12 Human Single Neuron Reward Processing in the Basal Ganglia and Anterior Cingulate

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Animals are fundamentally governed by rewards. It is a central component of our behavior and the pursuit of which represents the integration of a broad range of cognitive capacities. These functions take place in a distributed reward network and include regions such as the frontal cortex, cingulate cortex, basal ganglia, and midbrain dopaminergic systems (see figure 12.1, plate 12). Although better understanding the role of these brain regions has been the focus of many recent studies, the vast majority of studies are conducted in animal models that ultimately serve only as a proxy for human reward processing. Imaging modalities such as functional magnetic resonance imaging (fMRI) allow us to correlate whole brain activity with behavior in human subjects, however at the cost of poor temporal and spatial resolution and only indirect measures of neural activity. Within the last decade, a few pioneering studies have explored reward processes in the human brain at the single neuronal level (table 12.1), providing the first evidence on how this integral cognitive function is represented at the level of the individual neuron. In this chapter, we will highlight these studies in the context of previous animal physiology and human imaging studies. Finally, we will conclude with a section on how future studies can help to expand our understanding of human reward processing.

Basal Ganglia

The basal ganglia were classically thought of as a set of nuclei related to motor function given pathophysiological evidence from movement disorders and original anatomical evidence pointing to dense connectivity with motor cortical areas (Nauta & Mehler, 1966). However, recently, this view has changed substantially as growing evidence has unraveled a wide range of cognitive components to the basal ganglia network based on both anatomical and physiological data. Functions such as reward processing, motivation, and learning have since been attributed to basal ganglia circuits.

These discoveries originated from anatomical evidence in the early 1970s demonstrating the connectivity of the ventral striatum and the ventral pallidum with cortical areas (Heimer & Kalil, 1978). It was later discovered that many cortico–basal ganglia–thalamocortical loops (basal ganglia loops) existed, and projected to various cortical regions, including sensorimotor,

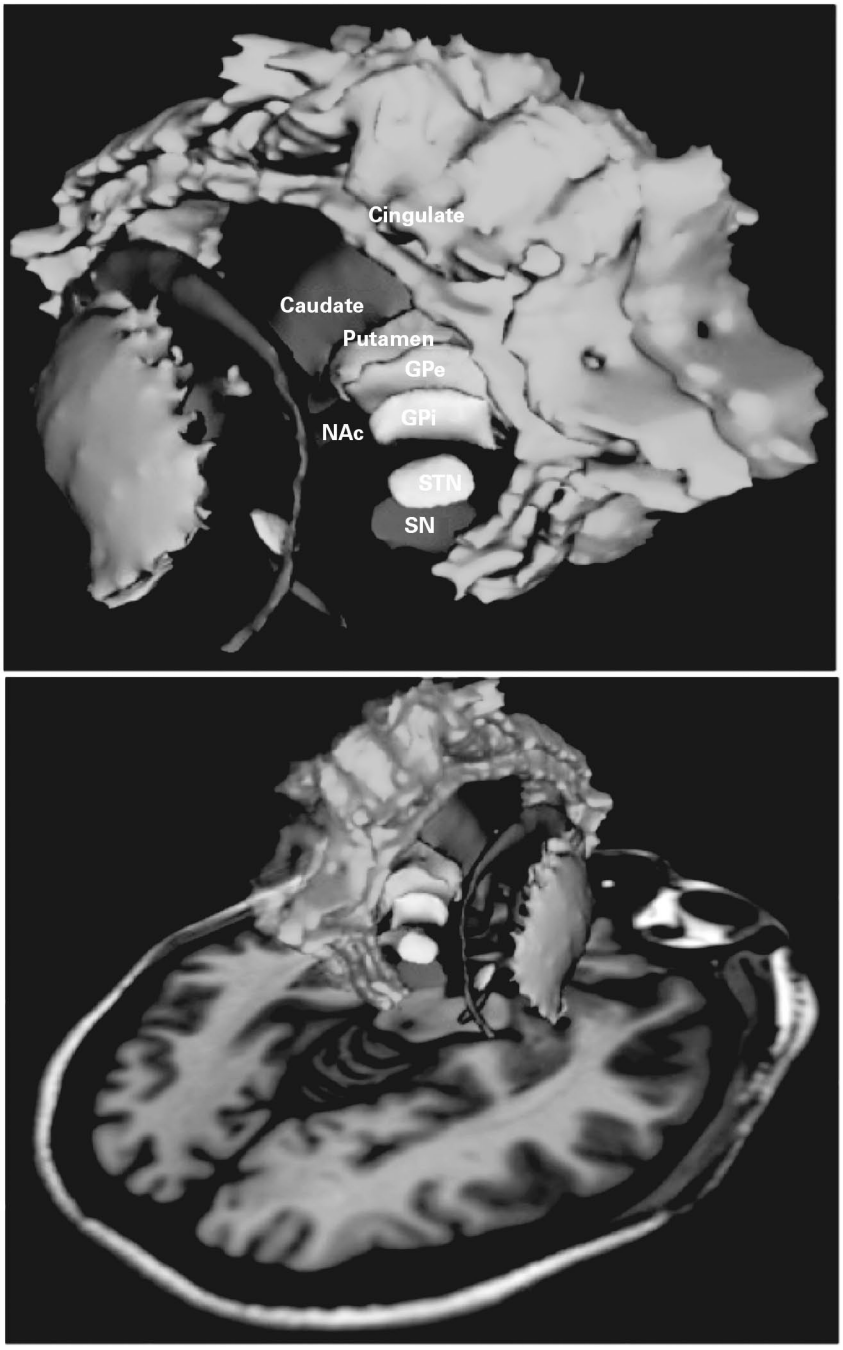

Figure 12.1 (plate 12)
Anatomical relationship of corticostriatal structures implicated in reward processing, reinforcement learning, and decision making. The cingulate cortex is thought to play an important role in cognitive functions, including reward anticipation, error detection, and decision making. The nucleus accumbens (NAc) is frequently studied for its role in addiction, but it also participates in learning and motivation through its connections with dopaminergic neurons, limbic areas, and prefrontal cortex. The substantia nigra (SN) sends dopaminergic signals to the striatum and cortex and encodes prediction error signals that drive learning. STN, subthalamic nucleus; GPe, globus pallidus externa; GPi, globus pallidus interna. Images provided by Kirk Finnis, Ph.D., and Medtronic, Inc.

