CHAPTER

25

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Representation of Subjective Value in the Striatum

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OUTLINE

INTRODUCTION

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Overview

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p0010 A primary goal of neuroeconomics is to explain how brains choose. In contrast to a correlational approach, recent technological innovations facilitate a process approach that examines how distinct neural components promote subsequent choice. We review animal and human studies that focus on the representation of subjective value in the striatum. Converging evidence suggests that ventral striatal regions represent anticipated value while dorsal striatal regions represent the value of outcomes in the service of choosing future actions, suggesting a temporal flow of information through the striatum during incentive processing in the service of estimating and acquiring gains. These emerging findings highlight the dynamic, componential, and ultimately subjective nature of valuation, and hold implications for informing public policy and diagnosing mental illness.

Background

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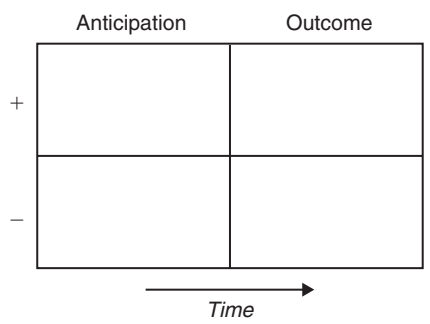
p0020 While neuroeconomics aims to explain how the brain chooses (i.e., often with respect to resource allocation), different disciplines have historically approached this question from different vantage points. Three prototypical views can be identified – those of

neuroscientists, psychologists, and economists. Neuroscientists typically start from neurons, or the cells that make up the brain. Psychologists typically start from experiential phenomena related to affect, cognition, and behavior. Economists typically start from axioms or mathematically consistent specifications. These different views can subtly bias the assumptions and goals of each type of investigator. For instance, neuroscientists might want to use axioms to model neural activity, while economists might want to use neural activity to verify axioms, and psychologists might want to map intermediate links between neural activity and axioms (including affect, cognition, and behavior) (see also Chapter 10 of this volume). All researchers, however, can benefit from using neuroscientific methods to improve prediction of choice.

p0030 To investigate how the brain chooses, researchers have typically adopted one of two strategies. One "correlational" strategy seeks to identify neural correlates of choice (consistent with behavioral neuroscience, behavioral psychological, and revealed-preference economic approaches). Another "process" strategy seeks to determine how different neural components causally influence future choice (consistent with cognitive neuroscience, cognitive psychology, and prospect-theoretic economic approaches). Since a process strategy assumes that value is represented before choice, it implicitly encourages dynamic and componential decomposition of value representation, which should then facilitate prediction. At minimum, for instance, valuation can be broken down into positive and negative representations of anticipated and received incentives (Figure 25.1; Knutson and Cooper, 2005). Critically, such a decomposition does not assume that gain is the opposite of loss, or that anticipation is the same as outcome. Methods with advanced spatiotemporal resolution can facilitate process analyses by enabling researchers to measure value representation before as well as after choice. For the purposes of this chapter, we specifically refer to subjective valuation, or the value that a given individual (rather than an experimenter or society) places on a stimulus. This subjective value is computed before contact with the stimulus, and can facilitate approach towards or avoidance of the stimulus, but also can be updated based on experience with the stimulus. Thus, we minimally assume that subjective value is represented in the brain prior to choice (potentially by multiple components), can influence subsequent choice, and can be dynamically assigned (and thus updated). Consistent with these criteria, below we review (1) historical findings implicating the striatum in the representation of subjective value, (2) structural delineation of different striatal components, (3) functional studies attempting to localize subjective value to striatal components, (4) prediction studies attempting to use striatal signals to predict choice, and (5) conclusions and implications.



f0010 **FIGURE 25.1** Minimal scheme for a process analysis of incentive valuation. Reproduced from Knutson and Cooper (2005), with permission.

History

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p0040 One popular "information processing" analogy likens the brain to a computer (Newell and Simon, 1972). This analogy fits to some extent, since the brain includes many small but interconnected components (neurons) capable of converting continuous (or analog) to binary (or digital) signals (Rumelhart and McClelland, 1986). However, the analogy's fit is also somewhat forced, since it fails to consider a critical functional constraint on brain design. The brain is not like just any computer – it is a computer specifically designed to facilitate its host's survival and procreation (Dawkins, 1989; Glimcher, 2003). Thus, the brain must subjectively evaluate incoming information in the light of these overarching goals before acting upon it. Conceptually, this scheme implies an inward funneling in which sensory impulses must be filtered and then subjectively evaluated, followed by an outward funneling in which completed evaluations then flexibly link to appropriate motor responses. Physiologically, this scheme implies the existence of evolutionarily-conserved subjective valuation mechanisms that can link sensory impressions to motor responses.

p0050 Where in the brain's haystack of neurons might the needles of subjective value lie? The funneling scheme implies that if one could directly stimulate neural circuits that represent value, one could unconditionally elicit relevant behavior (i.e., approach or avoidance). Following lesions and recording, brain stimulation is one of the oldest of neurophysiological methods. While introductory neuroscience textbooks typically

feature studies in which researchers used electrical stimulation to map sensory and motor cortical organization (Jasper and Penfield, 1954), fewer focus on electrical stimulation of subcortical regions. As illustrated by early studies in which subcortical electrical stimulation unconditionally elicited enraged behavior in cats (Hess, 1959), electrical stimulation of subcortical regions can unconditionally elicit approach or avoidance behavior. For instance, decades of research suggest that electrical stimulation of brain regions that lie along the ascending trajectory of dopamine neurons (i.e., projecting from the ventral tegmental area to the lateral hypothalamus to ventral striatal regions and the medial prefrontal cortex) can unconditionally elicit approach behavior (Olds and Fobes, 1981), while electrical stimulation of other regions (i.e., descending from the insular cortex and lateral amygdala to the stria terminals and medial hypothalamus to the periaqueductal gray) unconditionally elicits avoidance behavior (LeDoux, 2000). Beyond experimenter-administered electrical stimulation, animals also self-administer brain stimulation, as initially dramatically demonstrated in rats (Olds and Milner, 1954). Many of the regions that elicit self-administration overlap with those that unconditionally elicit approach behavior after stimulation (listed above), implicating these regions in motivation as well as motion. Some of the regions that elicit the most vigorous self-stimulation include ventral parts of the striatum (Olds and Fobes, 1981). Thus, striatal circuits provide a promising starting point in the search for the neural substrates of subjective value.

STRUCTURE

The striatum is a set of subcortical structures located in the center of the brain, behind the frontal lobes and below the thalamus. The striatum includes three structures: the caudate, the putamen, and the nucleus accumbens (NAcc). The caudate (Latin: "having a tail") is the most superior, and has the appearance of a comet in its anterior aspect, with a tail curving around both sides of the lateral ventricles towards the posterior part of the brain. Thus, parts of the caudate have been named the head, the medial aspect, and the tail, curving from front to back. The putamen (Latin: "peel, husk, or shell of seed or fruit") is the most inferior, and has the appearance of a shell, curving upward from the base of the brain. The caudate and putamen are diagonally divided in primates (but not in rodents, in which they are called the caudate-putamen) by a white matter tract called the internal capsule, which carries nerves from the motor cortex to the red nucleus near the base of the brain (Herrero *et al*., 2002). In fact, the striatum (Latin: "striped") takes its name from the striped appearance of the internal capsule due to interposed gray (neurons) and white (glia) matter (Finger, 1994). The nucleus accumbens (Latin: "kernel which lies against" the wall of the third ventricle) has the appearance of two tubes connecting the caudate and putamen ventrally, where the internal capsule ends (Figure 25.2). While comparative researchers have divided the NAcc into medial shell and lateral core aspects using cell identification techniques (Zahm and Brog, 1992), most neuroimaging methods presently lack such fine spatial resolution.

