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Contributions of the putamen to cognitive function

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ABSTRACT

It is now well accepted that the basal ganglia contribute to cognition. Much of the cognitive functionality of the basal ganglia has been attributed to the striatum in general, and the caudate nucleus and nucleus accumbens in particular. The putamen, however, has inherited the motor functionality classically ascribed to the basal ganglia. Although there is no doubt that the putamen plays a critical role in motor execution and motor learning, recent data suggest a role for the putamen in learning and memory that is not directly tied to motor functioning. These data suggest that the putamen, much like the caudate and accumbens, is actively involved in a variety of cognitive functions such as episodic memory, cognitive control, and category learning. In this chapter, we review anatomical, electrophysiological, lesion, and imaging data supporting the putamen's role in cognition.

INTRODUCTION

For decades, the basal ganglia (BG) were synonymous with motor function. There is now widespread recognition that the BG are also critical for a variety of cognitive functions. The vast majority of this cognitive functionality has been attributed to the striatum in general, and the nucleus accumbens and caudate nucleus in particular. The remaining striatal nucleus, the putamen, has inherited the label of motor structure that was historically assigned to the BG in its entirety. There is a growing body of evidence, however, implicating a role for the putamen in cognition.

There is overwhelming evidence supporting the role of the putamen in a variety of movement-related functions. The putamen is critical for actual (e.g., DeLong & Georgopoulos, 1981) and imagined (Guillot et al., 2008; Lorey et al., 2011; Wagner et al., 2008) body movement. In fact, the putamen is even responsive to the illusion of movement (Kovacs, Raabe, & Greenlee, 2008). It is abundantly clear, however, that the putamen is involved in more than just the organization and/or execution of movements. For instance, putamen neurons are sensitive to the behavioral context in which movements are made (Kimura, 1986). Right putamen lesions have been associated with unilateral neglect (Karnath, Himmelbach, & Rorden, 2002). The putamen has also been associated with a variety of basic cognitive processes across the lifespan (Aizenstein et al., 2006; Rubia et al., 2006). The activity of the putamen in neuroimaging experiments has even been shown to be correlated with such high-level cognitive functions as learning the meaning of novel nouns (Mestres-Misse, Rodriguez-Fornells, & Munte, 2010) and resolving ambiguity in word meaning (Ketteler, Kastrau, Vohn, & Huber, 2008).

In this chapter, we review converging evidence that implicates the putamen in cognition. We begin with a brief overview of the functional anatomy underlying the putamen's role in cognition. The studies of functional anatomy converge in suggesting that the rostral putamen mediates cognitive function whereas the caudal putamen contributes to sensorimotor function. We then review evidence highlighting the wide array of cognitive processes to which the putamen makes a contribution. In particular, we focus on the putamen's contribution to stimulus-response-outcome learning, working memory, episodic memory, cognitive control, and category learning. A synthesis of these data in which we map function to structure along the rostrocaudal extent of the putamen challenges the strict rostrocaudal division suggested by the analysis of functional anatomy.

Finally, we discuss the contribution of the putamen to cognition at the systems level by virtue of its position in local BG networks and cortico-BG-cortical networks.

Functional Anatomy

Corticostriatal Input

Virtually all of the neocortex sends excitatory (glutamatergic) projections to the striatum (i.e., caudate nucleus, nucleus accumbens, and putamen) (Reiner, 2010). Corticostriatal input is massively convergent with estimates ranging from 5,000 to 10,000 cortical neurons converging on a single striatal medium-spiny neuron (Bolam et al., 2006; Kincaid, Zheng, & Wilson, 1998; Wilson, 1995). A slightly more controversial factor is the extent to which individual corticostriatal projections diverge. Any given corticostriatal neuron synapses within the dendritic field of multiple medium-spiny neurons. The degree of divergence, however, is thought to be extremely small relative to the degree of corticostriatal convergence with each corticostriatal neuron innervating approximately 100 medium-spiny neurons (Wickens & Arbuthnott, 2010). Given that medium-spiny neurons require the widespread activation of many of their cortical afferents in order to generate action potentials, several prominent researchers have gone so far as to argue that the cortical input of each medium-spiny neuron is unique (Gerfen & Bolam, 2010; Wickens & Arbuthnott, 2010; Wilson, 2000; Zheng & Wilson, 2002). Further research on the convergence and divergence of corticostriatal input will be critical for elucidating the cognitive functionality of the striatum in general, and the putamen in particular.

