (a gift certificate in the mail after a week or more) rewards activated the ventral striatum (including nucleus accumbens) and MPFC in choices involving at least one immediate reward, but not two delayed rewards. Interestingly, time-course plots suggested an earlier response of nucleus accumbens than MPFC, although this was not noted or analyzed explicitly [34•].

These findings importantly extend prior findings by allowing investigators to dissociate different phases of reward processing. Even after learning has occurred, anticipation of monetary reward activates ventral striatum, while monetary reward outcomes activate the MPFC. In paradigms that include both positive and negative incentive conditions, effects are stronger for gains than losses. A novel finding is that consideration of risky choices activates the anterior cingulate, which is consistent with a proposed role for this region in conflict and performance monitoring [35], since risk involves consideration of both potential gains and losses. Findings are also beginning to suggest that surprise and motor demands cannot fully account for ventral striatal activation in the context of reward.

If reward representations transcend sensory modality, then similar findings should obtain for different types of reward. Besides secondary (learned) incentives such as money, some studies have utilized primary (unlearned) incentives. For instance, a study of beverage preferences indicated that ingestion of preferred beverages activated the MPFC, but presentation of brand information both altered preferences and activated dorsolateral prefrontal cortex and hippocampus [36]. Other studies utilized secondary reinforcers such as visually pleasing art. One such study reported that attractive versus unattractive art activated OFC, MPFC, and visual areas [37], but a second found that attractive versus unattractive art activated right medial caudate, left cingulate, bilateral fusiform, and visual regions [38]. Whereas none of these studies reported subcortical activation, none explicitly manipulated or modeled reward prediction. However, earlier studies of primary rewards (e.g. taste and smell) signaled by reward cues have reported anticipatory ventral striatal activation [17,39].

fMRI researchers have begun to extend reward paradigms to the study of cognition and social behavior. In the realm of cognition, one study investigated the relationship between working memory and motivation for monetary reward. The investigators found that monetary reward improved task performance and activated nucleus accumbens, caudate, insula, premotor cortex, and superior parietal cortex. The investigators also reported a reward by memory maintenance interaction in the right superior frontal sulcus and bilateral intraparietal sulcus, as well as a reward by memory retrieval interaction in the dorsolateral prefrontal cortex [40•]. A second study found that anticipation of monetary reward improved incidental memory for reward cue features and this improvement was related to midbrain and ventral striatal modulation of medial temporal lobe activation during encoding [41•].

An increasing number of studies also examined reward in the context of social interaction. Extending prior work, one study found that in the context of a Prisoner's Dilemma game using monetary incentives, subjects showed increased activation in the MPFC, OFC, and nucleus accumbens when a partner outside the magnet cooperated with the subject (i.e. maximized the pair's monetary gains) and deactivations of these same regions when the partner defected (i.e. maximized their own monetary gains at the subject's expense). Similar results were obtained in play with a computer partner, but not as robustly [42], suggesting that social interactions can potentiate the value of monetary reward. A second study investigated neural responses to faces of people who had previously cooperated or defected in a Prisoner's Dilemma game. Relative to neutral faces, faces of cooperators elicited activation of lateral OFC, nucleus accumbens, putamen, insula, fusiform gyrus, and superior temporal sulcus, while faces of intentional relative to nonintentional cooperators further enhanced activation in these regions, suggesting that social interactions can potentiate anticipated reward value as well [43•]. This finding relates in an interesting way to a PET study indicating that rostral caudate activation predicts willingness to punish someone who has defected against the subject in the past [44]. Together, these findings build on the observation that anticipation of monetary gains activates the ventral striatum, while monetary gain outcomes activate the MPFC [45], by suggesting that social interactions may potentiate reward value.

Finally, in the past year, investigators have increasingly applied fMRI studies of reward processing to clinical issues. In some studies, investigators extended established paradigms to new samples. For instance, one study extended a gambling paradigm to an adolescent sample, replicating findings of MPFC, lateral OFC, and ventral striatal activation to reward outcomes [46]. A second study compared adult and adolescent samples using a monetary incentive delay task. These investigators replicated the earlier dissociation of nucleus accumbens activation during reward anticipation but MPFC activation in response to reward outcomes. Across all subjects cue-elicited excitement correlated with nucleus accumbens activation, independent of age [47]. Other studies combined event-related fMRI with pharmacological manipulations. Consistent with prior drug-infusion studies, one study found that amphetamine infusion activated MPFC, rostral anterior cingulate, and ventral striatum in naïve subjects [48]. A second study combined oral amphetamine administration with a monetary incentive delay task. Relative to placebo, amphetamine 'smoothed' nucleus accumbens activation during gain anticipation (i.e. decreasing the peak and increasing the tail), consistent with comparative studies of the effects of amphetamine on nucleus accumbens dopamine activity [49•], and had parallel effects on cue-elicited excitement. A number of studies began to probe reward circuitry responsiveness to clinically relevant stimuli. For instance, one study illustrated that putamen, anterior cingulate, and MPFC activation to alcohol cues predicted speed of relapse in a sample of alcoholics [50]. A second study integrated both fMRI and PET to find not only that alcohol cues activated striatum and MPFC in alcoholics versus healthy volunteers, but also that alcoholics had fewer dopamine receptors in the ventral striatum, which was correlated both with craving and higher MPFC activation to alcohol cues as measured with fMRI [51••]. These initial forays suggest that event-related fMRI studies of reward processing can inform clinical research.