Table 12.1
Table of current human single neuron studies on reward processing

Task	Brain region	Comments	Results	Reference
• War Task	Nucleus accumbens	Examined binding stimulus value to action	• Prediction of future financial decisions on a trial-by-trial basis and under conditions of uncertainty Encoding of positive/negative prediction error signals	Patel et al. (2012)
• Rewarding Stimuli Task	Nucleus accumbens	Examined processing of reward information	• Activity encoded reward anticipation Alpha oscillations are sensitive to positive feedback Beta oscillations exhibit higher power during unrewarded trials	Lega et al. (2011)
• Mental Arithmetic Counting Stroop Emotional Stroop Interference	Caudal anterior cingulate	Examined impact of emotional valance and cACC responsiveness to complex attention tasks	• cACC neurons may act as salience detectors when faced with conflict and difficult or emotional stimuli	Davis et al. (2005)
• Mental Arithmetic Counting Stroop Word Generation	Anterior cingulate	Examined responses to painful stimulus applied to skin	• First report of single neurons in humans with modified firing rates by cognitive tasks that require attention Painful stimuli did not alter the firing rate	Davis et al. (2000)
• Two-choice selection	Dorsal anterior cingulate	Examined the role of the dACC in reward-based decision making	• dACC activity increased when instructed to alter movement direction Highest response occurred when instruction also indicated an affiliated reduction in reward Level of activity predicted whether a correct choice was going to be made dACC ablation increased errors when required to change behavior based on reward reduction	Williams & Eskander (2004)
• Multi-Source Interference Task	Dorsal anterior cingulate	Examined dACC function by using functional imaging and single unit recordings in human subjects undergoing surgical cingulotomy	• dACC activity is modulated by previous trial activity producing a behavioral adaptation that accelerates reactions to cues of similar difficulty and delays reactions to cues of different difficulty These effects are abolished by ablation of dACC	Sheth et al. (2012)
• Probabilistic Learning	Substantia nigra	Examined reward properties of dopaminergic neurons using virtual financial reward	SN neurons' responses to positive and negative feedback were mainly driven by unexpected outcomes suggesting a role in reward-based learning modulated by the discrepancy between the expected and the realized outcome.	Zaghloul et al. (2009)

cACC, caudal anterior cingulate cortex; dACC, dorsal anterior cingulate cortex; SN, substantia nigra.

associative, and limbic regions (Parent & Hazrati, 1995). The notion of parallel and segregated basal ganglia loops became the dominant thinking of basal ganglia architecture. This organizational scheme was optimally suited for integration of discrete associative and limbic streams of information while connecting with motor cortical and motor output regions within the basal ganglia—requirements for adaptive behavior.

Midbrain Dopamine and Reward Signaling

Midbrain dopaminergic neurons play a critical role in moderating reward processing and adaptive behavior (Schultz, 2002). The two primary dopamine centers innervating the cerebrum are the ventral tegmental area (VTA) and the substantia nigra pars compacta (SNpc).

The VTA lies medial to the substantia nigra (SN) and ventral to the red nucleus in the midbrain. The VTA primarily receives glutamatergic input from the prefrontal cortex (PFC), lateral hypothalamus, and superior colliculus. It also receives gamma-aminobutyric acid (GABA) input from medium-spiny neurons in the ventral pallidum and nucleus accumbens (NAcc). Approximately 60% of the cell bodies are dopaminergic, of which most project densely to the ventromedial striatum, specifically the NAcc core and shell (Swanson, 1982); GABA-ergic (Carr & Sesack, 2000) and glutamatergic containing neurons are also present (Lavin et al., 2005).

The SNpc is a mesencephalic structure that lies immediately dorsal to the cerebral peduncles. Roughly, 90% of cell bodies are dopaminergic and project primarily to the dorsal striatum and PFC (Haber & Knutson, 2010). Interestingly, the SNpc receives very little reciprocal innervation from the dorsal striatum but instead receives dense projections from the ventral striatum.

The role of midbrain dopaminergic neurons in reward processing has been extensively studied (Schultz et al., 1997; Schultz, 2002). Most notably, midbrain dopaminergic neurons demonstrate a rapid phasic increase in firing rate to unexpected rewards. In other words, when there is a difference in expected and actual outcome—a prediction error signal—midbrain dopaminergic neurons rapidly fire at the onset of the unexpected reward. Furthermore, if a stimulus is consistently presented prior to the delivery of the reward, the dopamine-mediated change in firing rate transitions from the receipt of the reward to the onset of the predictive cue. This feature is thought to drive reward-based learning and adaptive behavior.

It is important that animals be able to respond to rewards, but it is in addition advantageous for them to be able to make predictions about future rewards. More recently, neuroimaging studies have found that the amygdala, orbital-frontal cortex, and ventral striatum are implicated in reward prediction (Knutson et al., 2001; Gottfried et al., 2002; O'Doherty et al., 2002). In its simplest form, this type of prediction can occur through classical conditioning. In such cases, a previously neutral stimulus which is paired with a rewarding outcome is assigned a predictive value in future instances. It is thought that phasic dopaminergic activity is the neural substrate of this type of learning (Schultz, 1998).

Human neuroimaging studies also support this notion (McClure et al., 2003; O'Doherty et al., 2003). Using classical conditioning tasks, two studies were able to identify prediction error profiles using event-related fMRI in downstream targets from midbrain dopaminergic

systems. These signals were seen in the ventral striatum and orbital-frontal cortex. Although these are indirect measures of neural activity, further evidence using positron emission tomography (PET) has found dopamine release in the striatum during reward prediction errors (Zald et al., 2004).

There are many difficulties in using fMRI to measure changes in midbrain dopaminergic systems because of its proximity to tissue boundaries, endogenous motion due to its nearness to the carotid artery, and partial voluming from its small size (Haber & Knutson, 2010). Despite this, researchers have reported increases in midbrain activity to anticipation of pleasant tastes (D'Ardenne et al., 2008; O'Doherty et al., 2002) and monetary rewards (Knutson et al., 2005). Interestingly, in these studies, midbrain activity did not attenuate to expected rewards that were ommitted, in contrast with findings from nonhuman primate (NHP) work (Schultz et al., 1997). Although this may reflect an insensitivity of the imaging modality, it remains a critical point in understanding reward processing in the human brain.

The first study to explore single neuronal correlates of dopaminergic neurons in the human brain was that of Zaghloul and colleagues (Zaghloul et al., 2009). They were able to record activity from individual neurons in the human SN in patients undergoing deep brain stimulation surgery for Parkinson's disease. In this study, they asked patients to play a computerized task while surgeons performed microelectrode recordings to physiologically map the target brain region prior to implantation of the deep brain stimulation electrode (Zaghloul et al., 2009). It is worth noting that microelectrode recordings are a routine part of deep brain stimulation surgery and the only addition to the experimental design is the incorporation of the computerized behavioral task.