Classically, corticostriatal organization was thought to follow a fairly strict spatial topography (Kemp & Powell, 1970) and this pattern is observed at the level of individual striatal nuclei. Indeed, along the rostrocaudal extent of the putamen, the cortical afferents tend to be more prevalent from rostral to caudal cortical regions (Figure 1). For instance, rostral and ventral putamen receives input predominantly from orbitofrontal cortex, ventromedial prefrontal cortex, and anterior cingulate cortex. As one moves caudally and dorsally within the putamen, input from frontal areas 9, 46, and 8 becomes more prevalent (Calzavara, Mailly, & Haber, 2007; Haber, Kim, Mailly, & Calzavara, 2006; Selemon & Goldman-Rakic, 1985) followed by input from premotor regions with the most caudal motor and somatosensory cortical regions projecting preferentially to the caudal putamen (Alexander & DeLong, 1985; Flaherty & Graybiel, 1994; Nambu, Kaneda, Tokuno, & Takada, 2002).

Spatial topography holds as you continue caudally and ventrally in the putamen, with inputs coming from the parietal and temporal cortices as well as other extrastriate visual areas (Kemp & Powell, 1970; Selemon & Goldman-Rakic, 1985; Van Hoesen, Yeterian, & Lavizzo-Mourey, 1981; Webster, Bachevalier, & Ungerleider, 1993; Yeterian & Pandya, 1993, 1995, 1998; Yeterian & Van Hoesen, 1978).

An alternative view is that corticostriatal projections are both topographically and functionally organized (Parent & Hazrati, 1995; Selemon & Goldman-Rakic, 1985, 1988; Yeterian & Van Hoesen, 1978). In this view, non-topographic regions of cortex converge upon similar regions of the striatum. More recent revisions of this framework have emphasized the fact that functional domains are not isolated to particular striatal nuclei, but rather span striatal nuclei (Groenewegen & Uylings, 2010; Haber, 2010; Parent & Hazrati, 1995). For example, rostral portions of both the caudate and putamen receive dense input from a variety of prefrontal cortical regions, anterior cingulate cortex, and orbitofrontal cortex (Calzavara, et al., 2007; Haber, et al., 2006; Selemon & Goldman-Rakic, 1985, 1988).

As one moves caudally, both the caudate and putamen receive input from across parietal cortex (Yeterian & Pandya, 1993) and temporal cortex (Yeterian & Pandya, 1995, 1998) as well as pre-supplementary and supplementary motor areas (Lehericy et al., 2004; Selemon & Goldman-Rakic, 1988). Importantly, the functional view has received further support from recent studies in humans describing the functional connectivity of the striatum (Di Martino et al., 2008; Draganski et al., 2008;