As is common in neuroanatomical nomenclature, other terms refer to striatal structures or their parts, potentially causing confusion. The "basal ganglia" (Latin: "lower swelling") refers to a set of subcortical gray matter structures that includes the striatum, but also the globus pallidus (Latin: "pale clump," a motor output region), the subthalamic nucleus (a relay to the prefrontal cortex), and the substantia nigra

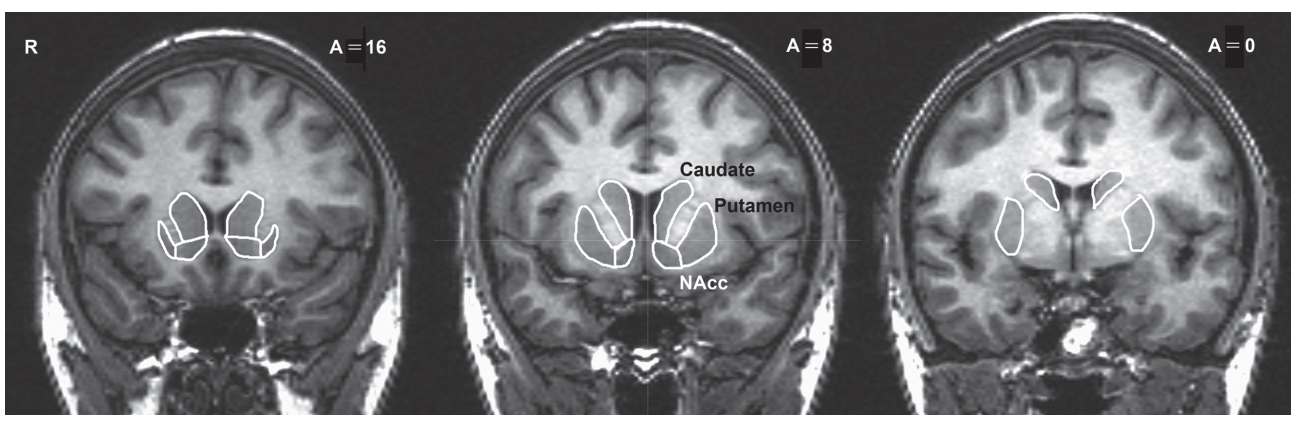
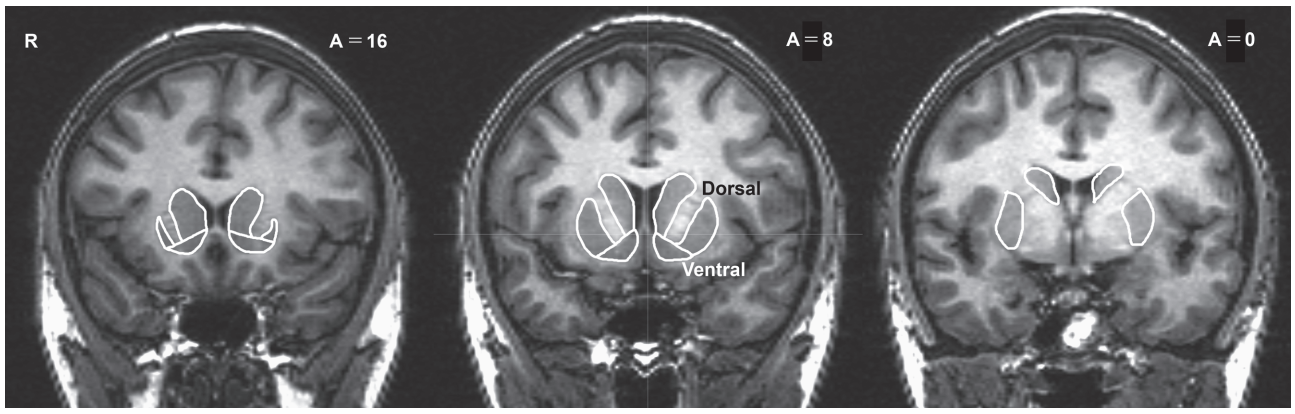


FIGURE 25.2 Nucleus accumbens (NAcc), caudate, and putamen. Reproduced from Breiter *et al*. (1997), with permission.

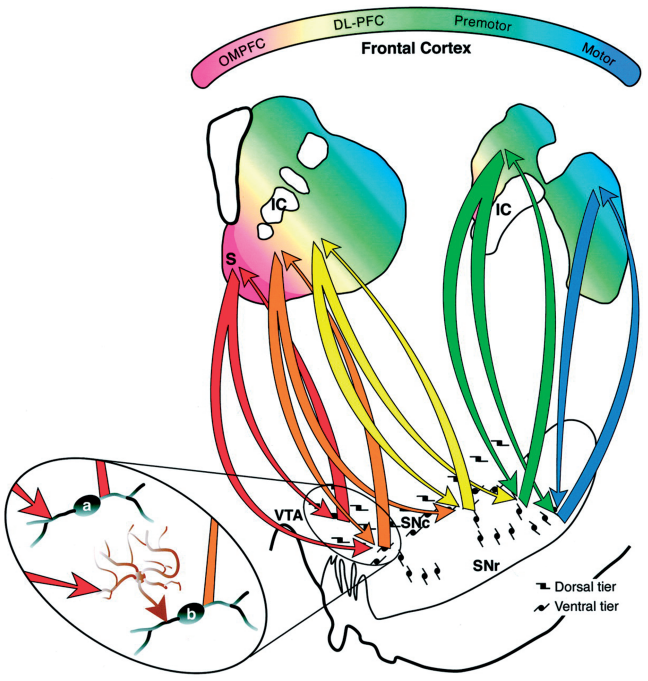


f0030 **FIGURE 25.3** Ventral and dorsal striatum. Reproduced from Mawlawi *et al*. (2001), with permission.

(Latin: "black substance", which provides dopaminergic input to the dorsal striatum). The putamen curves around the globus pallidus (which contains both internal or medial and external or lateral portions), and these two structures have together been referred to as the "lentiform" (Latin: "lentil-shaped") nucleus. Historically, the boundaries of the NAcc have not been clearly anatomically delineated (see, for example, the Talairach atlas (Talairach and Tournoux, 1988)), leading researchers to refer to the same region as both the NAcc and the head of the caudate. Finally, many researchers simply divide the striatum into lower (ventral) versus higher (dorsal) sections, with the ventral striatum encompassing the NAcc and lower portions of the putamen and caudate (and olfactory tubercle), while the dorsal striatum encompasses higher parts of the putamen and caudate (Gerfen and Wilson, 1996) (Figure 25.3). Researchers have recently proposed rotating this ventral–dorsal scheme by 45 degrees, forming a ventromedial to dorsolateral gradient (Voorn et al., 2004).

p0080 Given these ambiguities, the anatomical definition of striatal components poses a challenge for neuroimagers. In humans, the caudate and putamen are clearly bounded on most sides by white matter or ventricles, but both share gray matter (and thus ambiguous) borders with the NAcc. Inspired by studies of neural connectivity, anatomical schemes for distinguishing ventral from dorsal striatum have been developed for positron emission tomography (PET) imaging (Drevets *et al*., 2001; Mawlawi *et al*., 2001) (Figure 25.3). Functional magnetic resonance imaging (fMRI) can provide finer spatial resolution, and thus the basis for identifying smaller striatal components delineated in comparative studies on the basis of cell type. According to one scheme, after orienting a brain in Talairach space, the NAcc can be distinguished from caudate dorsally by drawing a line from the tip of the internal capsule medially to the ventricle, and from the putamen laterally by drawing a line from the tip of the internal capsule ventrally to white matter (Breiter *et al*., 1997). The anterior limit suggested by these authors extends to white matter, while the posterior limit was not specified, but has been set at or anterior to the anterior commissure in other studies (Haber and McFarland, 1999; Knutson *et al*., 2001a; Figure 25.3).

