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Using fMRI to Study Reward Processing in Humans: Past, Present, and Future

Kainan S. Wang[1], David V. Smith[2], Mauricio R. Delgado[1,2]*

[1] Behavioral and Neural Sciences Graduate Program, Rutgers University, Newark, NJ 07102, USA
[2] Department of Psychology, Rutgers University, Newark, NJ 07102, USA

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Address for correspondence:
Mauricio R. Delgado, Ph.D.
Department of Psychology
101 Warren Street, Room 340 Smith Hall
Rutgers University
Newark, NJ 07102
delgado@psychology.rutgers.edu

Abstract

Functional magnetic resonance imaging (fMRI) is a noninvasive tool used to probe cognitive and affective processes. Although fMRI provides indirect measures of neural activity, the advent of fMRI has allowed for a) the corroboration of significant animal findings in the human brain and b) the expansion of models to include more common human attributes that inform behavior. In this review, we briefly consider the neural basis of the blood oxygenation level dependent (BOLD) signal to set up a discussion of how fMRI studies have applied it in examining cognitive models in humans, and the promise of using fMRI to advance such models. Specifically, we illustrate the contribution that fMRI has made to the study of reward processing, focusing on the role of the striatum in encoding reward-related learning signals that drive anticipatory and consummatory behaviors. For instance, we discuss how fMRI can be used to link neural signals (e.g., striatal responses to rewards) to individual differences in behavior and traits. While this functional segregation approach has been constructive to our understanding of reward-related functions, many fMRI studies have also benefitted from a functional integration approach that takes into account how interconnected regions (e.g., corticostriatal circuits) contribute to reward processing. We contend that future work using fMRI will profit from using a multimodal approach, such as combining fMRI with noninvasive brain stimulation tools (e.g., transcranial electrical stimulation) that can identify causal mechanisms underlying reward processing. Consequently, advancements in implementing fMRI will promise new translational opportunities to inform our understanding of psychopathologies.

Introduction

Functional magnetic resonance imaging (fMRI) is an excellent tool to probe neural function. Even though it indirectly measures neural activity by tracking correlative hemodynamic changes, it has the capability to map task-dependent whole-brain activation. This feature, along with its noninvasive nature, makes fMRI a tremendous asset to the study of cognitive and affective processes in both healthy and patient human populations. Indeed, the application of fMRI to study the human brain has allowed for a) confirmation of core findings from non-human animal studies that have shaped models of cognitive and affective processing; and b) extension of those findings and new directions for such models by probing characteristics more accessible in humans. One noteworthy example is the study of reward processing, which has been informed by a rich non-human animal literature employing an array of techniques, from selective lesions to electrophysiological recordings, to delineate a neural reward circuit (e.g., Berridge and Robinson 2003; Robbins and Everitt 1996; Schultz 2006). An explosion of fMRI studies over the last decade or so (Fig. 1) has substantiated this reward circuit in the human brain, with emphasis on higher-level functions that are more commonly observed in humans. Many of these fMRI studies have also examined deficits in the reward circuit in patient populations. As a result, the use of fMRI to study reward processing has greatly expanded our understanding of its neural basis in humans.

Despite the many advantages that fMRI has afforded the study of reward processing, there are some inherent challenges that discount the full promise of fMRI. For instance, the neurophysiological nature of the fMRI signal can cloud its potential neural interpretations. While we address these limitations, our synthesis of the literature highlights the promise of fMRI in advancing models of cognitive and affective processes. First, we describe the fMRI blood oxygenation level dependent (BOLD) signal and consider potential pitfalls related to its neural interpretations. Second, we illustrate the use of fMRI in both confirming key findings and extending such findings to advance models of cognitive and affective processing. We specifically anchor our discussion on the study of reward processing as an exemplar topic because it has garnered considerable experimental efforts across techniques and species. In the last section, we highlight the promise of fMRI in studying

reward processing and describe how it fits into the progressive multimodal and across-technique approach to study such psychological phenomena.

A Neural Interpretation of the BOLD Signal in fMRI

Functional magnetic resonance imaging (fMRI) detects neural activation by measuring changes in the blood oxygenation level dependent (BOLD) signal. The BOLD signal is coupled to hemodynamic changes such as blood flow (Logothetis and Wandell 2004) and decreasing levels of deoxygenated hemoglobin (deoxyhemoglobin; Ogawa et al. 1992), whose paramagnetic nature allows BOLD to indirectly track the underlying neural activity. Taking into account the many comprehensive and informative reviews (Buxton et al. 2004; Logothetis 2008; Logothetis and Wandell 2004) on the technical underpinnings of fMRI and its BOLD signal, we provide below a succinct and generalized account of the neural interpretation of the BOLD signal and how it is typically analyzed in fMRI experiments to infer neural functions. In doing so, we hope to provide readers of all backgrounds with sufficient understanding of the fMRI findings we present throughout the review and appreciation for the advantages of fMRI we subsequently discuss for the rest of the paper.

The Cellular Underpinnings of the BOLD Signal

Throughout various fMRI studies, most experimental protocols observe BOLD signals that correspond to localized increases in cerebral blood flow (CBF). These CBF increases, coupled with smaller positive changes in the cerebral metabolic rate of oxygen consumption, lead to the production of a hemodynamic response (Buxton and Frank 1997; Hoge et al. 1999; Raichle et al. 1976). Importantly, unlike the immediate nature of neuronal spiking activity (Lauritzen and Gold 2003), the hemodynamic response has a lagged response that begins approximately two seconds after neural stimulation and peaks four to six seconds thereafter (Bandettini et al. 1992). Although the hemodynamic response was initially interpreted to represent neuronal output (Rees et al. 2000), subsequent studies soon reported robust BOLD signals in the absence of spiking activity (Rauch et al. 2008; Viswanathan and Freeman 2007), fueling the interpretation of BOLD signal as an

indicator of the underlying local field potential (LFP; Goense and Logothetis 2008; Logothetis 2002; 2008; Magri et al. 2012; Nir et al. 2007). Because LFP underlines the synaptic inputs and dendritic processing in a particular region (Berens et al. 2010), the LFP-driven hemodynamic response is more strongly encoded by aggregate cellular activity within a localized excitation-inhibition network rather than single cell activity (see review by Logothetis and Panzeri 2015). Thus, the neurophysiological underpinnings of the BOLD signal are thought to reflect local field potential during neural stimulation.

Some experimental protocols also detect negative BOLD responses (NBR) that are postulated to reflect neuronal suppression (Wade 2002). Although there is no widely accepted neurophysiological explanation of NBR, it is clear is that one cannot simply assume that NBR is the neurophysiological inverse of a hemodynamic response (Mullinger et al. 2014). The current neuronal explanation of NBR is divided into two camps of thought. On one end of the debate, Shmuel and colleagues (2006) observed that NBR was tightly coupled to local decreases in LFP, which led to the view that NBR is a representation of neural deactivation (Hayden et al. 2009; Klingner et al. 2010; Mckiernan et al. 2003; Pasley et al. 2007). On the opposite end lie those who, guided by Logothetis and his metabolic-increasing excitation-inhibition microcircuit viewpoint (Logothetis 2008), put forth the argument that NBR encodes underlying neural activation (Kim et al. 2014; Schridde et al. 2008; Shulman et al. 2007). In essence, the interaction between CBF and blood volume changes encodes the excitation-inhibition balance, giving rise to NBR (Huber et al. 2014). Despite the irresolute nature of this debate, continued progress on understanding the neural nature of NBR is important to provide more insights on the BOLD signal and to further refine the role that different neural regions play in cognitive processes.