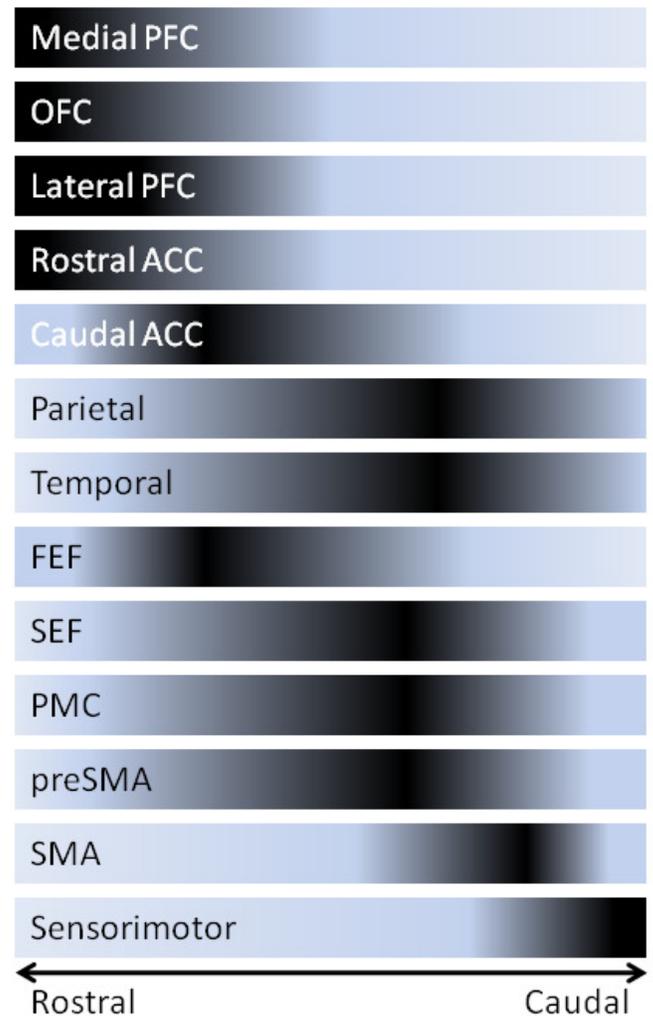


Figure 1. Relative density of selected cortical input along the rostrocaudal extent of the putamen. Lighter colors imply relatively sparse projections whereas darker colors imply relatively dense projections. PFC – prefrontal cortex, OFC – orbitofrontal cortex, ACC – anterior cingulate cortex, FEF – frontal eye fields, SEF – supplementary eye fields, PMC – premotor cortex, SMA – supplementary motor area.

Postuma & Dagher, 2006). For instance, a meta-analysis conducted by Postuma and Dagher (2006) revealed differences in functional connectivity between rostral and ventral putamen consistent with anatomical work from nonhuman primates.

Subcortical Input

The thalamus provides another major source of input to the striatum with some estimating that as much as 40% of medium-spiny input could be thalamic (Wilson, 2004). The majority of the thalamostriatal projections originate from the intralaminar nuclei, particularly the centromedian/parafascicular complex (Smith, Galvan, Raju, & Wichmann, 2010). There are, however, less prominent projections from non-intralaminar nuclei such as the motor related nuclei in the ventroanterior/ventrolateral complex, as well as the pulvinar and mediodorsal nuclei (Smith, Raju, Pare, & Sidibe, 2004). Thalamostriatal projections synapse on both medium-spiny neurons and a variety of striatal interneurons (Smith, et al., 2004). Most notable among the interneurons are the cholinergic tonically-active neurons due to the likely role of plasticity at these thalamostriatal synapses in learning and memory (Aosaki, Graybiel, & Kimura, 1994; Ashby & Crossley, 2011; Kimura, Rajkowski, & Evarts, 1984). In general, thalamostriatal input is in a position to modulate processing in all striatal nuclei by virtue of cortico-thalamo-striatal connections and striatal-thalamo-striatal feedback (Smith, et al., 2010).

Perhaps the most prominent subcortical input to the striatum originates in the dopaminergic neurons of the substantia nigra pars compacta. The so-called nigrostriatal dopaminergic system plays a critical role in learning and memory by representing reward-related information (Schultz, 1998) and providing a substrate for striatal plasticity (e.g., Wickens, 1993). In addition, the striatum also receive input from the globus pallidus (Voorn, 2010) and modulatory input from the serotonergic neurons of the dorsal raphe nucleus and from the noradrenergic neurons of the locus coeruleus (Emson, Waldvogel, & Faull, 2010).

Corticostriatal loops

Medium spiny neurons in the striatum project directly (or indirectly) to the basal ganglia output nuclei (internal segment of the globus pallidus and substantia nigra pars reticulata) with projections from the BG output nuclei targeting cortex (via the thalamus). Some of the output to cortex returns to the source of corticostriatal input, thereby forming a number of closed loops (i.e., motor, oculomotor, prefrontal,

orbitofrontal, cingulate) (Alexander, DeLong, & Strick, 1986). Indeed, the idea that cortico-BG-cortical connections are organized according to functionally distinct parallel loops has been so dominant that we speculate that it is the classic assignment of the putamen to the motor loop within this framework that has led to a consistent bias to equate the putamen with motor function.