During surgery, a computer monitor and input device (button box) is mounted to the operating bed. After the neurosurgery team makes two small craniotomies, microelectrode wires are then inserted and lowered along the planned trajectory before the final stimulating electrode is permanently implanted. This procedure is performed to physiologically map the gray/white matter boundaries to confirm the electrode position and to functionally isolate the motor compartment of the subthalamic nucleus (STN). This is a standard component of deep brain stimulation surgery and helps to ensure optimal placement of the stimulating electrode. Although the SN is not currently an approved deep brain stimulation surgery target, it rests immediately inferior to the STN and can be reached when mapping the ventral boundary of the STN during the microelectrode recording portion of the surgery.

The task required the subjects to draw a card from one of two decks of cards. The subjects were informed that one deck probabilistically carried a higher chance of resulting in a financial reward. The researchers recorded 67 neurons from the SN and limited their analysis to 15 neurons that met stringent criteria (firing rate, waveform morphology, and feedback responsive) of dopamingeric cells. By comparing differences in observed and expected feedback, the researchers reported that 14 of the 15 dopaminergic neurons in the SN encoded both positive and negative prediction error signals, consistent with previous NHP and neuroimaging studies. This was the first concrete evidence of prediction error signals in human dopaminergic neurons.

An unavoidable confound when interpreting any human single neuronal study is the underlying disease pathology of the study population. In this case, Zaghloul et al. recorded from dopaminergic cells in the SN of subjects with severe Parkinson's disease—atrophy of which is itself the pathophysiological cause of Parkinson's disease. Although it is difficult or, in some cases, impossible to control for these effects, a discussion is necessitated to address these issues. The researchers in this case performed a very strict analysis of the physiological properties of the neurons they recorded: Through this analysis they reduced the 67 recorded neurons to 15 dopaminergic cells that were used for this analysis. The rationale is that they were able to study the remaining active dopaminergic cells and their output. The caveat is that this activity may be attenuated due to the degeneration of the cell population and therefore the healthy network.

Ventral Striatum and Reward Processing

The link between the ventral striatum and reward processing has been known since the 1950s when Olds and Milner demonstrated that rats would continually self-stimulate their reward circuit through an implanted electrode, even at the cost of maintaining basic homeostatic needs like eating and sleeping (Olds & Milner, 1954). Ever since, the ventral striatum has become a focal point in studies of reinforcement learning, reward processing, and drug addiction.

In the late 1970s, Lennart Heimer coined the term "ventral striatum." In humans and primates, the ventral striatum is the composite of the NAcc and the amorphous boundary blending caudally into the caudate and putamen in the dorsal striatum. Interestingly, neither cytoarchitectural or histochemical features demarcate a border between the ventral and dorsal striatum (Haber & Knutson, 2010); instead, anatomical connectivity provides the most consistent feature to identify the two regions.

The ventral striatum, like the dorsal striatum, receives three major inputs: a massive topographic glutamatergic input from the cerebral cortex, a large glutamatergic input from the thalamus, and a smaller dopaminergic input from midbrain dopaminergic centers (Haber & Knutson, 2010). The NAcc is classically thought of as the "motor–limbic interface" because of its rich limbic afferents from the hippocampus, amygdala, and frontal cortices and its efferent projections to motor output centers in the basal ganglia (Mogenson et al., 1980). Given this anatomical connectivity, the NAcc is in a unique position to integrate a wide range of information to modulate behavior. Furthermore, the NAcc receives widespread input from midbrain dopaminergic centers, thus placing it under the influence of reward centers. This combination makes the NAcc well suited for processing reward information, guiding goal-directed behaviors, and playing a role in drug addiction.

The role of dopamine in the striatum continues to be poorly understood. A central tenet of dopamine's influence on striatal activity (both dorsal and ventral) is that it exerts its influence via two mechanisms: tonically and phasically active neurons. Evidence suggests that tonically active neurons, thought to be cholinergic interneurons that make up about 1% of striatal neurons, may perform a gating function allowing the passage of information (Tremblay et al., 1989; Pessiglione et al., 2005) whereas phasically active neurons, thought to be the medium spiny neurons

that make up about 95% of striatal neurons, are more relevant to strengthening functional circuits during instrumental conditioning and procedural learning (Graybiel, 2008; Jog et al., 1999).

In contrast, neurons in the NAcc also send reciprocal projections back to midbrain dopamine neurons. These projections are GABA-ergic and inhibitory in nature. Although the NAcc is not the only region that exerts control over midbrain dopamine centers, it provides the largest afferent control. The exact function of these projections is not well understood; however, computational approaches have led to very interesting hypotheses. One particular example is the actor–critic model of reinforcement learning (van der Meer & Redish, 2011; Montague et al., 2004). In this model, an actor signal maintains stimulus–response associations based on historically rewarding experiences while the critic signal serves as a "teaching signal" to update the actor to newly rewarding stimulus–response associations. In this sense, the striatonigral projection to midbrain dopamine centers could regulate responses to rewards, serving as a control mechanism for learning. An integral component of this system is that neurons in the NAcc/ventral striatum are sensitive to reward probability.

To interrogate neuronal activity during reward processing, Schultz and colleagues trained monkeys to perform a computer-guided task. In this task, one of three different conditioned stimuli were presented on any given trial, to which they learned the corresponding associations through brute-force training: (1) make a reaching action and receive reward, (2) refrain from performing any action and receive reward, and (3) make a reaching action followed by an auditory tone and no reward. The animals performed this task while researchers recorded single neuronal activity from the ventral striatum. Upon examination of the phasically active subgroup of neurons, the researchers found that the responses were very heterogeneous to task-related epochs. Among the findings, however, they noticed the largest and consistent categories of responses were in anticipation of a rewarding event (during the presentation of the conditioned stimulus that predicted reward) and during receipt of the reward (Hollerman & Schultz, 1998). This activity occurred irrespective of whether a movement was required, suggesting that the these neurons are not encoding a general reinforcing signal, but rather a signal for appetitive rewards.

These data were further supported by human PET and fMRI studies that have shown that the NAcc/ventral striatum is activated with receipt of both primary (food, sounds, etc.) and secondary (monetary gains) rewards (Small et al., 2001; Blood & Zatorre, 2001; Martin-Solch et al., 2001; O'Doherty et al., 2004). Further evidence using ligand-based imaging techniques have shown dopamine release in the NAcc with feelings of euphoria (Drevets et al., 2001), drug and alcohol consumption (Boileau et al., 2003), and even gambling (Koepp et al., 1998). Using event-related fMRI, researchers found that activity in the NAcc increased during the anticipation of primary and second rewards (Knutson et al., 2001; O'Doherty et al., 2002; Knutson et al., 2003). Knutson and colleagues further demonstrated that NAcc activation increases proportional to the magnitude of the anticipated monetary reward (Knutson et al., 2001).