From BOLD Signals to Inferences on Brain Function

Neuroimaging studies tend to visualize the hemodynamic response (e.g., plot the time-series of the data) but more commonly report parameter estimates summarizing the fit of a statistical model to the BOLD data (e.g., Fig. 2). To obtain these parameter estimates, the known stimulus functions based on preset experimental conditions are first convolved with a canonical hemodynamic response function to establish the predicted BOLD responses. Predicted BOLD responses are subsequently used to test, under the framework

of the general linear model (Friston et al. 1994; Worsley and Friston 1995), whether activity in brain regions is related to any of the BOLD input functions (e.g., the raw data). Most fMRI studies report statistical fit of the BOLD functions as a series of parameter estimates, which can have both positive and negative deflections relative to pre-stimulus activation (for details on fMRI analysis and issues such as multiple comparisons please see Poldrack et al. 2011). It is important to distinguish these negative deflections from NBR because negative parameter estimates reflect relative deviations from the implicit baseline in the model rather than the measured BOLD signals. In addition, we note that statistical inference in fMRI studies can suffer from many of the same problems that affect neurophysiological studies, including circular analyses (Kriegeskorte et al. 2009) and erroneous interactions (Nieuwenhuis et al. 2011). Nonetheless, these parameter estimates derived from BOLD responses have served fMRI researchers well, as we will discuss in detail throughout the rest of this review, in advancing the understanding of neural activity during task-induced cognitive and affective processes.

Using fMRI to Study Reward Processing in the Striatum

Given its noninvasive nature and potential to visualize function in the whole brain, fMRI became a powerful and practical tool to study cognitive and affective processes in humans. Over the years, the use of fMRI proved to be an important asset in studying such processes as it afforded a way to confirm basic findings characterized in non-human animal studies, and extend such findings to appreciate various aspects of human life, from distinctively human stimuli (e.g., money) to behaviors (e.g., cognitive emotion regulation) that translated to better understanding of neuropsychiatric disorders (e.g., mood disorders). One such phenomenon that benefitted from the proliferation of fMRI studies is reward-related processing and its relation to decision making (Fig. 1). Rewards can be broadly defined as stimuli that elicit approach behaviors, induce subjective feelings of pleasure during consumption, and lead to reinforcement of cues and actions (Schultz 2006; 2015). The regulation of the psychological and behavioral responses to rewarding stimuli is coordinated by a collection of cortical and subcortical structures that together make up the brain's reward circuit (see review by Haber and Knutson 2010). At the core of such circuit

is the striatum (Fig. 3), a subcortical structure that is involved in reward-related learning and how it informs approach and consummatory behaviors.

Building on a large repertoire of studies using non-human animal models (Daw and Doya 2006; Hikosaka et al. 1989; Robbins and Everitt 1996; Schultz et al. 1997), many fMRI experimental efforts have focused on elucidating how the striatum—the input unit of the basal ganglia and a structure with strong connections with cortical regions and midbrain dopaminergic centers (Middleton and Strick 2000; Wang et al. 2015b)—contributes to reward processing (Fig. 3; e.g., for review see Bartra et al. 2013; Clithero and Rangel 2014; Delgado 2007; Haber and Knutson 2010; Smith and Delgado 2015). In the following section, we will provide a brief discussion of research findings from both non-human animals and humans focusing on the striatal role in reward-related processing, particularly in approach and consummatory behavior, and how they are shaped by learning.

Approach Behaviors in Reward Processing

Approaching a potential reward is a typical behavior observed across species that is elicited by the anticipation of the pleasure a reward may bring. In non-human animals, this was initially characterized in studies where presentation of a conditioned stimulus that predicted a reward elicited a conditioned approach response in pigeons (Brown and Jenkins 1968; Williams and Williams 1969) and rats (Locurto et al. 1976; Peterson et al. 1972). This conditioned cue-induced approach behavior was found to depend on the integrity of the striatum, such that lesion (Parkinson et al. 1999) or dopaminergic depletion in the ventral parts of the striatum, particularly the NAcc (Parkinson et al. 2002), decreased approach behavior to a conditioned stimulus paired with reward (Di Ciano et al. 2001; Parkinson et al. 2000).

In non-human primates, a similar link between striatum neurophysiological signals and anticipatory responses to reward-related cues that can elicit approach behaviors have been observed. For instance, striatal neurons have been found to increase their firing rates during the anticipatory phase preceding reward delivery, highlighting a potential influence on reward-seeking approach behaviors (Ito and Doya 2015; Kawagoe et al. 1998; McGinty et al. 2013; Samejima et al. 2005). Interestingly, distinct subsections of the striatum can show different contributions to approach behaviors. Ventral striatal neurons, for example,

have been shown to increase their firing rates in response to cues predicting rewards (Cromwell and Schultz 2003; Hassani et al. 2001; Hollerman et al. 1998; Schultz et al. 1992). In contrast, dorsal striatal neuronal responses have been linked with tracking the values of available actions for reward attainment (Lau and Glimcher 2007; 2008; Tai et al. 2012).

In humans, initial fMRI studies served to replicate findings from non-human animals identifying the striatum as a key region involved in responding to cues that predicted potential rewards and could exert influences on approach behavior. For instance, initial efforts showed that BOLD responses in the ventral striatum, which includes the nucleus accumbens (NAcc; Fig. 3), were correlated with craving of potential drug rewards (Breiter et al. 1997), relating to a motivational construct of 'wanting' which can lead to approach behaviors such as reward seeking (Berridge and Robinson 1998). This was quickly followed by reports of increased BOLD responses in the striatum to conditioned cues that predict potential primary rewards including pleasant liquids (O'Doherty et al. 2002) or odors (Gottfried et al. 2002), and secondary rewards such as money (Knutson et al. 2001). As in non-human animals, distinct contributions of subsections of the striatum have also been reported, with the dorsal striatum, encompassing the caudate nucleus and putamen (Fig. 3), being more specifically recruited when participants performed an action (e.g., pressing a button) in response to cues predicting reward (O'Doherty et al. 2004; Tricomi et al. 2004). While dorsal striatum activity has been linked to the encoding of action values used in action selection during reward-seeking behaviors (FitzGerald et al. 2012), ventral striatum activity has been shown to correlate with participant's passive viewing responses to conditioned stimuli (Chumbley et al. 2014). This observation is in line with the actor-critic model (Sutton and Barto 1998) suggesting that the dorsal striatum can serve a potential function of an "actor" that facilitates action selection whereas the ventral striatum can serve as a "critic" to guide future reward attainment (O'Doherty et al., 2004).