It is highly unlikely, however, that these loops are functionally independent as there are numerous points at which information could be integrated across loops (Haber, 2010). Striatal output can also target cortical regions other than the source of striatal input, thereby providing a powerful mechanism for integrating information from functionally distinct cortical regions. In light of the high likelihood for crosstalk between loops and functional views of corticostriatal input, several researchers have proposed revisions to the Alexander et al. (1986) model (e.g., Haber, 2003; Parent & Hazrati, 1995). These revisions generally suggest a smaller number of functionally defined loops that span the caudate and putamen (e.g., affective, cognitive, sensorimotor). The revised loops have received considerable support in monkeys (e.g., Calzavara, et al., 2007) and humans (Di Martino, et al., 2008; Draganski, et al., 2008; Postuma & Dagher, 2006). Anatomical data suggests that the putamen is involved in all loops, and as such, is in a position to participate in information processing within, and perhaps across, corticostriatal loops.

Cognitive functionality

In this section, we provide a selective review of the evidence supporting a role for the putamen in various aspects of cognition. We focus primarily on anatomical, electrophysiological, lesion, and neuroimaging studies in human and nonhuman primates as these methodological approaches address the issue of putamen involvement in cognition most directly. Such a focus necessarily excludes an extensive literature on striatal contributions to cognition in rodents where the caudate and putamen are not separate anatomical structures (e.g., Yin & Knowlton, 2006). Even the often cited homology between the rat dorsolateral striatum and the primate putamen is restrictive as the rat dorsolateral striatum is homologous to the portions of the primate putamen caudal to the anterior commissure (Joel & Weiner, 2000). Similarly, we do not draw on the extensive literature describing the impact of Parkinson's disease on cognition. Although many argue that early stage Parkinson's disease has the greatest impact on the putamen (Fernley & Lees, 1997; Nobili et al., 2010), the damage is still

quite diffuse and also affects brainstem structures and other neurotransmitter systems (Braak et al., 2003), as well as the intralaminar nuclei of the thalamus (Halliday, 2009). Moreover, even early stage Parkinson's disease patients demonstrate abnormalities in cortical processing (Monchi, Petrides, Mejia-Constrain, & Strafella, 2007) that would further limit any inferences about the contribution of the putamen to cognition.

The goal of this chapter is to highlight the contribution of the putamen to nonmotor aspects of cognition. As such, we do not discuss studies using paradigms where there is a significant motor learning component (e.g., sequence learning tasks). It should be noted, however, that even after excluding motor learning tasks it is often difficult, if not impossible, to rule out motor contributions given that most cognitive tasks require a motor response. Although one can gain some insight into nonmotor function if appropriate control conditions are included, it is quite challenging to control for all motor-related functioning. Of course, such limitations are also an issue when investigating the contributions of any brain region to nonmotor cognition (e.g., the caudate nucleus).

Finally, it is important to note that although we focus on the putamen in this chapter, the majority of the studies cited in this review focus on the caudate, striatum and/or BG. In order to make the length of this chapter manageable, we opted not to discuss the contribution of other BG nuclei in most cases. Thus, our interpretation of the results of these studies should not be taken to suggest that other BG nuclei were not associated with task performance unless stated otherwise.

The Learning of Stimulus-Response-Outcome Associations

The anatomy and physiology of the neostriatum is ideally suited for the learning of associations between stimuli, responses, and outcomes (e.g., Horvitz, 2009) with the putamen playing a critical role. For instance, a series of studies by Kimura and colleagues (Kimura, 1986, 1990; Kimura, et al., 1984) demonstrated a subpopulation of putamen neurons that respond to sensory stimuli, but only when the stimuli are predictive of learned movements, suggesting that the putamen contributes to a context-specific representation of stimulus-response associations. A subset of these sensory-related neurons, along with other classes of putamen neurons, demonstrate movement-related activity that reflects movement execution (DeLong & Georgopoulos, 1981) and/or context-specific movement preparation (Kimura, 1986). The movement itself does not appear necessary

to trigger putamen activation as some putamen neurons increase their firing rate when movement to non-rewarding stimuli must be inhibited (Romero, Bermudez, Vicente, Perez, & Gonzalez, 2008).