p0090 Distinguishing between different striatal components is important, because these components connect to different brain regions and thus may support distinct functions. Early lesion studies suggested that different parts of the striatum projected to different parts of the prefrontal cortex via thalamic relays, which then projected back to the striatum, forming "loops" (Alexander *et al*., 1986). Primate anatomical tracing studies have supported this scheme, demonstrating that the NAcc is connected to medial and ventral parts of the prefrontal cortex, while medial regions of the caudate and putamen connect to more dorsal regions of the anterior cingulate, and dorsal regions of the caudate and putamen connect to the dorsolateral prefrontal cortex (Haber, 2003). In addition, these studies indicated some overlap in projections, such that ventral loops connected to more dorsal loops in an ascending spiral running from ventromedial (i.e., NAcc/orbitofrontal cortex) to more dorsolateral (i.e., caudate tail/motor cortex) regions (Figure 23.4). Recent diffusion tensor imaging studies have verified this ascending spiral scheme of striatal-prefrontal connectivity in humans (Lehericy *et al.,* 2004). Thus, the striatum indirectly projects to the prefrontal cortex via inhibitory (i.e., GABAergic) projections that run through the subthalamic nucleus, pallidum, and thalamus. Reciprocally, a large part of striatal input comes from the frontal cortex via excitatory (i.e., glutamatergic) projections. Additionally, subcortical regions



f0040 **FIGURE 25.4** Ascending spirals of connectivity of the striatum to midbrain (downwards) and prefrontal cortex (upwards). Haber *et al*. (2000).

including the anterior insula, basolateral amygdala, and hippocampus project to the ventral striatum (specifically, the shell of the NAcc) via excitatory (i.e., glutamatergic) projections (Friedman *et al*., 2002). Finally, the ventral striatum sends prominent inhibitory (i.e., GABAergic) projections to the hypothalamus (Groenewegen *et al*., 1999).

p0100 In addition to input and output involving simple excitatory (e.g., glutamate) and inhibitory (e.g., GABA) amino acid neurotransmitters, which act at specific synapses on a sub-second timescale, striatal activity is also modulated by larger biogenic amine and peptidergic neurotransmitters, which are likely to operate more broadly over multiple synapses on slower timescales of seconds or more. Of the biogenic amines, two midbrain dopaminergic nuclei prominently project to the striatum. Specifically, the more ventral and medial ventral tegmental area (VTA) nucleus projects to the ventral striatum, while the more dorsal and lateral substantia nigra (SN) nucleus projects to the dorsal striatum. Echoing the ascending spiral theme of striatal–prefrontal connectivity described above, the striatum sends descending inhibitory (GABAergic) projections to midbrain dopaminergic nuclei in a medial to lateral spiraling scheme (Haber *et al*., 2000), implying that the striatum can exert some control over dopamine firing (Figure 23.4). Noradrenergic projections from the locus coeruleus of the midbrain to the striatum are much sparser, and primarily target the caudal NAcc shell and medial caudate adjacent to the stria terminalis, but not other striatal components (Berridge *et al*., 1997). The caudal NAcc shell also receives the densest serotonergic projections from the dorsal raphe nucleus of the brainstem, with few serotonergic projections to the dorsal caudate, and sparse but evenly distributed projections to the putamen (Jacobs and Azmitia, 1992). Finally, tonically active neurons reside in and release acetylcholine in the striatum. Many peptides also innervate the striatum, mostly emanating from subcortical midline projections. While space limits preclude a full review of these peptidergic projections, comprehensive summaries can be found elsewhere (Nieuwenhuys, 1985; Holt *et al*., 1997).

In summary, the human striatum connects to the p0110
rest of the brain (and particularly the prefrontal cortex) in a manner consistent with the notion that different components subserve different functions. Specifically, ventral striatal regions (i.e., NAcc, ventral caudate, and medial putamen) reciprocally target ventromedial cortical and subcortical regions implicated in emotion and motivation, while more dorsolateral striatal components (i.e., dorsolateral caudate and putamen) target dorsolateral cortical and subcortical regions implicated in movement and memory. The ascending loop trajectory implies that information flows through the striatum in a ventral to dorsal direction. This connectivity also implies that the striatum is ideally situated to coordinate valuation and subsequent action (Mogenson *et al*., 1980).

FUNCTION s0060

As early as 1664, British physician and scholar p0120
Thomas Willis observed striatal lesions in patients and speculated about function, noting "For here, … the animal Spirits, preparing for the force of the thing willed, are directed into appropriate nerves" (reprinted in Finger, 1994). Lesion studies still provide one of the few authoritative means of determining whether a structure provides a necessary (but not sufficient) substrate for a given behavioral function. A comprehensive meta-analysis of consequences of striatal lesions indicated that patients with lesions of the putamen (and globus pallidus) primarily presented with motor disturbances (e.g., dystonia), while patients with lesions of the caudate primarily presented with "behavioral" disturbances related to low motivation (e.g., abulia) (Bhatia and Marsden, 1994). Since NAcc was not distinguished from caudate in this review, some of the caudate lesions may also

have included NAcc lesions. Overall, consistent with Willis' early speculation, ventral striatal lesions were more likely to compromise motivation, while dorsal striatal lesions were more likely to compromise motor behavior.

p0130 A second historic body of lesion findings arises from characterization of diseases that compromise dopaminergic input to the striatum (rather than lesions of the striatum itself), such as Parkinson's disease. Typically, Parkinsonian degeneration progresses from the substantia nigra to the ventral tegmental area, and thus depletes dopamine from the dorsal striatum first and the ventral striatum second. Dorsal striatal dopamine depletion compromises affected individuals' ability to initiate or control movement. Patients also show cognitive deficits, however, particularly in the domain of feedback-dependent learning (Packard and Knowlton, 2002). Thus, in addition to examining motor deficits, researchers of these disorders have begun to explore motivational variables. Based on these findings and animal lesion studies, one influential theory describes the ventral striatum as primarily converting motivation to motor behavior (Mogenson *et al*., 1980).

p0140 Beyond investigating the long-term impact of lesions, scientists can directly record the rapid firing of neurons. As with lesion studies, researchers have typically focused either on the firing of neurons in the striatum (primarily GABAergic medium spiny output neurons), or on dopaminergic projections to these striatal neurons. Seminal primate studies have established that dopaminergic projections to the striatum fire in response not only to unexpected reward delivery, but also to reward cues, and decrease firing when predicted reward do not occur – all consistent with a role in reward prediction (Schultz *et al*., 1997; see also Chapters 21 and 22 of this volume). However, these findings specify neither which striatal regions the dopamine neurons target, nor whether dopamine release varies across these targets. Primate studies of striatal neural activity suggest regional variation, with ventral striatal sensitivity to anticipated reward magnitude (Cromwell and Schultz, 2003) and dorsal striatal sensitivity to dynamically changing reward outcomes in the caudate (Hikosaka *et al*., 1989) and to habitual movements in the putamen (Rolls, 1994). While these correlational firing patterns imply that different striatal components might subserve different functions, causal manipulations of the activity of single neurons are both difficult to implement and often have little effect on overt behavior. Since other chapters prominently cover primate electrophysiology studies, we focus below primarily on studies of rodents and humans.

p0150 While lesions last forever and neural firing takes milliseconds, choices are made on an intermediate timescale of seconds. Over the past decade, technological advances now enable researchers to measure subcortical dopamine release (or correlated changes in activity) on a second-to-second timescale. Some methods provide greater chemical sensitivity but reduced temporal resolution, while other recent methods provide greater temporal resolution but reduced chemical sensitivity. Remarkably, and possibly due to improvements in temporal resolution, findings in rats and humans have begun to converge.