More recently, fMRI studies have extended these initial findings of striatal involvement in eliciting reward-related approach behavior to demonstrate how they relate to everyday human behaviors. Increased activation in the striatum to pictures of appetizing food items, for example, has been found to correlate with increased reward-seeking behavior (as assessed by greater weight gain months after initial data acquisition; Demos et

al. 2012). Similarly, increased activation in the striatum to positive, arousing images (Knutson et al. 2008), and cues that predict monetary rewards (Kuhnen and Knutson 2005) is associated with elevated risk-taking behaviors. The relation between striatal BOLD activity and risk-taking behaviors is observed in different domains, such as drug-related cues elevating craving responses (Sinha et al. 2007), which can have an influence in maladaptive behaviors such as drug-seeking. Finally, this response in the striatum is also dependent on state of an individual (e.g., stressed: Porcelli et al. 2012; or sleep deprived: Venkatraman et al. 2011) or context in which a reward is perceived. For example, the presence of a peer can change reward-related responses in the striatum (Chein et al. 2011; Fareri et al. 2012), which can relate to increased risk-taking behaviors in some cases (e.g., adolescence; Chein et al. 2011). These studies collectively highlight the use of fMRI in understanding how the brain processes reward-related information and how it contributes to approach behaviors that complement and extend the knowledge gained from non-human animal studies.

Consummatory Behaviors in Reward Processing

A consummatory behavior occurs during the delivery or receipt of a reward. The consumption of rewards, such as food and sex, induces a pleasurable sensation which can be experimentally elicited in rats when neural regions such as the septal areas (Olds and Milner 1954) and NAcc (Olds 1956) are stimulated. Comparable studies in non-human primates (Porter et al. 1959) and humans (Bishop et al. 1963) have similarly shown that electrical stimulations delivered to the NAcc generates a pleasurable sensation. The hedonic aspects of reward are generally associated with opiate receptors in the NAcc (Peciña and Berridge 2000), but more general affective processing that can inform the reinforcement of actions is evident during reward consumption, being associated to dopamine release into the NAcc (Nakahara et al. 1989) and the firing of striatal neurons (Apicella et al. 1991; Hikosaka et al. 1989; Klein and Platt 2013; Schultz et al. 1993). In rodents, an interesting distinction is further noted where lesions to ventral parts of the striatum disrupt approach behaviors whereas lesions to the more dorsal parts disrupt consummatory behaviors (Everitt and Robbins 2005).

In humans, reward consumption is typically probed during the outcome phase of a given task, where, for example, a participant may receive the resolution of a decision (e.g., monetary gain) or be presented with a stimulus that carries a positive value (e.g., liquids when thirsty, pleasant pictures). Several fMRI studies have observed activation in the striatum in response to a rewarding or positive outcome (Fig. 2). This extends to a variety of stimuli, from the most basic such as food (e.g., chocolate; McCabe et al. 2010), money (Fig. 3; Delgado et al. 2000), or just positive feedback (e.g., correct; Delgado et al. 2004; Foerde and Shohamy 2011) related to goal achievement (Tricomi and Fiez 2008) to the more abstract positive feelings elicited from observing a beautiful face (Smith et al. 2010), art (Lacey et al. 2011), receiving social feedback (Izuma et al. 2008), or even thinking about the self, such as when one discloses information about oneself to another (Tamir and Mitchell 2012), or recalls autobiographic positive memories (Speer et al. 2014). Interestingly, individual differences in the striatal BOLD signals associated with the consumption of such rewards have been shown to be very important in understanding questions of human behavior and health that can be studied with fMRI. For instance, striatal responses to evaluation of the self from others has been linked with pubertal status and age (Jankowski et al. 2014), while simple responses to monetary gains and losses in the striatum correlated positively with the sustainment of real-world positive emotions (Heller et al. 2015) and negatively with early life stress such as emotional neglect (Hanson et al. 2015b). Taken together, these findings highlight the contribution of using fMRI to explore reward-related processing in the human brain and links to behavior and health outcomes.

Reward-related learning

The observations of the striatum responding to stimuli that predict rewarding outcomes support a prominent role for striatal circuits in reward-based learning. Indeed, the striatum has been implicated in a variety of learning studies involving cues that predict reward (e.g., O'Doherty et al. 2004) to probabilistic reinforcement learning tasks where feedback that allows for correction of behavior is presented, both in fMRI studies (e.g., Dickerson et al. 2011) and in studies with Parkinson's Disease patients, who have compromised function in the basal ganglia (e.g., Shohamy et al. 2004).

An influential theory of reward-based learning has been the prediction error hypothesis, which stems from theories of how errors can shape associative connections (Rescorla and Wagner 1972) and temporal-difference reinforcement learning models (Sutton and Barto 1981). Specifically, this hypothesis posits that the neural circuitry of reward has the ability to update the expectation of future rewards and subsequently allow for the adaptation of behavior (Schultz 2002).

A prediction error can be characterized as the calculation of whether a reward is better or worse than expected (Glimcher 2011). A positive prediction error is generated when an unexpected reward occurs, leading to an increase in phasic firing of dopaminergic cells in the midbrain (Bayer and Glimcher 2005; Schultz et al. 1997). In contrast, a negative prediction error is recorded when an expected reward fails to occur. Although there is some debate whether the tonic firing rate of dopamine neurons makes it difficult to encode a negative prediction error (Bayer and Glimcher 2005), there is nonetheless depression of dopaminergic firing during the omission of an expected reward (Schultz et al. 1997). Both positive and negative prediction error signals are correlated to reward-evoked dopamine release onto the ventral striatum (Hart et al. 2014). These dopamine neurons show sensitivity to the temporal aspect of reward delivery, which correspond to a key feature of the prediction error signal—a temporal learning element that allows for predictions about future rewards to be formulated and updated (Hollerman and Schultz 1998; Kobayashi and Schultz 2008; Roesch et al. 2007). Collectively, these findings and others point to dopamine a key neural signal involved in signaling prediction errors.

In humans, a few fMRI studies have also reported dopaminergic midbrain activation during the generation of reward prediction errors (D'Ardenne et al. 2008; D'Ardenne et al. 2013). However, most have found evidence of a reward prediction signal in the striatum (for review see Garrison et al. 2013). Some of the first observations of this involved simple comparisons of unexpected juice delivery (positive prediction error) and omission (negative prediction error), which evoked activation in dorsal (McClure et al. 2003; O'Doherty et al. 2004) and ventral (Berns et al. 2001; Gläscher et al. 2010; O'Doherty et al. 2003) striatum. These were soon followed by other studies demonstrating how such learning signals in the striatum could correlate with efficacious learning and performance (e.g., Schönberg et al. 2007).

In parallel with the reward prediction error hypothesis, reward-based reinforcement learning has also been demonstrated to involve two dissociable but related processes: one that encodes response-outcome associations to govern goal-directed behaviors, and the other that characterizes stimulus-response association to drive habitual behaviors (Balleine and O'Doherty 2010). Concurrent with studies in rodents, these two processes have been shown to also involve the human striatum (for review see Dolan and Dayan 2013). To further illustrate how the striatum encodes habitual and goal-directed action selection, investigators have utilized computational models to capture the performance of these behaviors. For instance, a model-free approach is contingent upon the interaction between the learner and the reward stimulus to update the reward cue values through trial and error while reinforcing successful actions in a habitual manner (Balleine et al. 2008; Rangel et al. 2008). This approach supports neurophysiological data from dopamine (Bayer and Glimcher 2005; Schultz et al. 1997) and striatal neurons (Oyama et al. 2010; Stalnaker et al. 2012) and BOLD signal from the striatum (Garrison et al. 2013), hence drawing a parallel with the prediction error hypothesis. On the contrary, a model-based learning scheme encompasses a more flexible way of incorporating striatal prediction error signals into the calculation of value to inform goal-directed decision making (Dayan and Berridge 2014). This approach takes into account additional information about the expected reward, such as sensory attributes or associated costs (Doll et al. 2012), to allow the learner to form a “state-dependent” prediction error that encompasses the surrounding environment in order to drive goal-directed reward-maximizing actions (Gläscher et al. 2010). This state prediction error is dependent on not only the striatum, but also significant contributions from several cortical areas such as lateral prefrontal cortex (Gläscher et al. 2010).