In 2009, Cohen and colleagues performed the first study, to the best of our knowledge, to directly sample human ventral striatum activity during a reward learning and decision-making

task (Cohen et al., 2009). Five patients underwent deep brain stimulation surgery for the treatment of major depressive disorder (MDD), in which a stimulating electrode was surgically implanted into the ventral striatum. Following the implant surgery and before the electrode leads were attached to the pulse generator (which occurs in a second operation after a few days), the researchers connected the leads to an acquisition system and had the subjects engage in a computer-guided task. This allowed researchers to correlate local field potential data from the NAcc to the behavior engaged in during the task. Their behavioral paradigm consisted of two tasks: a "learning" and "choosing" task. In the learning task, one of two cues was presented on any given trial. Unbeknownst to the subject, one cue was the "safe" cue, which always resulted in a small reward, while the other, "risky" cue, resulted in a high reward 75% of the time. The subjects quickly learned these associations and were able to verbally report their findings. In the "choosing" task, the subjects were now presented with both cues and asked to make a selection. Again, unbeknownst to the subjects, these cues retained the same reward contingencies as in the "learning" task. The dichotomy of these two tasks allowed researchers to interrogate the role of the NAcc in associative learning versus reward-guided behavior. The results were consistent with imaging studies, that NAcc activity reliably encodes the anticipation of reward proportional to reward magnitude. More specifically, activity increased from losses to safe to risky rewards. Interestingly, their data suggested that at the feedback period, NAcc activity does not encode a prediction error (difference between expected and actual outcome) because the activity should be zero for safe rewards (e.g., where expectation and outcome are equal). We will find that this is in contrast with single neuronal findings from the NAcc.

In 2011, Lega and colleagues presented the first single neuronal evidence from a human subject undergoing deep brain stimulation surgery (Lega et al., 2011). This subject was a 42-year-old female undergoing deep brain stimulation surgery for treatment refractory major depression. During the microelectrode recording portion of the surgery, the research team asked the subject to participate in a computer-guided visual-reward task; single neuronal and local field potential data were collected during the performance of the task. In a preoperative session, the participant was exposed to a set of 120 images from 11 categories to which she ranked her preference in a pairwise fashion. These images were then used as the rewarding stimuli during the recording session. In the operating room, at the beginning of each trial, the subject was cued to the category from which the subsequent rewarding stimuli would be presented if the trial was successfully completed. An object would then appear from either the left or right side of the screen; the subject was asked to appropriately press the left or right mouse button. If the trial was successful, the corresponding reward image from that category would be presented along with a positive reinforcing tone. If the trial was incorrect, a negative image was presented along with an aversive tone. Two neurons were identified from the recording. One neuron showed significant increase in activity during the feedback period to positively rewarding outcomes but not to negative or neutral trials. Similarly, the local field potential data showed a stark increase in alpha-band activity during the feedback of successful trials, again in comparison with negative and neutral outcomes. The authors note that their single neuronal findings most likely result from the

tonically active subpopulation of NAcc neurons. Although the data here are limited and must be interpreted with caution, they provided some evidence at a time where little existed.

In 2012, Patel and colleagues performed a more detailed examination of single neuronal activity in the NAcc during a financial decision-making task (Patel et al., 2012). This study was performed in patients undergoing deep brain stimulation surgery for the treatment of MDD or obsessive–compulsive disorder (OCD). The researchers implemented a computerized gambling task based on the classic card game War. In this task, the subject is presented with a card on a computer monitor. Following the presentation, the subject is given the opportunity to place a wager, either $5 or $20, via a button box. Once the wager is entered, the opponent's card is revealed—the player with the higher card wins. A feedback period follows with an image of the wager amount and the words "win" or "lose" depending on the outcome of the trial. A total of 19 neurons were examined from 8 subjects (5 MDD and 3 OCD). Similar to the results from Schultz and colleagues, the data revealed that neuronal responses in the NAcc were very heterogeneous to task-related epochs. However, there were two epochs that clearly carried most of the phasic activity: the go-cue and feedback period (the point in the trial at which the computer's card is revealed and the first point at which the subject realizes the outcome of the trial). The researchers report two main findings from the study. The first is that NAcc population activity predicts, on a trial-by-trial basis, the upcoming financial decision up to 2 s before the wager is physically manifested. This activity is time-locked to the onset of the go-cue (the first point at which the wagers appear on the screen, allowing the subject to initiate the bet). The second is that NAcc population activity encodes positive and negative prediction error signals during the feedback period. Activity in trials with expected positive and negative outcomes showed no difference during the same period.

These data provide the first single neuronal evidence from both animal and human studies that a decision signal is encoded in the NAcc (van der Meer & Redish, 2011). Although more work is needed to explore this signal, it may provide significant evidence for the role of the "actor" signal within the reinforcement learning framework. Furthermore this data provides concrete evidence that a prediction error signal is represented in the NAcc, which is more and more proving to be a ubiquitous signal represented throughout the brain.

Cingulate

Anatomy of Anterior Cingulate

Many subregions of the PFC are implicated in a greater network for reward circuitry. A major component of the reward circuitry in the PFC is the anterior cingulate cortex (ACC). The ACC covers a large region of the medial wall and is abutted to the corpus callosum (Paus, 2001). Importantly, the ACC is uniquely situated to handle an array of functions with respect to reward. Furthermore, each subregion of the ACC is predominately involved with distinct roles, such as motivation and cognition (Paus, 2001). Notably, these areas are not homogeneous and demonstrate some overlap in function. Nevertheless, there is a general agreement as to the primary role

of each subregion. Two of the major parts are the dorsal ACC (dACC) and ventral ACC, which is also known as the ventral medial prefrontal cortex (vmPFC).

The portion of the ACC implicated in reward processing and cognition is the dACC. The dACC is often divided into Areas 24b and 32. Much of the dACC is located in the anterior cingulate sulcus (ACS). Each subdivision has robust anatomical connectivity to other brain regions that serve parallel functions (Haber et al., 2006). A dense set of dACC efferents are focal projections that reach a large part of the dorsal striatum, primarily from the caudate head and rostral putamen to these regions bordered by the anterior commissure. Projections to the ventral striatum are much more sparse. The area reached by focal projections of the dACC is increased by diffuse projections (Haber et al., 2006). These diffuse projections also infiltrate other parts of the striatum, such as the dorsolateral caudate and ventral putamen. Moreover, regions of the putamen that are caudal to the anterior commissure also receive afferents from the dACC. Overall, the dACC is able to interact with a large part of the dorsal striatum.