Microdialysis

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p0160 Microdialysis allows researchers to sample neurochemical activity in behaving animals (Zetterstrom *et al*., 1981). In microdialysis, a probe consisting of two concentric tubes with a membrane at the end is placed in a brain region. Fluid passes from the outer tube to the inner tube, and molecules in the extracellular space that are small enough to pass through the membrane are sampled. Microdialysis has increased neurochemical specificity but relatively reduced spatial and temporal resolution relative to voltammetric methods (discussed below). For instance, over the past decades, researchers have sampled neurochemicals in regions as small as 0.3 millimeters every 2 minutes (Westerink, 1995; Salamone, 1996). The recent advent of capillary- and microfluidic-based systems will allow the collection of smaller samples, which may significantly improve temporal resolution to a scale of just a few seconds for amino acid and peptidergic neurotransmitters (Kennedy *et al*., 2002). Nonetheless, because microdialysis probes are larger than electrochemical probes, they can cause greater tissue displacement.

p0170 Several microdialysis studies indicate that feeding and drinking significantly increase NAcc dopamine release (Hernandez and Hoebel, 1988; Radakishun *et al*., 1988; Yoshida *et al*., 1992; Young *et al*., 1992; Di Chiara *et al*., 1999), with a few exceptions (Sabol *et al*., 1990; Cenci *et al*., 1992). Feeding and drinking also increase dopamine release in dorsal striatal regions such as the caudate (Young *et al*., 1992), and other mesolimbic regions including the mesial prefrontal cortex (MPFC) (Cenci *et al*., 1992; Young *et al*., 1992) and the VTA (Yoshida *et al*., 1992). While all of these studies included food- or water-restricted rats, even in non-restricted rats, consumption of a palatable food can increase NAcc dopamine release beyond that evoked by consumption of a non-palatable food (Martel and Fantino, 1996). Given the limited temporal resolution of microdialysis, these studies cannot

distinguish anticipation of food or liquid rewards from consumption – a shortcoming which can be partially addressed with experimental manipulations. For instance, presentation of food pellets every 45 s (which also generates anticipatory behavior) increases NAcc dopamine release more than massed presentation of the same amount of food (McCullough and Salamone, 1992). Further, observation of food prior to eating elicits dopamine release in the NAcc (and MPFC), prior to dopamine release elicited by eating, and food-specific satiety blunts this anticipatory release (Ahn and Phillips, 1999). NAcc dopamine release also robustly increases during mating in both males and females (Pfaus *et al*., 1990), as well as in experienced males when presented with an estrous female behind a screen (Damsma *et al*., 1992). Compared with other motorically engaging activities (Martin and Myers, 1976), NAcc dopamine release increases more during copulation than in response to a novel environment or vigorous locomotor activity (Damsma *et al*., 1992).

p0180 Striatal dopamine release is not limited to rewarding circumstances, since many researchers also report increases in NAcc dopamine release during presentation of punishing stimuli such as foot shock (Sorg and Kalivas, 1991), tail shock (Abercrombie *et al*., 1989), or restraint stress (Imperato *et al*., 1992). Cues that predict footshock can also increase NAcc dopamine release (Young *et al*., 1993). While most of these studies did not compare relative levels of dopamine release in response to rewarding versus punishing stimuli, they do suggest that presentation of punishing stimuli can elicit dopamine release. However, some of these studies suggest that NAcc dopamine release is greater during the offset than during the onset of the aversive stimuli, which may still support an appetitive role for NAcc dopamine, even under aversive circumstances. For example, greater increases in NAcc dopamine release are often observed when animals work to actively avoid footshock than when they actually receive footshock (McCullough *et al*., 1993). Further, while NAcc dopamine increases during an initial session of restraint stress (40 min), this effect diminishes over the course of several repeated sessions, but increases after the offset of restraint stress, and these effects grow more pronounced over several repetitions (Imperato *et al*., 1992). Finally, some aversive cues reduce rather than increase NAcc dopamine, such as taste cues associated with the induction of nausea (Mark *et al*., 1991).

p0190 In a "unified" interpretation of NAcc dopamine release, Ikemoto and Panksepp (1999) proposed that, under aversive circumstances, NAcc dopamine increases as a function of an animal's perception that it can escape a stressor, which presents a positive rather than negative incentive. According to this theory, the anticipatory nature of NAcc dopamine release may especially hold for the NAcc shell, which is associated with incentive processing more than the NAcc core, which is associated with generating motor output. This "escapability" hypothesis is consistent with the findings of a study in which novel appetitive but not aversive stimuli increased dopamine release in the NAcc shell (Bassareo *et al*., 2002), while both novel appetitive and aversive stimuli increased dopamine in the NAcc core and MPFC. Further, when aversive stimuli were removed, dopamine increased 10 minutes later, but these increases were blocked by reintroduction of the aversive stimulus. A second piece of support for the escapability hypothesis comes from a study in which administration of footshock increased dopamine in the MPFC but not in the NAcc. NAcc dopamine only increased over repeated testing sessions, as rats learned to avoid the shock (Wilkinson *et al*., 1998).

p0200 In summary, although microdialysis lacks the temporal resolution to reveal phasic changes in dopamine release, experiments designed to distinguish appetitive (or anticipatory) from consummatory (or outcome) phases of reward processing indicate increased NAcc dopamine release during reward anticipation. Interestingly, dopamine release increases in response to the offset of aversive stimulation in the NAcc shell (but not other regions like the MPFC).

Voltammetry s0080

p0210 During the last quarter of the twentieth century, researchers refined electrochemical methods for indexing dopamine activity (i.e., chronoamperometry and cyclic voltammetry) (Kissinger *et al*., 1973). In these methods, researchers apply an electrical potential to an electrode to oxidize nearby molecules in the extracellular space. Molecular identity can then be inferred from "redox" properties of the oxidized material (i.e., a combination of peak oxidation, peak reduction potential, and electron transfer kinetics) (Phillips and Wightman, 2003). Relative to microdialysis, advantages of electrochemical methods include increased spatiotemporal resolution (i.e., 5- to 30-micrometer diameter carbon fibers that can typically sample at 50–100 ms) and decreased disruption of surrounding tissue (Peters *et al*., 2004). The primary disadvantage involves decreased chemical selectivity, particularly if different molecules with similar electroactive potentials are near the sensor (Wightman and Robinson, 2002). Additionally, background pH changes associated with neural activity can interfere with dopamine detection

in chronoamperometry (which produces "dopamine-like" signals), which can be corrected for in voltammetry (Wightman and Robinson, 2002). Thus, while microdialysis indexes tonic changes in dopamine, electrochemical methods index phasic changes in dopamine, which usually result from dopamine "overflow" outside the synapse into the extracellular space following burst-firing of dopamine neurons.

p0220 Cyclic voltammetry studies (1 sample/1 s) have revealed phasic increases in dopamine release in the NAcc shell (<10 s) as rats enter novel environments, and these phasic increases habituate upon subsequent reintroductions (Rebec *et al*., 1997). Using chronoamperometry (1 sample/2 s), phasic increases in NAcc dopamine-like signals have been documented in food-restricted rats as they anticipated responding for milk droplets. These dopamine-like signals decreased after responding with a lever-press and during milk consumption (Richardson and Gratton, 1998). In a related chronoamperometry study conducted at a slower sampling rate (1 sample/60 s), NAcc dopamine-like signals increased after presentation of a cue that predicted a palatable liquid meal, but remained elevated during food consumption (Phillips *et al*., 1993). Using pulsed voltammetry (1 sample/120 s), investigators noted an increase in dopamine in the NAcc shell and medial part of the dorsal striatum in response to presentation of a novel appetitive odor (banana) (Besson and Louilot, 1997; Jeanblanc *et al*., 2002). This increase was prevented during a second testing session by pairing the smell with a nausea-inducing injection of lithium chloride, relative to the increase observed in a control group who had the smell paired with an injection of vehicle.