Implications

Improvements in the spatial and temporal resolution have caused fMRI of reward processing to mature from

infancy to adolescence in the span of a few short years. Last year (2004–2005) produced dual shifts in methodology from block designs to more temporally sensitive designs and in conceptualization from a monolithic to a dynamic view of reward processing. Findings from both dynamic and event-related studies broadly support earlier observations that while the ventral striatum (including the nucleus accumbens) plays a role in reward prediction and anticipation, the MPFC instead plays a more prominent role in processing reward outcomes. New findings also point towards a central role for the anterior cingulate in risk assessment (which requires concurrent consideration of both potential rewards and punishments), and a role for the dorsal caudate in associating reward with action. Studies are beginning to suggest that reward anticipation can modulate subsequent sensory, motor, cognitive, and social processing.

Despite the proliferation of recent findings, current reviews of fMRI research on reward processing (including the present one) may yield premature conclusions for both methodological and conceptual reasons. Methodologically, researchers continue to gain increasing (if often implicit) technical expertise in visualizing transient activity in small subcortical nuclei with fMRI. Adoption of these improved methods is currently preliminary and uneven. For instance, researchers can better resolve activations in small subcortical structures by utilizing commensurate voxel size and spatial smoothing kernels (i.e. $\sim$4 mm) and limiting reliance on cluster criteria. Investigators can also minimize signal loss at the bottom of the brain by utilizing dropout-resistant pulse sequences (e.g. spiral in/out, z-shimming) in conjunction with lower-field magnets (i.e. $\leq$3 T) and correction for physiological noise. Furthermore, as is the case with different cortical regions, investigators are beginning to realize that different parts of the striatum play distinct roles in reward processing. While a consensus has not been reached on anatomical criteria for distinguishing and identifying different striatal structures (e.g. the nucleus accumbens does not appear in the traditional Talairach atlas), useful candidate schemes exist and could be adopted [52].

Conceptually, investigators are just beginning to tease apart the various components of reward processing experimentally, including affective valence and arousal, attention, motor demands, contingency, etc. The scheme for incentive processing presented in Figure 1 implies that both reward anticipation and outcomes should be controlled. Periodic protocols (including block and slow event-related designs) introduce anticipatory confounds, which can be addressed via adoption of nonperiodic event-related designs. Further, to verify valence-specificity of effects, many designs now include both positive- and negative-incentive control conditions, as well as parametric manipulations of incentive magnitude. While methodological and conceptual advances present a moving target for research, they also ultimately promise to improve replicability, and thus to pave the way for future quantitative rather than qualitative reviews.

Looking ahead, we foresee continued enhancement of the spatial and temporal resolution of event-related fMRI. Additionally, statistical methods for model comparison and analysis of functional connectivity should advance research on reward processing. Investigators have begun to uncover the physiological basis of the blood oxygen-level-dependent signal indexed by fMRI, and progress in this area (particularly with respect to dopaminergic modulation of postsynaptic activity) should also provide critical information. These technical, analytic, and physiological advances will buttress ongoing applications to predicting cognitive (e.g. memory) and behavioral (e.g. choice) phenomena, as well as the extension of existing paradigms from healthy to clinical samples.

Indeed, the seminal clinical case of Phineas Gage provides some of the first clues about the neurally distributed nature of reward processing. For Gage, prefrontal damage seemed to increase emotional reactions to immediate stimuli, but decrease emotional reactions to distal stimuli (e.g. in the case of planning). If, as suggested by current event-related fMRI findings, the ventral striatum anticipates reward, while the MPFC processes reward outcomes, then a lesion to the MPFC may unleash appetitive impulses. In the words of Gage's physician, such an injury might have the appearance of undoing a cultivated balance, liberating 'animal' passions at the expense of more 'intellectual' faculties. Thus, the surprising message from current brain-imaging findings is that a prefrontal cortex may not be necessary for reward prediction – at least in the short term. However, a prefrontal cortex may be necessary for changing reward predictions. Hence, fMRI findings may shed new light on old puzzles.

Conclusion

For fMRI studies of reward processing, 2004–2005 marks a critical transition period. In the remarkably short span of a few years, research has moved beyond the essential step of localization into charting dynamics. Ultimately, we anticipate that studies will lead back out of the brain to behavioral prediction. Glimmers of these developments are already on the horizon. Under current circumstances, prediction of future reward would appear both rational and justified.

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