Interestingly, the ACC is also connected to motor areas of the brain. This part of the ACC is rostral and includes part of the cingulate sulcus. The rostral cingulate motor area, also known as Area 24c, has a strong influence over the primary motor cortex and other motor areas (Picard & Strick, 1996). Moreover, Area 24c is strongly connected to the striatum (Kunishio et al., 1994). It should be noted that other cortical and subcortical areas, such as the striatum, activate Area 24c. Finally, Area 24c is likely influenced by neuromodulators, such as dopamine and other monoamines. This type of connectivity may facilitate the motor outputs of behaviors and is likely influenced by cognition.

Another part of the ACC that has received attention is the ventral region, often referred to as the vmPFC. The vmPFC is strongly connected to the limbic system, which is a group of brain structures that are implicated in several functions such as emotion, motivation, and memory. Some of the main components of the vmPFC are the rostral ACC (rACC) and subgenual ACC. Like the dACC, the vmPFC also has subdivisions that are known as Area 24a and Area 25. Generally, efferents to the striatum are less robust than those of the dACC (Haber et al., 2006). However, the bulk of the focal projections from the vmPFC target the shell of the NAcc in the ventral striatum. Moreover, and in lesser amounts, the vmPFC targets some of the caudate.

Anterior Cingulate and Prediction Error Signaling

Memories linked to emotional events, such as rewarding experiences, guide behavior. The ability to regulate the expression of such memories is necessary for survival. Moreover, this ability requires a fine-tuned interaction between structures of the basal ganglia with different regions of the PFC. One region of the PFC that is implicated in reward processing is the ACC.

A wealth of evidence describes the neural signatures of prediction error related to reward in dopaminergic systems. Dopaminergic systems send robust projections to the ACC. Accordingly, neurons in the ACC also signal prediction error. Unlike the dopaminergic systems, distinct populations of neurons in the ACC signal either positive or negative events. The increased activity when an error occurs likely modifies subsequent behavior in NHPs (Michelet et al., 2009). This

further supports the idea that the ACC monitors the consequences of actions and mediates subsequent changes in behavior. As described previously, signals of prediction error are represented in the NAcc region of the ventral striatum of humans (O'Doherty et al., 2004), and the behavioral choice based on predicted reward is influenced by the dorsal striatum. Both regions of the striatum are likely to become under control of the ACC, given the anatomical projections of the ACC.

One aspect of cognition that allows a species to thrive is the ability to update the value representation when expected reward is higher or lower than the level of reward received. Consequently, the magnitude and frequency by which the discrepancy occurs directly affects the update. In humans, several techniques have been used to implicate the ACC in updating. The ACC is implicated in processing errors and helps optimize behavior. Early work in humans began with noninvasive approaches, such as electroencephalography (EEG) and measured error-related negativity (ERN). ERN is thought to arise from the dACC (Ullsperger & von Cramon, 2001; Holroyd et al., 2004). Some studies focused on changes in the ERN to help understand the neural mechanisms of behavior in humans (Gehring et al., 1993).

The ACC is necessary for error detection and is involved in the selection of correct choice. Experimental data using PET in humans implicated the ACC when learning was influenced by feedback in a prelearned task (Jueptner et al., 1997a, 1997b). ERN studies suggest that activity in ACC serves as an error detection between choices (Coles et al., 2001). Data from EEG and fMRI studies demonstrate that the ACC becomes active when an error is committed (Braver et al., 2001). The increase in activity is likely involved in driving behavior to correct errors for subsequent events. Notably, fMRI data suggest that errors are processed differently depending on whether a subject's choice was based on the subject's own volition or based on a command (Walton et al., 2004; Rushworth et al., 2007).

Converging lines of evidence support the idea that the PFC is necessary for cognitive control and behavioral flexibility. One type of behavioral flexibility is predictability. Predictability requires calculations based on previous experience, risk of change, and level of reward to be obtained (Kennerley et al., 2006). More neurons respond in the ACC than other PFC subregions in NHPs (Kennerley & Wallis, 2009). In primates, early work involving lesions of the ACC rendered subjects unable to allow new information to influence subsequent choices (Kennerley et al., 2006). Several reports implicate the ACC in prediction error and the respective influence on behavioral modification in humans (Nieuwenhuis et al., 2004; Jocham et al., 2009).

Furthermore, the ACC of NHPs is thought to play a key role in assigning and reevaluating possible outcomes (Ito et al., 2003; Matsumoto et al., 2003; McCoy et al., 2003; Samejima et al., 2005). The ACC evaluates associations in the presence of varying amounts of reward. Neural activity in the ACC, the cingulate motor areas or ACS, responds when reward is reduced (Shima & Tanji, 1998). Consistent with this view, activity in the ACC increases when levels of reward change throughout a training session (Amiez et al., 2006). Interestingly, a reversible lesion blocked this effect. The ACC is also affected by temporal factors. For example, activity in the ACC of humans was further increased if a loss had recently occurred (Gehring & Willoughby, 2002). It is also likely that dopaminergic inputs drive this response (Holroyd & Coles, 2002).

Anterior Cingulate and Temporal Signaling

Future behavior is manipulated by the ACC, which signals prior experiences. Anatomical inputs to the ACC include basal ganglia, the primary motor cortex, and premotor areas. Given the convergence of various signals in the ACC, it is likely that the ACC is able to access information in a unique matter that links potential outcomes that drive behavior in NHPs (Hayden & Piatt, 2010). Activity in the ACC is necessary to adapt to a changing environment.

One behavioral situation that can influence the ACC is that of previous experiences. Previous experiences, both recent and remote, involve associative learning that influences future decisions in NHPs and humans (Samejima et al., 2005; Daw et al., 2006). This type of associative learning requires an intricate system of brain structures that can link potential outcomes with variable actions. Several brain regions, such as the midbrain in NHPs (Bayer & Glimcher, 2005) and striatum (Samejima et al., 2005), interact with the cortical system when the value of a decision is relearned and updated. There are a few components of the prefrontal cortical system that are involved, such as the ACC (Procyk et al., 2000; Walton et al., 2004).

Previous influences of the environment affect subsequent behavior. Behavioral tasks in NHPs are often designed such that levels of reward or aversive stimuli are changed to indicate that the subjects need to modify their behavior. Data from lesion studies suggest that the ACC is recruited under these conditions (Kennerley et al., 2003). However, some reports suggest that the size of the lesion to the ACC influences the ability to modify behavior (Rushworth et al., 2004; Kennerley et al., 2006). For example, subjects with large lesions were able to modify their behavior but could not maintain choice after contingencies were switched (Kennerley et al., 2006). In this study, NHPs with lesions only considered recent trials to modify their behavior whereas monkeys without lesions considered many previous trials. Together, these data suggest that the ACC is necessary for relating behavior to the outcome of an event.