p0230 As with microdialysis, pulsed voltammetry (1 sample/60 s) has revealed increases in NAcc dopamine-like signal in male rats exposed to an estrus female, ovariectomized female, or another male rat (Mas *et al*., 1995). However, a chronoamperometric study with greater temporal resolution (1 sample/5 s) revealed greater NAcc increases in dopamine-like signals in response to bedding from an estrus female, compared to bedding from an ovariectomized female, or another male rat (Mitchell and Gratton, 1991). Increases in dopamine-like signal were also greater in the NAcc than in dorsal striatal regions. Finally, cyclic voltammetry studies (1 sample/0.1 s) have now demonstrated robust increases in NAcc dopamine in male rats exposed to a receptive female rat (Robinson *et al*., 2001), and when male rats were initially introduced to conspecifics. These phasic increases were often followed by increased social investigation (Robinson *et al*., 2002). Other cyclic voltammetry studies have clearly demonstrated increases in NAcc dopamine prior to self-administration of food (Roitman *et al*., 2004) and cocaine (Phillips *et al*., 2003).

p0240 Taken together, the few voltammetric studies with second-to-second temporal resolution (e.g., <1 s) indicate not only that NAcc dopamine increases in anticipation of reward (particularly in the shell), but also that these increases are more robust than those that occur during consumption. The findings are consistent with rat lesion studies linking the ventral striatum to acquisition of appetitive behavior, and the dorsal striatum to the maintenance of habitual behavior associated with consuming rewards (Robbins *et al*., 1989). The findings also cohere remarkably well with primate studies on the firing of dopamine neurons in response to rewarding incentives (Schultz *et al*., 1997). Specifically, ventral striatal dopamine release occurs in response to unexpected reward cues, but tracks reward cues once their predictive association is learned (Figure 25.5). Fewer studies have focused on the dorsal striatum or on dopamine release in response to aversive stimuli. Such comparisons may provide promising lines of inquiry for future research.

p0250 Neurally, humans differ from rats. For instance, humans have a more highly elaborated prefrontal cortex. However, subcortically (and especially in the striatum), differences are less pronounced. Although microdialysis and *in vivo* cyclic voltammetry of dopamine release have not yet been applied to humans,

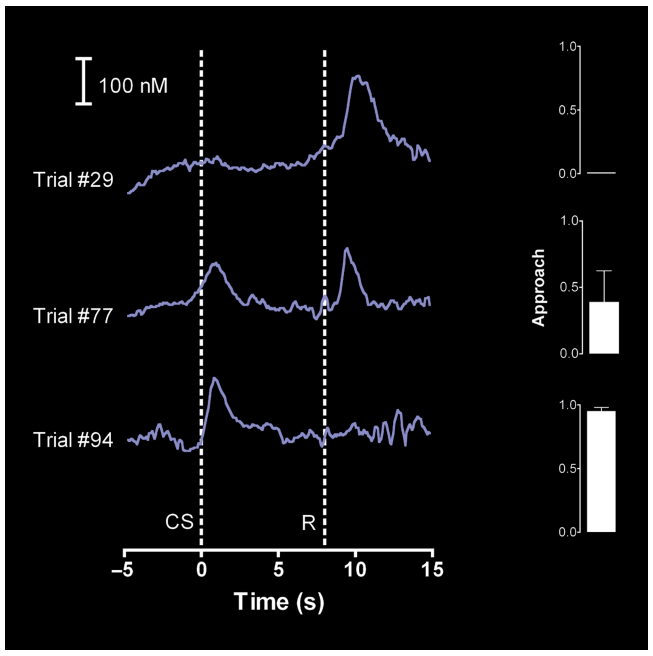


FIGURE 25.5 Nucleus accumbens dopamine release shifts from juice delivery to reward cue presentation over the course of training, and correlates with approach to the cue (CS, conditioned stimulus; R, reward). J.J. Clark and P.E.M. Phillips (unpublished data). f0050

two parallel neuroimaging methods have been implemented over the past decade. Specifically, ligand-based PET scanning allows researchers to make inferences about dopamine release, but only on a timescale of ~60 minutes. On the other hand, FMRI scanning assesses changes in blood oxygenation rather than dopamine release, but on a timescale of seconds. Humans also differ psychologically from rats. Conveniently for neuroeconomics research, humans have devised a consensual symbolic representation of value called "money." Use of monetary incentives not only allows researchers to compare neural responses to scaled gains versus losses, but also facilitates analysis of economic choice (e.g., deciding to purchase a product or share in a company). Thus, here we primarily consider neuroimaging studies that focus on monetary incentives and related choices.

s0090 ## Positron Emission Tomography (PET)

p0260 Positron emission tomography (PET) includes a variety of techniques that enable researchers to visualize metabolic and neurochemical changes in brain activity. In metabolic PET, researchers typically inject radioactively tagged oxygen or glucose into subjects, which is taken up into active brain regions as subjects perform a task. The tagged positron decays, emitting two electrons at 180 degrees that can be coincidentally detected with a PET camera. The two most popular metabolic PET techniques measure changes in cerebral blood flow (rCBF) with ^{15}O-water or in regional cerebral metabolic rate for glucose utilization (rCMRglc) with ^{18}F-fluorodeoxyglugocse (FDG).

p0270 In ligand-based PET, researchers inject a radioactively tagged ligand (or chemical that mimics a neurotransmitter) that travels to the brain and binds to specific receptors. As subjects perform a task, they release neurotransmitter, which displaces the tagged ligand. Relative displacement can be detected when a task condition involving neurotransmitter release is contrasted with a control condition in which the neurotransmitter is not released. Thus, unlike FMRI, PET can facilitate neurochemical inference and does not suffer from artifacts in regions near tissue boundaries (see the next section). However, PET typically has less spatial (~8 mm) and temporal resolution (>2 min) than FMRI.

p0280 The effect of monetary incentives on neural activity was initially investigated with regional cerebral blood flow PET (Thut *et al*., 1997). In this study, subjects performed a delayed go–no go task, in which correct answers were rewarded either with either money or with a non-monetary affirmative prompt. Monetary reward increased activity in the midbrain, thalamus, OFC, and dorsolateral prefrontal cortex to a greater extent than did the prompt. The authors concluded that this pattern of activation might reflect the assessment of consequences in goal-directed behavior. In a second PET study using a pattern-recognition task, monetarily rewarded conditions activated the left cerebellum, midbrain, striatum, anterior cingulated, and MPFC, whereas symbolically rewarded conditions activated only the anterior cingulate and MPFC (Kunig *et al*., 2000).

p0290 Given the strong association between reward and dopamine release in animal research, it is no surprise that dopamine ligand-based PET studies of humans have also focused on the striatum. Interpretation of results from these studies is limited by two factors, however. First, it is unclear whether reward processing increases dopamine release in non-striatal regions (e.g., amygdala, thalamus, and cortex) since the relatively low density of dopamine receptors in these areas precludes visualization with current variants of ligand-based PET. Second, the D2 agonist raclopride (the radiotracer used in most dopamine PET studies) is the only ligand that has been shown to be displaceable in real time by endogenous neurotransmitter in response to behavioral manipulations (although other more sensitive ligands are in development).

p0300 The first study to investigate the relationship between dopamine release and non-pharmacological reward utilized raclopride displacement while subjects played a goal-directed motor task (videogame) (Koepp *et al*., 1998). As subjects gained points during the game, there was a decrease in raclopride binding in the ventral striatum (NAcc and caudate), indicating increased dopamine release and binding at D2 receptors. These results are similar to the increased raclopride displacement in the ventral striatum observed following the presentation of unexpected monetary gain (Pappata *et al*., 2002). Although the amplitude of this effect was moderate, there was no detectable change in dopamine release following unexpected monetary loss, which represents a condition that should control for arousal. Further raclopride displacement studies suggest complex changes in striatal dopaminergic activity during a gambling task involving monetary reward (Zald *et al*., 2004).