For both model-free and model-based approaches, the striatum might very well be the site where these two approaches are integrated to facilitate reward-based learning (Daw et al. 2011; Wunderlich et al. 2012), yet the underlying mechanism of how the striatum(and its distinct subsections) encodes reward prediction error has not been fully resolved (e.g., see study by Stenner et al. 2015). A recent multimodal study employing both PET and fMRI reported that dopamine level in the ventral striatum is responsible for regulating the balance between model-free and model-based control on reward-related

behavior (Deserno et al. 2015), further suggesting that the importance of dopaminergic modulation on the striatum cannot be discounted in either learning mechanism.

In short, these fMRI-based learning models demonstrate that the neural mechanism underpinning reward processing relies on diverse brain regions that interact with the striatum. Further progress in understanding how this reward-processing neural circuit encodes reward-related functions in humans will be contingent upon capitalizing on the many advantages that fMRI supplies, which will be scrutinized in subsequent sections.

The Promise of fMRI in Advancing Models of Reward Processing

As previously discussed, fMRI is a noninvasive way to study the human brain that provides us with correlative measurements of neural activity to allow for inferences in various affective and cognitive processes. We have focused thus far on how fMRI has confirmed prior findings from non-human studies and extended the knowledge to behaviors typically observed in humans. In this section, we now discuss advantages of a neuroimaging approach that have the potential to significantly advance models of reward processing.

Individual Differences

Due to its relative ease in application, fMRI studies have the potential to utilize relative large samples of subjects. Researchers can exploit these large samples by relating variation in brain structure and function to variation in behavior across individuals (Braver et al. 2010; Yarkoni and Braver 2010). While this approach can be problematic in underpowered studies (Yarkoni 2009), it provides a unique opportunity to identify candidate mechanisms that contribute to a range of psychological constructs (Braver et al. 2010; Hariri 2009).

Inter-individual variability is often discussed in terms of structural and behavioral differences. Structural differences, which can be commonly detected using methods such as voxel-based morphometry from anatomical MRI images (Ashburner and Friston 2000; Good et al. 2002) and fractional anisotropy from diffusion tensor imaging (Jbabdi et al. 2015; Johansen-Berg and Behrens 2013), have been observed within both control

population and pathological subgroups (Barrós-Loscertales et al. 2011; Pantelis et al. 2005; Thompson et al. 2001; Wright et al. 2014). These anatomical differences in grey matter volume and white matter integrity have been linked to inter-individual behavioral differences (Kanai and Rees 2011), which includes measures such as reaction time (Jensen 1992), variable trait sensitivity to reward (Van den Berg et al. 2015) and working memory (Just and Carpenter 1992).

The link between neural anatomy and behavioral manifestation can be bridged by the functional inter-individual variability, which stems from differences in neural responses recorded by fMRI. For example, fMRI studies looking at anhedonia, defined as the impaired capacity to experience pleasure (Treadway and Zald 2013), have found that increasing trait anhedonia not only correlated with reduced NAcc and caudate volume but also with decreasing NAcc response to rewarding outcomes (Harvey et al. 2007; Wacker et al. 2009). In the same vein, fMRI studies investigating trait measures such as sensitivity to reward (Davis et al. 2004; Franken and Muris 2005) and behavioral indexes such as learning aptitude have been reported to correlate with striatal activation in response to reward anticipation (Beaver et al. 2006; Carter et al. 2009) and reward outcomes (Rieckmann et al. 2010; Schönberg et al. 2007). In addition, responses in striatum are predictive of individual differences in relative motivation to obtain different rewards (Clithero et al. 2011) and differences in strategic preferences (Venkatraman et al. 2009). These findings have been extended to patient populations where trait impulsivity (Chamorro et al. 2012; Cloninger et al. 1994) correlated with hyporesponsiveness in the ventral striatum during reward anticipation in both individuals with attention-deficit/hyperactivity disorder (Plichta and Scheres 2014) and detoxified alcoholics (Beck et al. 2009). Taken together, these findings suggest that inter-individual behavioral variability to rewards is intricately tied to variations in striatum neural function.

These fMRI observations provided new translational opportunities to extend these findings to patient populations to predict susceptibility to psychopathologies. Linking behavioral differences with neural functional differences has major implications on the diagnosis of many psychopathologies and their individualized treatments. One example is a study by Telzer and colleagues (2014) where ventral striatal activation in adolescents exhibiting greater prosocial behaviors (e.g., donate money to family members) predicted

longitudinal declines in depressive symptoms. In contrast, ventral striatal activation in adolescents who engaged in more selfish and risky reward-seeking behaviors predicted longitudinal increases in depressive symptoms (Telzer et al. 2014). Yet another example of how behavioral differences is associated with neural functional differences in psychopathologies is shown by Hanson and colleagues (2015a) who demonstrated that early life stress during childhood and adolescence, which leads to increased anxiety and depression (Norman et al. 2012), predicted diminished reward-related ventral striatal activity in adulthood. Collectively, these studies highlight how fMRI can be used to understand variation across individuals, which can be precursors of psychopathological conditions.

Brain Connectivity and Functional Integration

Much of the work that was discussed in the preceding sections is predicated on the principle of functional segregation, which relates functions (e.g., reward-related) to populations of neurons or single brain regions (e.g., striatum; Friston 2005; Raichle 2003). Yet, given the diverse anatomical inputs to each brain region, there can be multiple functions associated with such regions, making it difficult to understand how specific brain regions contribute to behavior and individual differences (Friston 2005; Park and Friston 2013). Addressing this issue rests with our ability to quantify the interactions and connectivity between brain regions, a principle known as functional integration (Friston 2009). Characterizing functional integration thus requires simultaneous measurements of responses from multiple brain regions—a core feature of neuroimaging studies. Indeed, one of the earliest neuroimaging studies reported functional connectivity (e.g., statistical dependencies or correlations) between homologous cortical areas (Biswal et al. 1995). More recent studies employing functional connectivity have provided remarkable insights into the large-scale network architecture of the brain (Beckmann et al. 2005; Smith et al. 2009). These networks span multiple regions and are recapitulated across species. For example, the default-mode network—which includes medial portions of the prefrontal cortex, posterior cingulate cortex, and lateral parts parietal cortex (Raichle et al. 2001)—has been reported in rodents (Lu et al. 2012) and monkeys (Vincent et al. 2007). The ubiquity of large-scale networks has sparked several studies examining their functional

significance and impact on behavior. These studies have demonstrated that functional connectivity with networks is associated with phenotypic variation (Ingalhalikar et al. 2014; Smith et al. 2014b) and behavioral variation (Cole et al. 2010; Smith et al. 2015) across individuals. In addition, functional connectivity with networks is tied to psychopathology, particularly depression (Berman et al. 2011) and schizophrenia (Manoliu et al. 2014). These studies highlight how neuroimaging can leverage functional connectivity to gain insight into the organization and functional significance of neural networks.