The contribution of subcortical regions to the ACC depends on the amount of change in the environment, which would influence how fast the cortical system updates the expected outcome of the action (Behrens et al., 2007). Once updated, the ACC regulates activity in subcortical regions (Kunishio et al., 1994). Studies using fMRI in humans show increased activity when there is a change in current behavioral situations (Walton et al., 2004; Yoshida & Ishii, 2006). On the other hand, data from NHPs demonstrate that this increase in activity is no longer present when levels of uncertainty are diminished (Procyk et al., 2000). Integration of these distinct types of information likely occurs in the ACC. Accordingly, activity in ACC is increased when events are more likely to predict subsequent behavior (Behrens et al., 2007).

Learning a pattern that is uncertain can challenge the survival of a species. Experiments using lesions in NHPs suggest that the ACC is able to detect changes that are probabilistic (Kennerley et al., 2006). During learning, neuronal activity in ACC of NHPs is increased (Procyk et al., 2000). As with previous reports, neurons in the ACC signaled the amount of reward received (Amiez et al., 2006). Furthermore, another population of neurons responded to the likelihood that a reward would be received. That is, high reward was delivered with a high probability, and low reward delivered with a low probability. Conversely, high reward was delivered with low

probability, and low reward delivered with high probability. This could only be determined and learned over many trials. In this case, increased activity is thought to influence subsequent behavior to favor a reward. The ACC is necessary for learning the reward that is presented in a probabilistic, albeit fixed, manner.

In addition to the ACC's being responsible for the history of the expected value of reward received, the ACC can survey the amount of reward received. Other reports demonstrate that activity in the dACC increases when there is a loss of reward (Holroyd & Coles, 2002; Gehring & Willoughby, 2002; Bush et al., 2002). Neurons in the ACC also become active when rewards could have been obtained (Hayden et al., 2009). This is consistent with the idea that the loss of expected reward could be aversive (Kim et al., 2006). Moreover, complete absence of reward drives the ACC to influence behavior (Chudasama et al., 2012). One report observed an increase in single unit activity of the ACC as the amount of predicted reward increased. Furthermore, it is suggested that motivation to perform the task increased with an increase in predicted reward (Shidara & Richmond, 2002). Together, these studies provide strong support that uncertain situations influence activity in the ACC.

Anterior Cingulate Influences Goals

In humans, the dACC becomes more active as the amount of reward decreases (Bush et al., 2002). Moreover, activity in ACC increased if reward loss was sequential (Gehring & Willoughby, 2002). This is probably because the effects of accumulating losses are compounded. In some cases, the implicated role of the ACC is different between species. This difference could be explained by type of reward used; different reward types may not be represented equally across species (Schultz, 2000; Bush et al., 2002). For example, human studies often use monetary rewards whereas primate studies use a liquid reward. Thus, an unanswered question in the field is the contribution of either primary or secondary rewards to ACC activity in humans. However, the influence of reward magnitude to neuronal activity in ACC of humans is unclear.

Achieving a goal requires planning and action that could lead to a rewarding event. Linking a planned action to a certain stimulus is accompanied by an anticipated reward (Hadland et al., 2003). Single cells in the ACC, likely the ACS region, respond to rewards more so than associations of stimulus to rewards (Matsumoto et al., 2003). In one study, subjects were presented with different stimuli, responses, and reward deliveries. Another role of the ACC is that it may influence the amount of effort invested in the planning of goals. The planning required to obtain a reward requires the ACC (Hadland et al., 2003). Moreover, the expectation of reward influences this (Shima & Tanji, 1998; Procyk et al., 2000).

Little is known about the behavioral significance of increased activity in ACC. To address this issue, Eskandar and colleagues (Williams & Eskandar, 2004) recorded activity from single neurons from the ACC in patients undergoing planned surgery for cingulotomy. These subjects performed a behavior task with visual cues that instructed subjects to perform specific types of actions. During parts of the task, subjects adjusted their behavior for subsequent trials and reward amounts were changed. Neurons in the ACC increased the most when the amount of expected

reward was reduced. These data suggest that decreased activity in ACC is associated with reduced reward. After cingulotomy, subjects were less likely to change their behavior as instructed. This within-subject design allowed for assessment of the ACC before and after cingulotomy. Therefore, strong interpretations as to what the contributions of the ACC are to human behavior could be inferred. Thus, it is likely that the ACC is necessary for evaluating the net gain of reward and the influence on choice.

Anterior Cingulate and Cognitive Interference

Executive functioning is a conjunction of several cognitive processes and goal-directed behaviors, which require planning, decision making, and action control (Banich, 2004). Coordination of these cognitive resources requires regions of the PFC, such as the ACC. Thus, the ACC is thought to be an interface between emotion and cognition (Banich, 2004). Inherently, damage to the PFC diminishes top-down control. In said cases, subcortical and other automatic processes dominate (Banich, 2004). As described previously, the ventral division of the ACC is associated with emotional tasks whereas the dorsal division is associated with cognitive ones (Bush et al., 2000). Interestingly, these divisions can deactivate each other.

Furthermore, the ACC may monitor the presence of conflicts (Botvinick et al., 2001). Recently, an fMRI study was able to disentangle the role of ACC in monitoring and selection (Walton et al., 2004). This research used an elegant task design and demonstrated that the ACC became more active with selection. Further increase in activation was observed when subjects were required to monitor the outcome. Activity in ACC increased when subjects made a decision of their own accord. In stark contrast, activity in ACC was decreased when the a subject was influenced by an experimenter. Thus, the ACC is necessary for selection and monitoring (Holroyd et al., 2004; Rushworth et al., 2004).

Experiments focusing on conflict often involve a type of cognitive interference which occurs when characteristics of a stimulus hinder the processing of another property of that stimulus. The increase in reaction times is a result of cognitive interference and is commonly known as the "Stroop effect" (Vendrell et al., 1995; Bush et al., 1998), named after John Stroop, a forefather of interference theory (Stroop, 1935).

The two divisions of the ACC described are reliably activated in the Stroop task. As noted, examining cognitive interference can be achieved in the Stroop task. Paradigms like the Stroop task set up a situation known as a congruent stimulus response, where relevant information results in a correct response that occurs with a short reaction time (fast response). Here, a subject is required to make a correct choice as fast as possible by focusing on only a relevant characteristic of the presented stimulus while ignoring other irrelevant information that is presented. The conflict exists when the irrelevant information increases the risk of committing an incorrect response and results in long reaction times (slow response). For example, subjects may be presented with a word of a color that is printed in another color. Next, subjects identify the color of ink that the word is printed on, and not the word. This type of cognitive interference leaves a previous memory difficult to retrieve because of the presence of discordant information related

to color and creates a conflict. This conflict requires that the subjects inhibit an impulse to read the color, which increases response times.