p0310 Thus, while metabolic PET studies have not consistently implicated the striatum in processing of monetary reward, ligand-based PET studies of DA displacement more specifically implicate the ventral striatum, and at least one study suggests that equivalent punishing monetary incentives do not have similarly robust effects. Overall, due to limited temporal resolution, researchers have found it difficult to distinguish reward anticipation from outcome using

PET – an issue that has been addressed with event-related fMRI.

s0100

Functional Magnetic Resonance Imaging (fMRI)

p0320 fMRI enables researchers to visualize changes in blood oxygenation. In the blood oxygen level dependent (BOLD) effect (hereafter called "activation"), approximately 4–6 seconds after neural activity occurs, an excess of oxygenated blood is delivered to that brain region. This localized pooling of oxygenated hemoglobin creates a transient magnetic inhomogeneity that can be detected with a magnetic resonance scanner. fMRI activation correlates more closely with changes in postsynaptic membrane potential than with changes in presynaptic firing, and so has been postulated to index the combined input to a brain region (Logothetis *et al*., 2001). Unlike ligand-based PET imaging, fMRI cannot presently index specific neurochemical changes, although combined pharmacological and fMRI studies may eventually elucidate these links (Knutson and Gibbs, 2007). Additionally, many brain areas of central interest to reward researchers (e.g., the NAcc, orbital frontal cortex, and MPFC) lie near tissue boundaries (i.e., next to ventricles and sinuses), which can cause artifacts unless care is taken to minimize magnetic inhomogeneities (e.g., by use of special pulse sequences or acquisition parameters). Relative to PET, however, fMRI affords increased spatial resolution (e.g., as small as $1\,mm^3$ versus $8\,mm^3$) and, importantly, substantially increased temporal resolution (e.g., seconds rather than minutes). fMRI also has advantages of safety and convenience – since blood itself provides the signal, researchers need not inject radioactive compounds or other agents into subjects prior to scanning. These advantages have made FMRI one of the most popular methods for visualizing changes in the activation of small subcortical structures.

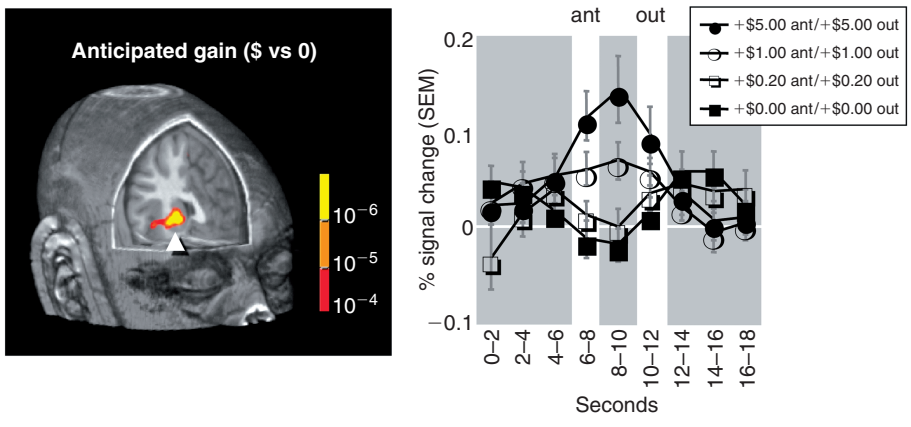
p0330 Shortly after its development, researchers began to use fMRI to examine neural responses to both primary (e.g., touch, juice, food, odors) and secondary (e.g., money) incentives. Primary and secondary incentives have yielded overlapping patterns of activation, but the extent of their similarity has not yet been fully characterized (see Chapter 24 of this volume; O'Doherty, 2004). Based on their direct relevance to neuroeconomic questions, we focus here on studies that utilized monetary incentives below.

p0340 Adopting a successful strategy from fMRI studies of vision research, initial fMRI studies attempted to "localize" or correlate regionally specific patterns of brain activation with responses to monetary incentives in the absence of choice. In an initial fMRI study utilizing a cued reaction-time task, trials involving monetary gain or loss activated striatal regions (including caudate and putamen) as well as other mesolimbic and motor regions (i.e., insula, MPFC, supplementary motor area, and motor cortex), relative to identical trials that lacked monetary incentives (Knutson *et al*., 2000). Trials involving monetary loss additionally activated anterior thalamus and anterior cingulate. However, incentive anticipation and outcomes were not separately modeled in this experiment, and the investigators were not able to acquire images in the anterior portion of the prefrontal cortex. In a second study utilizing a gambling task, trials involving financial gains activated striatal regions in the putamen (as well as the midbrain), while trials involving financial losses activated other subcortical regions (in the medial temporal lobe) (Elliott *et al*., 2000). Although this study identified distinct patterns of activation for gambles involving gains versus losses, the study's design did not allow separate analysis of incentive anticipation and outcomes. In a third study using a different gambling task that controlled for anticipation, gain outcomes elicited sustained activation of striatal regions in the caudate relative to loss and neutral outcomes (Delgado *et al*., 2000). In a fourth study using a reversal learning task, gain versus neutral outcomes activated medial prefrontal regions, while loss versus neutral outcomes activated more lateral prefrontal regions (O'Doherty *et al*., 2001). However, in this study investigators acquired data from the prefrontal cortex only, but not the striatum.

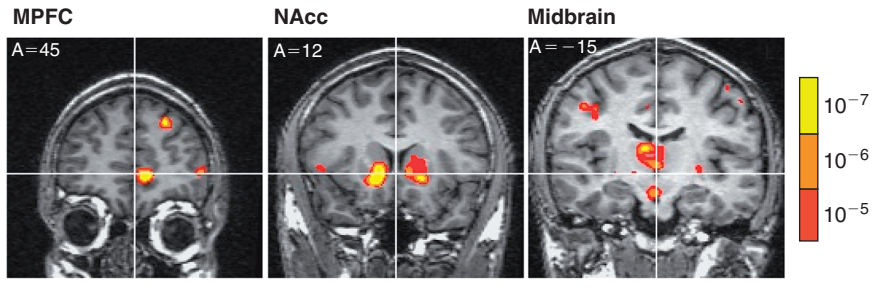
p0350 Subsequent fMRI studies utilizing monetary incentives attempted to dissociate incentive anticipation from outcomes. One study using a gambling task revealed activations of NAcc and other regions (medial OFC and cerebellum) for gain versus neutral gambles, but activations of other regions (temporal lobe, lateral OFC, and cuneus) for the loss versus neutral gambles (Breiter *et al*., 2001). The authors concluded that both anticipation and outcomes related to monetary gains activated ventral striatum as well as other mesolimbic regions (medial OFC, and hypothalamus). A second study using a cued reaction time task revealed proportional activation in the NAcc, medial caudate, and anterior thalamus during anticipation of increasing monetary gains, but only proportional activation in the medial caudate and anterior thalamus during anticipation of increasing monetary losses (Knutson *et al*., 2001a). NAcc activation also correlated with individual differences in self-reported positive arousal in response to seeing large ($5.00) reward cues. Based on these findings, Knutson *et al*.

(2001a) proposed that NAcc activation specifically and proportionally correlated with anticipated gain (Figure 25.6). Follow-up studies utilizing a similar design replicated the association between NAcc activation and gain anticipation, but further indicated that gain versus non-gain outcomes instead recruited medial caudate, MPFC, and posterior cingulate activation (Knutson *et al*., 2001b, 2003).