Beyond examining large-scale neural networks, functional connectivity has also been applied to the striatum in an effort to characterize connections with the reward circuit. For example, a landmark neuroimaging study with data from 1000 participants utilized functional connectivity to reveal five striatal zones linked to sensorimotor, premotor, limbic, and two association networks (Choi et al. 2012)—thus providing an *in vivo* characterization of careful tract-tracing studies performed in monkeys (Haber 2003). Recent neuroimaging work has added to these observations by quantifying how distinct cortical regions (e.g., orbitofrontal, dorsolateral, and parietal cortices) converge on similar parts of the striatum (Jarbo and Verstynen 2015), supporting the hub-like organization of striatal anatomical projections (Averbeck et al. 2014). Although corticostriatal interactions are important for reward processing, the striatum also interacts with midbrain nuclei, namely the substantia nigra and ventral tegmental area (Haber and Knutson 2010). In accordance, a recent neuroimaging study developed a probabilistic atlas of the substantia nigra and ventral tegmental area, allowing the authors to identify distinct patterns of functional connectivity with the striatum and cortical regions (Murty et al. 2014). The functional connections with the striatum have been exploited in a host of other studies, with several groups reporting disrupted corticostriatal interactions in social anxiety disorder (Manning et al. 2015), adolescent depression and anhedonia (Gabbay et al. 2013), and major depression and positive affect (Heller et al. 2013). Together, these observations reveal the interconnected nature of the striatum and underscore the importance of examining functional connectivity with the striatum.

Yet, neurophysiologists have long recognized that functional connectivity suffers from critical limitations that preclude insight into neuronal coupling (Gerstein and Perkel 1969). Correlations between regions and variations in those correlations may be

epiphenomenal, stemming from factors that are unrelated to neuronal coupling such as changes in another connection, observational noise, or neuronal fluctuations (Friston 2011). To ameliorate these issues, neuroscientists have developed computational approaches that estimate effective connectivity (Friston 2011; Friston et al. 1997; Valdes-Sosa et al. 2011), which has revealed key insights into how interactions with the striatum shape reward processing. Unlike functional connectivity, studies using effective connectivity quantify how one region contributes to the observed signal within another region according to a specific psychological context. These studies have broadened our understanding of how the striatum and its interconnected regions shape reward processing. For example, Kahnt and colleagues (2009) reported that, when participants computed reward prediction errors, dorsal striatum and ventral striatum were connected to the substantia nigra and ventral tegmental area, respectively. Strikingly, the contribution of dorsal striatum to the observed signal within substantia nigra predicted the impact of different reinforcement types on subsequent behavior (Kahnt et al. 2009).

Other work using effective connectivity has revealed the interplay between different neural structures and striatal systems during reward processing. For instance, some studies have demonstrated that stimulus generalization during learning is mediated by striatal contributions to the hippocampal response (Kahnt et al. 2012; Wimmer et al. 2012). Studies using effective connectivity have also shown that hippocampal contributions to striatal responses play a role in value-based decision making (Wimmer and Shohamy 2012) and episodic memory encoding (Wimmer et al. 2014). Recent work has built on these observations by revealing how acute stress exacerbates ventromedial prefrontal contributions to the striatum (Maier et al. 2015) and striatal contributions to the amygdala (Admon et al. 2015). Although these studies highlight key patterns of effective connectivity with the striatum, we emphasize that these relationships should not be interpreted as causal; such inferences are difficult within fMRI (Ramsey et al. 2010) and likely require causal modeling approaches (Friston et al. 2003) combined with faster imaging protocols (Feinberg et al. 2010).

These studies underscore the importance of using fMRI to investigate brain connectivity and functional integration—concepts that are central to our understanding of how the striatum contributes to reward processing. We believe that future work has the

potential to integrate effective and functional connectivity with structural connectivity. Indeed, structural connectivity with the striatum predicts personality characteristics (Cohen et al. 2009), such as recent observations of dissociable fiber tracts leading to the striatum being associated with individual differences in temporal discounting (van den Bos et al. 2014). These findings raise important new questions regarding the convergence and divergence of various forms of brain connectivity (Adachi et al. 2012; Honey et al. 2010). Answering these questions will further elucidate the role of the striatum as part of a larger and dynamic reward circuit.

Multimodal Approach Using fMRI

When used in isolation, fMRI—like all measurement techniques (e.g., single-unit recordings)—are inherently correlational and descriptive (Rorden and Karnath 2004; Smith and Clithero 2009). This limitation can be partially overcome with the application of multimodal approaches—combining cellular-based techniques (e.g., neurophysiological recordings) and neurotransmitter-based techniques (e.g., PET) with fMRI—to inform on the neural basis of fMRI-measured brain activity. The integration across modalities is gaining traction in the study of reward processing in particular. For example, researchers have been relating fMRI findings to PET results in both meta-analysis and empirical studies to investigate how striatal BOLD signal is associated with dopamine release during reward-related behavior (Heinz et al. 2014; Judenhofer et al. 2008; Schott et al. 2008), thereby informing the underlying neuronal basis of the hemodynamic response. Efforts have also been expended to combine neurophysiological methods with fMRI in an attempt to link neural hemodynamic responses (fMRI) with the brain's canonical electrophysiological responses (Bland et al. 2011; Lee 2012). For example, simultaneous application of electroencephalography and fMRI demonstrated that the event-related potential signal correlated with the BOLD signals in the ventral striatum during the delivery of rewarding outcomes (Carlson et al. 2014; Carlson et al. 2011; Foti et al. 2014), suggesting a convergence of neurophysiological and hemodynamic signals. In addition, one recent study successfully applied optogenetics with fMRI in an animal model to characterize how stimulation of the VTA produced activation in the ventral striatum that shaped reward-related behavior (Ferenczi et al. 2016), providing further insights to understand the

discrepancies (e.g., temporal resolution and cellular basis) between hemodynamic and neurophysiological measures. Collectively, studies integrating fMRI with other tools not only endows us with a deeper cellular-level understanding of the hemodynamic signal in fMRI (Goense and Logothetis 2008; Hayden and Platt 2011; Heeger and Ress 2002; Logothetis et al. 2001), but they also attribute fMRI findings in reward processing with potential cellular explanations.