Behavioral tasks adapted from the Stroop task involved separate regions of the ACC (Bush et al., 2000, 2003). For example, the rostral ACC is thought to resolve emotional conflicts (Etkin et al., 2006). The ventral region of the cingulate is activated much more in emotional versions of the Stroop task, which can measure bias to emotional stimuli and emotional processing. In emotional versions of the Stroop task, words are charged with emotion in a similar matter as the color conflict version. However, emotional processing requires distinct mechanisms that are influenced by attention and the emotional relevance of the words (McKenna & Sharma, 2004). The type of cognitive control involved in emotional Stroop tasks is modulated by the rACC (Milham et al., 2001; MacDonald et al., 2000; Bush et al., 2000). Single unit recording experiments in the rACC/vmPFC of humans are difficult. Future studies in patients undergoing planned surgery may consider measuring neural activity from the vmPFC.

Optimizing behaviors can be achieved with increased attention. This could occur, for example, after commission of an error, reduced reward, or in the presence of a distractor (Lavie, 2005). Increased attention may serve to minimize a decline in behavioral performance. Early work using fMRI implicates the ACC in cognitive processes and attention (Wager et al., 2004). Unfortunately, the amount of information that can be extrapolated from imaging data is limited. At the turn of the century, Davis and colleagues (2000) took advantage of a rare opportunity to measure behavior in attention-demanding tasks while recording activity from single neurons in the ACC of humans undergoing planned surgery (Davis et al., 2000). They hypothesized that neurons in the ACC signal attention. To test this, Davis and colleagues (2000) administered a set of tasks, including arithmetic and Stroop tests, and compared different levels of attention. In paradigms such as the Stroop task, a behavioral marker of increased attention is an increase in time required to perform a task, which can be measured by increased reaction times. Their results demonstrated that neurons in the ACC signal attention during tasks that require high levels of cognition.

The role of single neurons in ACC of humans during other cognitive processes remained largely unexplored. Using similar techniques as in their previous study on attention, Davis and colleagues (2005) administered emotional Stroop tests while recording activity from ACC in humans (Davis et al., 2005). Their results demonstrated that activity in ACC signals attention and responds to emotionally salient stimuli. Together, these findings suggest that the ACC is necessary to disentangle situations of uncertainty while processing emotions. Additionally, the increased attention and emotion may directly influence motivation (Botvinick et al., 2001). This supports the idea that the ACC may signal cognitive processes to modify subsequent behavior.

Much of what is known about the ACC and cognitive processes stemmed from studies using imaging (Botvinick et al., 1999; Kerns et al., 2004) and event-related potential recordings in humans (Gehring & Fencsik, 2001). The behavioral relevance of neuronal activity in the ACC during cognitive processes like conflict, however, is still unclear. Indeed, the uncertainty is partly due to the differences in paradigms used and technical limitations between studies. For example,

data from lesion studies in humans (Mansouri et al., 2007) have provided disparate conclusions compared to those from work using imaging.

The ability to measure the magnitude of cognitive interference is made possible by a counting version of the Stroop task, known as the Multi-Source Interference Task (MSIT). In the MSIT, subjects are presented with a picture on a screen that has three numbers. Two of the numbers are the same and are classified as "distractors," whereas one number is unique and is classified as the "target." The subjects are asked to indicate the position of the "target" by pressing the corresponding button: either one, two, or three, represented from left to right on the button box. In general, there are three levels of interference—namely, type 0, type 1, or type 2. The numbers are presented with distinct levels of interference. For example, for type 0 trials the number 1 would be presented in the leftmost position on the screen followed by two zeros. This is considered no interference, given that there is not an option for "zero" on the button box. For low-interference trials (type 1), the number 1 would be in the leftmost position on the screen followed by two other numbers of the same type, requiring that the first button on the box be pressed. For high-interference trials (type 2), on the other hand, the position of the target number on the screen did not correspond to its numerical position on the button box and was presented alongside two distractors. Accordingly, the reaction time in response to stimuli increases as the level of cognitive interference increases.

Recent reports demonstrate that the MSIT combines many sources of cognitive interference that robustly activate the dACC (Bush et al., 2003; Bush & Shin, 2006), providing a potential mechanism for how the dACC can modulate cognitive control (Fellows & Farah, 2005; van Veen et al., 2001). Increased cognitive control is required in the presence of emotional conflicts and incongruent stimuli. Indeed, increased cognitive interference with the MSIT would increase the probability of committing errors (Brown & Braver, 2005). Subsequently, there would likely be an increase in attention (Davis et al., 2000, 2005) to enhance decision making (Botvinick, 2007).

The behavioral function of signaling interference load by neurons in the dACC is unclear. Many hypotheses stemming from fields such as decision making and conflict monitoring suggest that activity in dACC from previous experience influences future levels of activity in dACC neurons. Due to technical limitations, no study has been able to provide compelling support for these hypotheses at the neuronal level. Moreover, some studies measuring single unit activity in NHPs do not support the role of ACC in monitoring conflict (Ito et al., 2003; Nakamura et al., 2005). To address this issue, Sheth and colleagues combined behavioral measures of the MSIT with imaging and single unit recording in patients undergoing planned surgery. As expected, behavioral responses and reaction times were similar to those in previous reports (Kerns et al., 2004; Botvinick, 2007; Ridderinkhof, 2002). Similarly, they reported a dose-dependent increase in fMRI and single neuronal signaling in dACC when comparing high-interference trials with low-interference trials (see figure 12.2, plate 13; Bush et al., 2003). Furthermore, Sheth and colleagues found that reaction times were faster if a previous trial was different than the current trial whereas reactions times were slower if a previous trial was the same as the current trial. Interestingly, they demonstrate that single unit activity in the dACC increased when