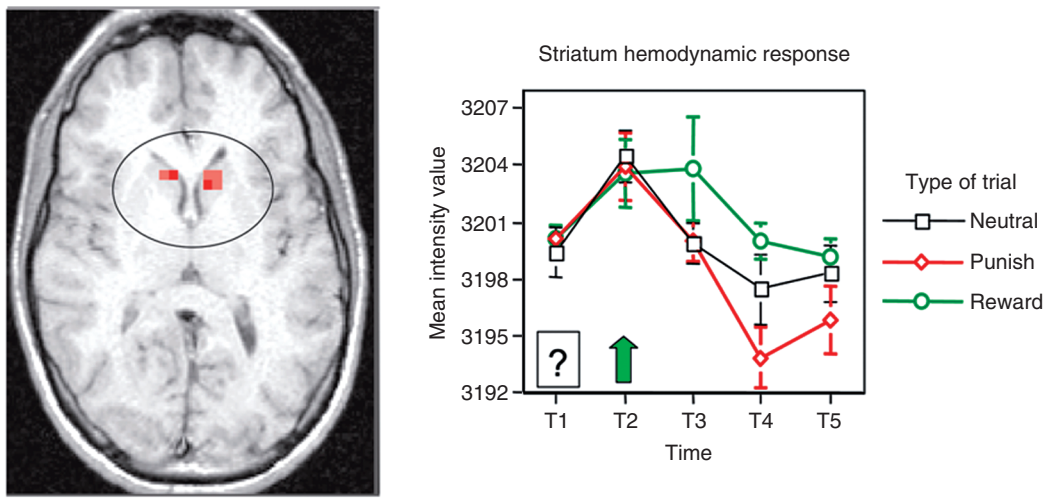
p0360 These early findings foreshadowed a steep linear increase in the number of fMRI publications utilizing monetary incentives, continuing to the present (Knutson and Cooper, 2005; Delgado, 2007). Some studies have focused on anticipation, others on outcome, and still others on learning. With respect to anticipation, researchers began to examine whether ventral striatal activation correlated with other aspects of anticipated gains, such as probability and delay. For instance, one study examined the foundational economic construct of expected value by independently manipulating the magnitude and probability of cued gains and losses. In a cued reaction-time task, anticipated gain magnitude times probability correlated with activation in midbrain, ventral striatum, and MPFC (Figure 25.7). However, decomposition of magnitude and probability effects suggested that while ventral striatal activation was sensitive primarily to expected gain magnitude, MPFC was additionally sensitive to expected gain probability (Knutson *et al*., 2005). Studies using gambling tasks similarly indicated that ventral striatal activation during gain anticipation increased as a function of magnitude, but peaked at an intermediate probability value (Dreher *et al*., 2006; Preuschoff *et al*., 2006 Cooper and Knutson, 2008). Other studies using gambling tasks, however, suggest that ventral striatal activation correlates with both the magnitude and the probability of anticipated gains (Abler *et al*., 2006; Yacubian *et al*., 2006). While all of these findings indicated that ventral striatal activation correlates with the magnitude of anticipated gain, the reasons for discrepant findings with respect to probability remain unclear. According to one possibility, a phasic signal may pass through the ventral striatum that correlates with both magnitude and probability, followed by a tonic signal that primarily correlates with magnitude (see also Chapter 21 of this volume). Alternatively, it is possible that a signal from the MPFC reduces ventral striatal activation in response to non-gain outcomes, which are more prevalent in low-probability trials, and that some of this reduction is being modeled during



f0060 **FIGURE 25.6** Anticipation of monetary gains of increasing magnitude elicits proportionally increasing NAcc activation. Reproduced from Knutson *et al*. (2001a), with permission



f0070 **FIGURE 25.7** Neural activation correlated with expected value (anticipated monetary gain magnitude times probability. Knutson *et al*. (2005).



f0080 **FIGURE 25.8** Caudate response to incentive outcomes. Reproduced from Delgado *et al*. (2004), with permission.

anticipation periods. Future research will doubtless resolve these issues. Other studies have focused on the delay of anticipated gains, but these designs have not yet distinguished between anticipation, choice, and outcome phases of incentive processing. In one delayed discounting task, ventral striatal, MPFC, and posterior cingulate activation was correlated with consideration of choices which featured an immediate and delayed option versus two delayed options (McClure *et al*., 2004). However, in a second study using a delayed discounting task in which that held the immediate option, activation in these same regions correlated with the discounted value (i.e., a combination of magnitude and delay) individuals placed on the delayed option (Kable and Glimcher, 2007).

p0370 With respect to incentive outcomes (i.e., when the probability of a gain or loss collapses from an intermediate value to either 1 or 0), researchers began to examine whether caudate activation correlated with outcome value, and whether this response to outcomes had implications for future choice. Further studies replicated and extended initial work on caudate responses to outcomes in which subjects received or did not receive monetary gains, indicating a parametric response of caudate activation to outcome valence and magnitude (Delgado *et al*., 2003, 2004) (Figure 25.8). Emerging evidence further indicated that caudate activation correlates with relative as well as absolute monetary gain outcomes (i.e., counterfactual or "fictive" outcomes in which an obtained outcome is compared to an obtained alternative outcome) (Kuhnen and Knutson, 2005; Nieuwenhuis *et al*., 2005; Lohrenz *et al*., 2007). This research has begun to forge connections with a separate literature that has historically focused on cognitive rather than incentive feedback (Elliott *et al*., 1997; Poldrack *et al*., 1999), indicating overlapping patterns of activation of the caudate, but with more robust recruitment in response to incentive feedback (Tricomi *et al*., 2006).

p0380 While these incentive outcome findings implicated the caudate in representing the value of incentive outcomes, they did not clarify whether increased caudate activation resulted from gain outcomes themselves or from the updating of action associations that produced gains (more akin to a traditional "reinforcement" signal). Some evidence implicated increased caudate activation when outcomes informed future choices in active but not passive tasks (O'Doherty *et al*., 2004), as well as when outcomes informed future behavior (Tricomi *et al*., 2004). These findings are consistent with rodent studies implicating the caudate in the representation of action values (Yin *et al*., 2005), but the putamen in the representation of more habitual actions (Yin *et al*., 2006). The action valuation account is also consistent with findings from recent studies in which caudate responses diminished as reward contingencies became predictable, and thus carried less information about the next best action (Haruno *et al*., 2004; Delgado *et al*., 2005a).

p0390 In summary, fMRI studies of monetary incentive processing consistently implicate the ventral striatum (including the NAcc) in the processing of monetary gain but not loss. A number of studies are beginning to suggest that activation of the NAcc occurs most robustly during anticipation of gains, while activation of the caudate occurs most robustly in response to gain outcomes that call for future action, consistent with the ascending spiral of connectivity implied by structural studies (Haber *et al*., 2000).