Translational models of reward processing will ultimately require multimodal approaches that complement the strengths of fMRI, without compromising any of its inherent advantages (e.g., widespread noninvasive application in the human population). Such multimodal approaches call for the inclusion of noninvasive brain stimulation tools (e.g., transcranial magnetic stimulation [TMS], transcranial electrical stimulation [tES]) to task-based fMRI investigations (Poldrack and Farah 2015). This conjunction permits the transient manipulation of neural activity during task conditions to allow researchers to causally link brain stimulation to fMRI-measured neural alterations and resulting behavioral changes (Driver et al. 2009). The concurrent use of TMS and tES with fMRI has received recent attention in the cognitive neuroscience community (Antal et al. 2011; Blankenburg et al. 2008; Jang et al. 2009; Rushworth et al. 2002; Sack et al. 2007). Specifically, one recent study have successfully implemented transcranial alternating current stimulation (tACS), a form of temporally-precise tES (Helfrich et al. 2014), to demonstrate that intact frontal-parietal connectivity is necessary for value-based decision making in humans (Polanía et al. 2015). Despite the relative success of such TMS/tES-induced neural stimulation, there are pre-existing hurdles left to overcome such as the regional specificity of stimulation (Paulus 2011; Walsh and Cowey 2000). Nevertheless, the co-application of TMS/tES and fMRI is promising because it provides a means to causally link context-dependent neural activity with behavior (Camprodon and Halko 2014; Saiote et al. 2013).

Extending these multimodal approaches to study reward processing in humans remains challenging. For example, noninvasive brain stimulation approaches (e.g., tES) cannot directly (or selectively) access deep-brain structures like the striatum (Wagner et al. 2007). In contrast, invasive brain stimulation techniques (e.g., deep brain stimulation) that can access the striatum are often too invasive to be extensively applied in human

participants. Therefore, one potential remedy that noninvasive multimodal studies in humans can exploit is to capitalize on the functional integration in the reward circuit to target the striatum and other deep-brain structures indirectly via their cortical connections. Application of tES to the prefrontal cortex, for example, alters connectivity with reward regions such as ventral tegmental area (Chib et al. 2013) and striatum (Polanía et al. 2012). Similar work have also demonstrated that tES administered to prefrontal areas including dorsolateral prefrontal cortex implicates reward-related behaviors such as risk-taking (Sela et al. 2012), probabilistic learning (Turi et al. 2015), and social perception of unfair rewards (Knoch et al. 2008). The next step for these tES studies is to employ fMRI simultaneously with cortical brain stimulation to assess the responses of the striatum and other neural regions, so as to inform on the functional integration in the reward circuit. These types of multimodal studies will provide an exciting opportunity to expand our knowledge on reward processing within the human brain, potentially providing the gateway to developing brain-stimulation-based therapeutic interventions for a host of psychopathologies.

Conclusions, Limitations, and Future Considerations

With the widespread application of fMRI, influential non-human animal findings on the role of the striatum in reward processing have been successfully corroborated in both healthy and patient human populations. Many fMRI studies have also broadened the understanding of reward processing in the striatum to human attributes such as distinctly human incentives (e.g., money) and social and environmental contexts more representative of human society. As fMRI matures into a powerful cognitive neuroscience tool, increased effort has been expended to use fMRI to investigate individual differences in neural functions, which can potentially explain the link between behavioral variability and susceptibility to psychopathologies. Moreover, greater emphasis on brain connectivity and functional integration may help refine existing neural models of reward processing. Brain connectivity findings could potentially be combined with noninvasive brain stimulation to draw causal inferences regarding the mechanistic links between corticostriatal pathways and reward. Collectively, these advancements in applying fMRI (Fig. 4) promise

561 translational opportunities that can inform on the diagnostic and therapeutic insights of
562 many psychopathologies.
563 Nevertheless, there are limitations on what fMRI can accomplish for translational
564 research. One notable limitation is that individual differences studies require a larger
565 sample than those typically recruited for fMRI experiments (Button et al. 2013; Yarkoni et
566 al. 2011). Further, variables within these large samples may interact (e.g., age and race).
567 The development of a population-based atlas can help mitigate this concern as it aims to
568 capture inter-individual variability and map functional cortical organization that can be
569 broadly applied in individuals across different groups (Wang et al. 2015a). Such continued
570 future efforts to maximize the exploration of individual differences will play an important
571 role in explaining behavioral variability that inform clinical preventive and diagnostic
572 applications (Poldrack and Farah 2015).
573 Another potential source of limitation of applying fMRI to translational research is
574 the difficulty of some fMRI-based functional integration analysis in drawing causal
575 inferences on neural connectivity. Without the capability to demonstrate directionality in
576 neural connectivity, it is challenging to develop effective target-specific treatment and
577 preventive measures. This barrier has been partially overcome with dynamic causal
578 modeling, which was shown to be reliable in making causal interpretations (Smith et al.
579 2011). Yet another shortcoming in the current fMRI literature is the flexibility in data
580 analysis procedures, with preprocessing and analytical options rivaling the number of fMRI
581 studies (Carp 2012). The practice of standardizing experimental reporting guidelines in
582 journal publications is gaining traction in the field (Poldrack et al. 2008), which will yield
583 greater transparency in both experimental design and analytic approaches as well as
584 improve the reproducibility of fMRI findings (Poldrack and Poline 2015).
585 Despite these limitations, fMRI has generated some interesting directions that will
586 help shape future research on cognitive and affective processes such as reward processing.
587 First, fMRI studies have began to explore the neural basis of many psychological constructs
588 that are inherent to the human reward processing mechanism. For example, the loss of
589 voluntary control in decision making (Haggard 2008), which is pertinent to many
590 maladaptive reward approach and consummatory behaviors (Bechara 2005; Volkow et al.
591 2011), has been studied with presence and absence of choices (Ernst et al. 2004; Leotti and

Delgado 2011), habitual reward-based learning (Tricomi et al. 2009), controllable and uncontrollable setbacks to goal-directed reward-seeking behavior (Bhanji and Delgado 2014), and compulsive reward-seeking and reward-taking behavior in addiction (e.g., food: Gearhardt et al. 2011; cocaine: Tomasi et al. 2015). Future studies will benefit from examining whether individual differences in behavioral variability (e.g., impulsivity) is predictive of the loss of voluntary control and how the neural connectivity is altered during these maladaptive decision making using fMRI-centric multimodal approaches. Further, future studies can also take advantage of brain connectivity to clarify and augment knowledge about how neural circuits, beyond a particular region of interest (ROI), may contribute to a psychological process. For instance, recent work has leveraged brain connectivity to distinguish representations tied to distinct properties of reward, particularly those related to affect (e.g., pleasure) and those related to information (e.g., reinforcement) to show that these properties are not distinguishable at the ROI level, but instead can emerge as a function of connectivity between corticostriatal circuits (Smith et al. In Press).

Second, the application of computational models to fMRI, such as those that gave rise to model-free and model-based learning mechanisms, have opened the door for new translational opportunities (Montague et al. 2012; Stephan et al. 2015; Wang and Krystal 2014). These new opportunities will revolve around using neural computational mechanisms to predict behavior and understand its adaptive consequences, which could have both diagnostic and prognostic values. Perhaps more importantly, the successful application of computational models may serve to bridge findings from diverse techniques while connecting animal models with human data (Bornkessel-Schlesewsky et al. 2015; Kepecs and Mainen 2012).

Third, improvements in fMRI acquisition (e.g., three-dimensional or multiplex EPI: Feinberg et al. 2010; finer-resolution fMRI: Yacoub et al. 2015) may help elucidate functional segregation within the striatum such as dissociating the functional role of NAcc core and shell in the human brain, which is currently not well-characterized in humans (Baliki et al. 2013). At present, there remains some technical obstacles to overcome for the acquisition of excellent subcortical signals such as those within striatal subregions (Kaza et al. 2011; Polanía et al. 2015). Nevertheless, the progress in refining fMRI technical

capabilities will greatly enhance the capacity to use fMRI to study functional dissociation within smaller human subcortical subregions (e.g., striatum) while also improve the ability to detect BOLD activation (Iranpour et al. 2015; Posse et al. 2012).