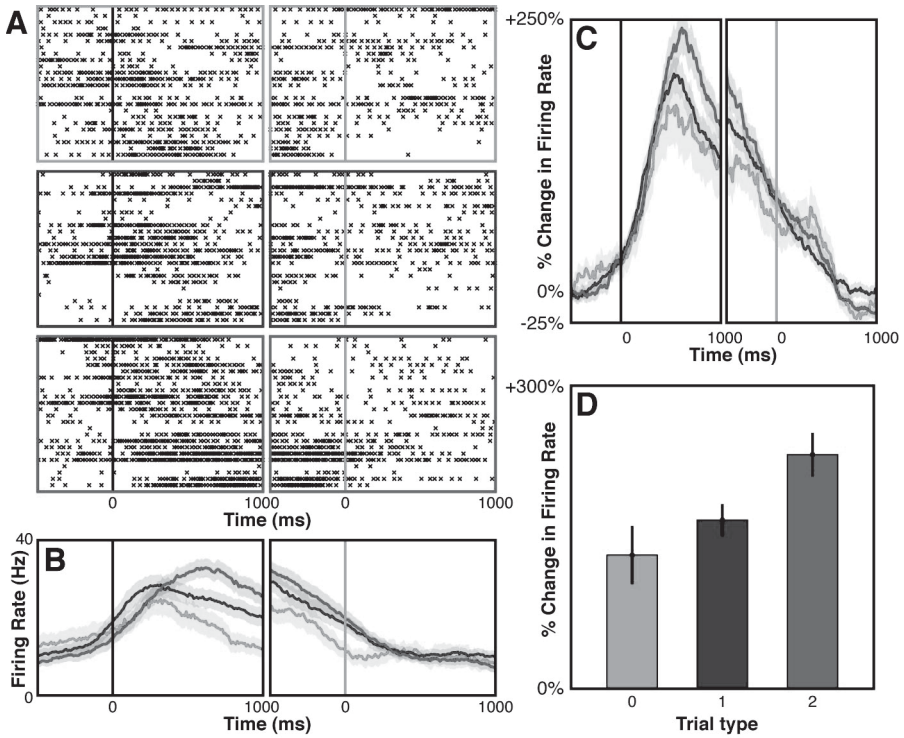

Figure 12.2 (plate 13)
Individual and population neuronal responses. (A) Example neuron showing modulation of firing based on cue-related interference. Rasters for Type 0 (green), 1 (blue), and 2 (red) trials are shown aligned to the cue (black line) and choice (gray line). (B) Average firing rates of the same neuron, demonstrating increasing firing with increasing interference. Error bars (SEM) are depicted with shading. (C) Average firing of all cue-related neurons. (D) Same as in (C), but showing activity averaged within a 200-ms-wide window centered 500 ms after the cue. Neuronal firing increased with cognitive interference ($p = 0.02$, analysis of variance), correlating with reaction time. From Sheth et al. (2012).

high-interference trials were preceded by high-interference trials, unlike results from previous imaging data demonstrating decreased activity in dACC when previous and current trials were the same (Kerns et al., 2004; Botvinick et al., 1999).

One possible explanation for the difference in findings between studies is the lack of temporal resolution of fMRI compared to single unit recordings (Sheth et al., 2012). Moreover, the peak signal in the dACC occurs much faster than previously thought. Interestingly, Sheth and colleagues successfully performed the planned cingulotomy and observed successful behavioral performance, albeit slower reaction between trials, in the presence of varying levels of interference.

The results of Sheth et al. showed that previous activity in the dACC influences current neuronal activity. They suggest that the dACC is necessary for behavioral adaptation, either by enhancing reactions to cues with similar levels of interference or hindering reactions to cues

with varying levels of interference. If true, then removal of the dACC would impair behavioral adaptation. Interestingly, Sheth et al. noted that subjects with lesions of the dACC had similar levels of success in behavior as compared to preoperative levels. On the other hand, dACC lesions eliminated the influence of previous trials to the modulation of reaction times. These results provided empirical support that the dACC is necessary to evaluate the influence of previous experience to current behavior.

Limitations of Methodology

Human single neuronal studies provide unique data for understanding and exploring neural mechanisms of human cognition. However, fundamentally, studies of this nature are limited not only by moral and ethical responsibilities but also by technical and physical constraints. Many considerations must be taken into account in designing and executing this type of study. Importantly, all experiments must be approved by an institutional review board, and consent must be obtained from any subject participating in the study.

Conducting research studies in the operating room can be demanding, but patient care is always the foremost priority. Generally, microelectrode research studies are limited to roughly 30 minutes, and thus careful attention must be taken when designing and implementing a behavioral task. Tasks should be simple and easy to understand with little requirement for training and should provide enough statistical power to adequately explore questions of interest. It can be helpful to chunk sessions into 10-minute groups to allow for multiple neuronal isolations during a study and provide brief breaks for subjects. The underlying disease pathology of the study population must also be considered when designing the task. For example, subjects with motor impairments (e.g., tremor or dystonia) may have difficulty in performing joystick-based or other movement-demanding tasks. Similarly, laterality of cognitive function must also be considered when designing an experiment.

Neurophysiological recordings are also susceptible to many issues within the operating room environment. Ambient electrical (60-Hz) noise from surgical or anesthesia equipment often poses the most common issue. This can generally be alleviated by turning off the culprit component. Another common issue when performing human microelectrode recordings is mechanical noise induced from cardioballistic effects. This occurs when the microelectrode is in close proximity to the vasculature and occurs through the expansion/contraction of the artery/arteriole.

Inherent in these experiments are limitations on the generalizability of the results. For obvious ethical reasons, invasive studies cannot be performed in normal subjects, and thus inferences must always be considered within the context of the study population. Despite this, there are a number of ways to address these concerns. Behavioral or fMRI data can be collected and compared in a matched healthy cohort, potentially corroborating microelectrode findings. Another possibility is performing the microelectrode study in orthogonal patient populations. For example,

the ventral striatum is the target for two underlying diseases, OCD and MDD. Similar findings from two separate populations can also strengthen the validity of the data.

Future Directions and Conclusions

Although there are relatively few human single neuron studies to date, and even fewer that have explored reward processing, human studies provide a unique data set that have the potential to guide both innovative basic and translational science. All of the studies presented in this review, with the exception of Sheth et al., represent correlative findings from microelectrode studies. With the advancement of invasive and noninvasive stimulation technology, such as intermittent deep brain stimulation or transcranial magnetic stimulation, future studies will explore cognitive functions through causal experimentation guided by the underlying neurophysiology. This is already a rapidly progressing avenue of research.

A fundamental limitation to these studies is that they are first and foremost guided by clinical care. With the proven effectiveness of deep brain stimulation surgery, more and more brain regions are being explored for the treatment of various neurodegenerative and neuropsychiatric disorders. As these studies progress, we will have the opportunity to investigate activity from many more regions of the widely distributed reward network. Human intraoperative studies will continue to be guided by NHP physiology and human imaging studies, which serve as a spotlight to focus these difficult and limited experiments.

In conclusion, we present evidence in this review of human single neuronal studies of reward processing in the anterior cingulate and basal ganglia. Much of the work contributed by these studies supports evidence from both NHP physiology and human neuroimaging studies. Although these studies are difficult and limited in many ways, they provide invaluable data for how we encode, represent, and process reward information within the context of the human brain. Currently, no other technique allows this type of access to the fundamental computational unit of our nervous system, and thus it will remain a gold standard for studying human behavior.

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