PREDICTION

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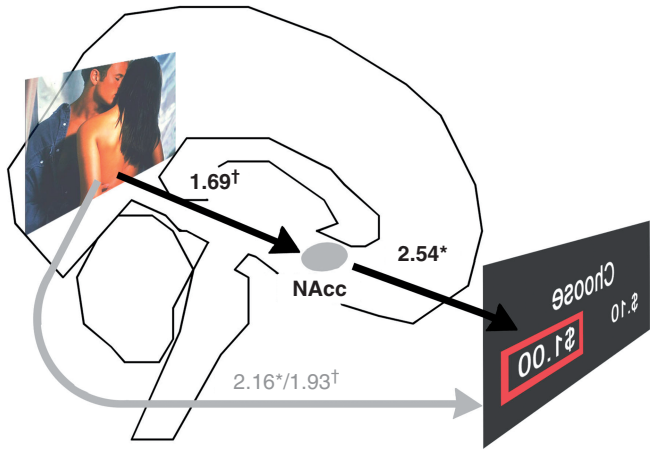
p0400 If striatal activation correlates with the representation of subjective value, then it should also contribute to subsequent choice (both economic and social) and perhaps even to memory. Indeed, direct infusion of dopamine-releasing agents into the ventral (but not dorsal) striatum of rats elicited increased approach to stimuli that have previously predicted reward (Parkinson *et al*., 1999), as well as unconditionally evoking appetitive (but not aversive) behavior (e.g., forward locomotion, sniffing, and 50-kHz ultrasonic vocalizations) (Burgdorf *et al*., 2001). Conversely, microstimulation of the caudate during outcome processing (but not during reward anticipation) improved monkeys' ability to learn the next appropriate response for rewards (Nakamura and Hikosaka, 2006). Event-related fMRI studies are now beginning to test whether striatal signals presage changes in choice and memory.

p0410 Studies have begun to suggest that activation of midbrain and ventral striatum can facilitate memory formation. In one study, cues that signaled monetary gain were better remembered than cues that did not 2 days after scanning, and this effect was correlated with cue-elicited activation of the midbrain, ventral striatum, and hippocampus (Wittmann *et al*., 2005). In a second study, subjects better remembered neutral stimuli that followed cues signaling monetary gain for successful memorization, and this effect was mediated by cue-elicited activation of the midbrain, ventral striatum, and hippocampus (Adcock *et al*., 2006). This growing body of research suggests that ventral striatal activation may influence memory formation, possibly by recruiting midbrain dopaminergic projections to hippocampal regions.

p0420 Other studies suggest that activation in these regions might contribute to economic choice. In one study, subjects chose between high- versus low-risk investments. Ventral striatal activation immediately prior to choice predicted that subjects would be more likely to switch to high-risk investments, above and beyond informational variables (e.g., wealth, prior outcome, uncertainty) and even when subjects' choices violated those of a rational actor (i.e., a Bayesian updating, risk-neutral agent) (Kuhnen and Knutson, 2005). In another study, subjects decided whether or not to purchase products at discounted prices. Ventral striatal activation not only correlated with preference while viewing products, but also predicted that subjects would be more likely to choose to purchase the product above and beyond self-reported preference (Knutson *et al*., 2007). These studies suggested



f0090 FIGURE 25.9 Activation of nucleus accumbens statistically mediates the influence of positive pictures on switching to a high risk financial gamble (Z-scores, *P < .025, †P < .05, one–tailed). Knutson *et al*. (2008).

that naturally occurring (or endogenous) changes in ventral striatal activation precede and can be used to predict subsequent choice. A third study further suggested that this influence could be externally (or exogenously) controlled. In this study, heterosexual male subjects saw positive (i.e., erotic), negative (i.e., snakes and spiders), or neutral (i.e., office supplies) pictures prior to choosing between high- versus low-risk gambles of equal expected value. Presentation of positive pictures increased switching to the high-risk gamble, and this effect was partially statistically mediated by increases in ventral striatal activation (Knutson *et al*., 2008) (Figure 25.9). Together, these studies are consistent with a causal account in which physiological events indexed by ventral striatal activation influence subsequent economic decisions.

p0430 A third group of studies has implicated ventral striatal activation in social decisions (see also Chapter 15 and 22 in this volume). For instance, ventromedial caudate activation not only occurred in response to reciprocated trust in a prisoner's dilemma game (Rilling *et al*., 2002), but also predicted subjects' tendency to invest in a partner who had cooperated with them in the past in a trust game (King-Casas *et al*., 2005). Thus, ventral striatal activation can come to represent future social gain. Consistent with this notion, information about reputation of social partners modulated the responsiveness of these regions to their behavior in the absence of any previous experience (Delgado *et al*., 2005b).

IMPLICATIONS

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p0440 In summary, consistent with the "ascending spiral" structural connections of the striatum in ascending

spirals of connectivity with prefrontal cortex and midbrain dopamine nuclei, different parts of the striatum appear to subserve different functions. Further, emerging evidence suggests that striatal activation can be used to predict choice (and memory) within trials. These advances have resulted from improvements in the spatial and especially temporal resolution of neuroimaging techniques. Together, these findings yield a picture of value processing in which the ventral striatum assesses expected gain and the dorsal striatum uses that estimate to inform future actions and cognitions.

p0450 Over the course of approximately a decade of research, we have learned lessons that might facilitate future investigations. First, valuation appears to be a dynamic and componential process. Second, different stages of this process recruit different striatal components, perhaps in an ascending progression (see also Chapter 24 of this volume). Third, spatiotemporal resolution is key for elucidating this process, and so further technical advances should facilitate theoretical developments. The findings have also forced a re-examination of some theoretical assumptions. First, neural processing of gains does not appear to be the opposite of processing of losses. Different circuits may handle these distinct incentive processing demands, enabling animals simultaneously to process potential gain and potential loss. Even within the striatum, the evidence for responsiveness to losses is weaker in the ventral striatum than in the dorsal striatum. Additional findings from our labs and others' suggest that other brain regions (the insula, for instance) may play a more prominent role in responses to loss. Second, the brain responds differently during anticipation of incentives than in response to incentive outcomes. While the ventral striatum appears more active during anticipation, the dorsal striatum appears to respond more robustly to outcomes, particularly if the outcomes inform what an animal needs to do next. Hopefully, re-examination of these assumptions will generate more robust assumptions that can support more inclusive and predictive theories of choice.

p0460 Mostly, we have learned how much we have yet to learn. For instance, other types of valuation beg for investigation. These include both positive incentives (i.e., probability, immediacy, certainty) and negative incentives (i.e., effort, risk, delay). Are these incentives processed by the same or by different neural circuits? If the latter, how does the brain integrate these components to inform future choices and expectations (i.e., learning)? Can researchers use these neural signals to better predict choice (e.g., beyond existing economic and psychological models)? How are the signals modulated by contextual economic and social variables? And how can people learn to better control these signals to promote choices most consistent with their long-term goals?

p0470 As implied throughout this review, if the past provides a guide to the future, technological innovations should continue to drive theoretical advances. Specifically, improvements in spatial and especially temporal resolution should improve inference about the function of different striatal components. Enhanced resolution will increase researchers' ability to compare neural signals to existing economic and psychological models, and to use these signals to predict economic choice and psychopathological symptoms. Enhanced spatiotemporal resolution will also facilitate bridge-building to animal research, as well as promoting integration of information from other measurement modalities (e.g., electrical and chemical). Eventually, the process approach may supplant the correlational approach.

p0480 A deep and revolutionary assumption underlies these predictions – choice cannot be understood without an understanding of subjective valuation. Past traditions in economics (e.g., revealed preferences) and psychology (e.g., behaviorism) assumed the opposite – that choice cannot be understood without translating (internal) subjective valuation to (external) objective stimuli (see Chapter 9 of this volume). Technology no longer forces us to adhere to this assumption. Subjective value stands at the nexus of sensory input and motor output, and tools that facilitate its measurement lie within our reach.

p0490 In conclusion, neuroscience findings suggest that valuation is a dynamic, componential, and ultimately subjective process. Technological advances now allow scientists to track these components of valuation, providing reason for hope rather than despair. Whether or not it is the site at which "animal spirits" transform sensory impressions into motor command, the striatum seems like a promising place to begin to search for the neural basis of subjective value.

Acknowledgments

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p0500 During chapter preparation, BK was supported by National Institute of Health Grant AG030778 and a FINRA Investor Education Award, MRD was supported by National Institute of Health grant DA022998, and PEMP was supported by National Institutes of Health grants AG30775, DA21793, DA24140 and MH79292, and a NARSAD Young Investigator Award. The authors thank Paul Glimcher and Jeffrey C. Cooper for helpful comments on earlier versions of the manuscript.

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