Although some scholars have questioned the utility of using neuroimaging to understand behavioral phenomena (Gul and Pesendorfer 2008), we contend that knowledge gained from neuroimaging studies can contribute to behavioral theories and potentially even impact policy (Clithero et al. 2008; Levallois et al. 2012; Venkatraman 2013). This approach has been observed in some reward-related studies. For example, neural estimates of reward have been used to optimize public goods allocation and solve the pernicious problem of free riders (Krajbich et al. 2009), while a novel theory of overbidding during auctions—e.g., loss contemplation, rather than risk aversion—was developed and tested based on reward-related responses observed in the striatum (Delgado et al. 2008). More recent studies have used neural data to access individual preferences in the absence of choices (Smith et al. 2014a) and to adjudicate between disparate theories of investor behavior (Frydman et al. 2014). These are just some examples that illustrate how neuroimaging can inform our understanding of behavior and policy.

Together, these new research avenues congregate on the fundamental notion that fMRI is a crucial and promising tool to study cognitive and affective processing in humans. Advancements in the study of these processes hinge on profiting from the advantages of fMRI while simultaneously implementing complementary tools, such as brain stimulation, to make causal inferences on neural functions and circuitry connectivity. This multimodal approach will endow us with a deeper and more comprehensive understanding of mechanistic underpinnings to these cognitive and affective processes and also provide the translational basis for both therapeutic and preventive healthcare measures.

Figure Captions

Figure 1: Proliferation of fMRI Studies in Reward Processing

The use of fMRI to study reward processing has been increasingly popular over the past 20 years. During this time, the number of publications on fMRI and reward has increased quasi-exponentially. We note that the shown data were extracted from pubmed.gov on March 27th, 2015 using the search term "(fMRI OR functional magnetic resonance imaging) AND reward".

Figure 2: Gains and Losses Modulate Activation in the Striatum

A) A popular approach to studying reward processing employs a card guessing task. In this paradigm, subjects are presented with a card and asked to guess whether the number on the card (range: 1-9) will be higher or lower than 5. If the subject guesses correctly, s/he wins money. However, if the subject guesses incorrectly, s/he loses money. B) Contrasting positive outcomes or win trials against negative outcomes or loss trials reveals activation within the striatum. Here we focus on the nucleus accumbens (NAcc). C) Within the NAcc, the responses to wins (depicted with parameter estimates) are higher than the responses to losses. Figure used data from Fareri et al. (2012).

Figure 3: Reward Processing and the Striatum

A) A large-scale meta-analysis of 506 neuroimaging studies indicates a selective association between the term "reward" and striatal activation (Yarkoni et al. 2011). These observations help illustrate the reliability of neuroimaging evidence in demonstrating the involvement of the striatum in reward processing. B) Anatomical subdivisions of the striatum in the human brain. These subdivisions include the putamen (blue), nucleus accumbens (NAcc; green), and caudate (red).

Figure 4: The Promise of fMRI in Understanding Reward Processing

Shown here is an anterior view of a translucent cortical surface for the right hemisphere. Bilateral striatal surfaces are shown for the putamen (blue), nucleus accumbens (green), and caudate (red). Our synthesis of the literature suggests that fMRI holds promise for

679 understanding individual differences and brain connectivity. In addition, multimodal
680 approaches that combine fMRI with other tools such as noninvasive brain stimulation may
681 reveal causal mechanisms that support reward processing. Brain surfaces were created
682 with Chris Rorden's Surf Ice software.

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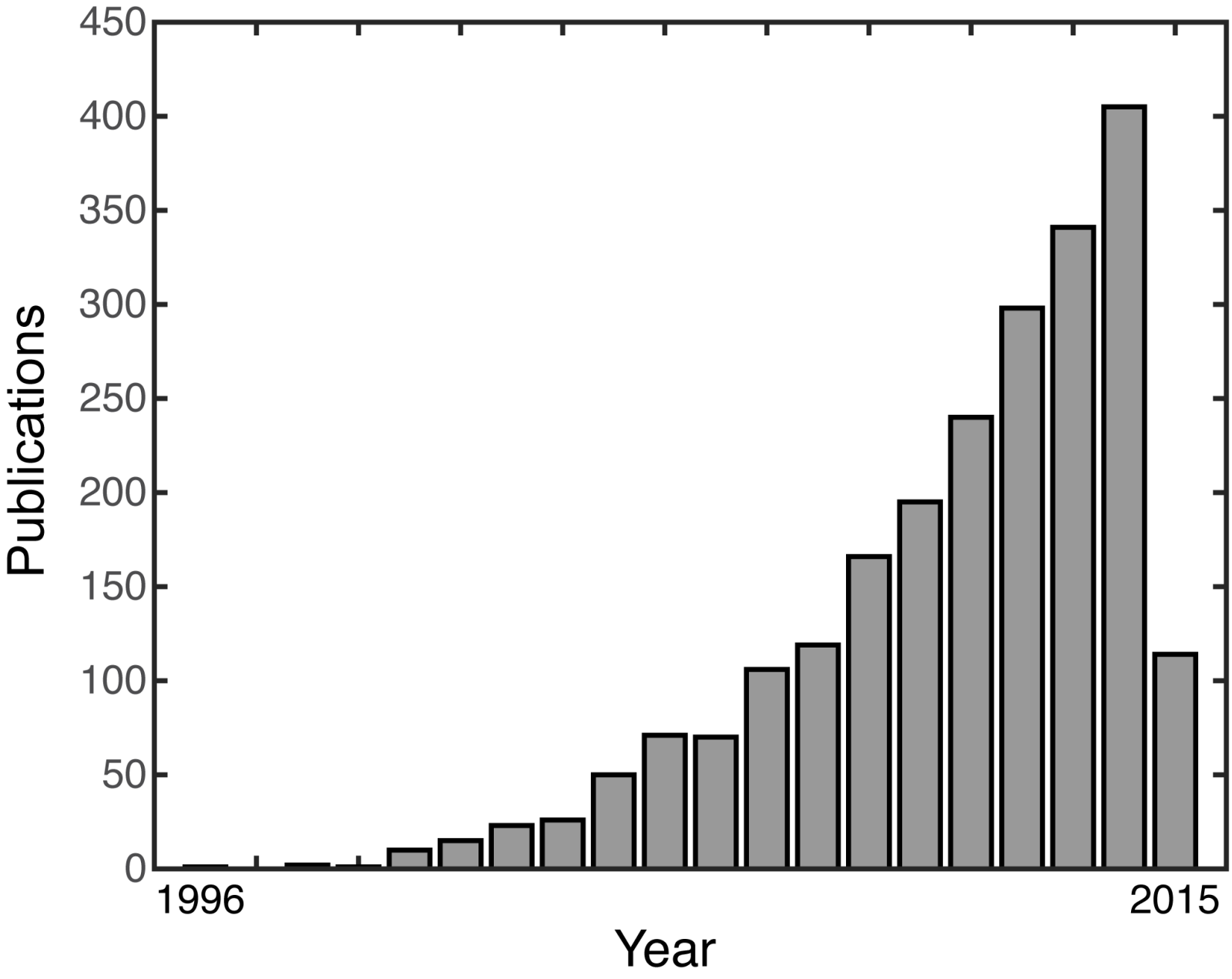
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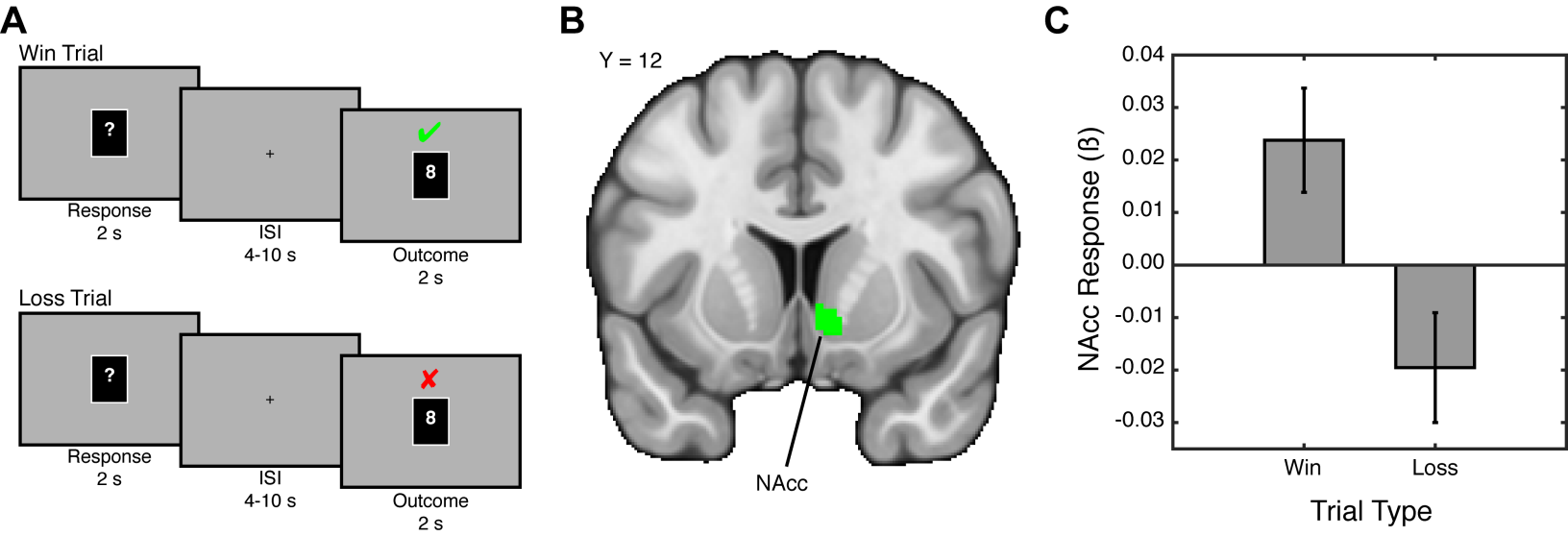
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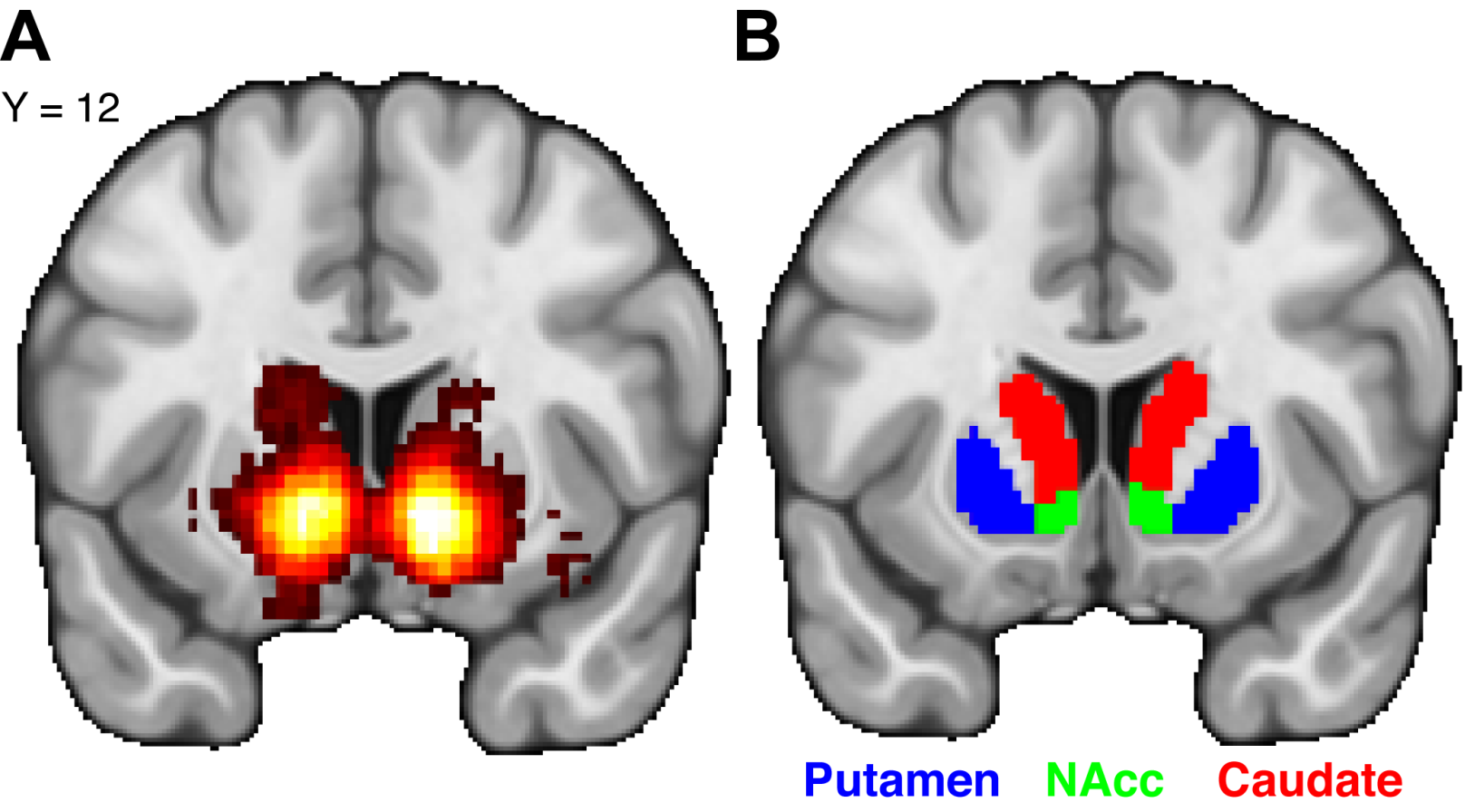
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Individual Differences

Relate reward-related responses to variation across individuals

Brain Connectivity

Characterize how brain regions interact to shape reward processing

Multimodal Approaches

Integrate fMRI with other approaches, such as noninvasive brain stimulation