The putamen is not only involved in the representation of context-specific behaviors, but also their acquisition. Inactivation of the putamen using the GABA antagonist muscimol impairs the ability of monkeys to select actions that are contingent upon recent reward history (Muranishi et al., 2011). Neuroimaging, lesion, and electrophysiological data are consistent with the hypothesized role of the putamen in the integration of stimulus, response, and outcome with activity in rostral regions of the putamen being most predictive (Bellebaum, Koch, Schwarz, & Daum, 2008; Cromwell & Schultz, 2003; Haruno & Kawato, 2006; Yamada, Matsumoto, & Kimura, 2004). Again, however, the contribution of the putamen in learning does not appear to be exclusively dependent upon movement requirements as putamen activity is correlated with reward magnitude (Cromwell & Schultz, 2003) and errors in the prediction of reward timing (McClure, Berns, & Montague, 2003). Specifically, McClure et al. (2003) showed that putamen, but not caudate, activation increased in response to unexpected delivery of a juice reward and decreased in response to the unexpected withholding of a juice reward.

Although there is considerable debate about the relative contribution of cortical and subcortical structures to the development of habitual behavior (Ashby, Turner, & Horvitz, 2010) one popular perspective argues that the rat homologue of the putamen (caudal to the anterior commissure) represents habitual stimulus-response associations (Yin & Knowlton, 2006). Recent neuroimaging data suggests that this finding may extend to humans (Tricomi, Balleine, & O'Doherty, 2009). In an adaptation of methodology commonly utilized in animal studies of the development of habitual behavior, Tricomi et al. trained people to learn associations between stimuli (i.e., fractal images), response (self-paced button pushes), and a food reward (candy or chips delivered following a variable interval schedule). Consistent with the aforementioned studies, putamen (and globus pallidus as well as other cortical regions) activity was correlated with the acquisition of the stimulus-response-outcome association. More importantly, however, caudal putamen activity was correlated with task performance after the reward was devalued (i.e., by asking participants to eat the food reward until it was no longer pleasant), implicating the caudal putamen in the development of habitual behavior in humans.

The extant data suggest that the putamen is important for the learning of associations between stimuli,

responses, and outcomes. Although the information represented by the putamen is critical for the acquisition and representation of context-specific stimulus-response associations, the contribution of the putamen does not appear to be restricted to movement-related representations per se. Instead, the putamen also represents non-movement related signals (e.g., reward expectation) that would be expected to be critical for the flexible acquisition of novel behavior. The dynamics of stimulus-response-outcome learning are not well understood, but it likely involves ongoing interaction between the putamen and other BG nuclei (e.g., Brovelli, Nazarian, Meunier, & Boussaoud, 2011) as well as cortico-subcortical interactions (e.g., Ashby, Ennis, & Spiering, 2007).

Working Memory

Working memory (i.e., the online maintenance and manipulation of information) was once thought to be mediated primarily by neurons in prefrontal cortex. Although it is clear that prefrontal cortex makes a significant contribution to working memory (D'Esposito, Postle, & Rypma, 2000; Fuster, 2008; Goldman-Rakic, 1995; Muller & Knight, 2006), it is also clear that working memory is distributed across many neural regions with several BG nuclei playing a critical role (Ashby, Ell, Valentin, & Casale, 2005; Durstewitz, 1999; Frank, Loughry, & O'Reilly, 2001; Monchi, Taylor, & Dagher, 2000). Most models emphasize the caudate nucleus, but neuroimaging studies suggest that the rostral putamen contributes to stimulus encoding and maintenance (Cairo, Liddle, Woodward, & Ngan, 2004) with putamen activity increasing in a load-dependent manner (Chang, Crottaz-Herbette, & Menon, 2007).

Studies testing individuals with putamen lesions due to stroke also implicate the putamen in working memory maintenance (Shu et al., 2009; Voytek & Knight, 2010). The results of Voytek and Knight (2010) are particularly important as they compared patients with BG (primarily putamen) lesions and patients with prefrontal lesions. Although both patient groups demonstrated impairment, behavioral and electroencephalography (EEG) data suggested different contributions of the putamen and prefrontal cortex. Patients with putamen lesions were generally impaired throughout the task and had a normal top-down-attention-related EEG signal. Patients with prefrontal lesions, in contrast, were impaired only for stimuli presented to the contralesional visual hemifield and had an attenuated top-down attention-related EEG signal. Importantly, these data are consistent with the hypothesis that the contribution of the putamen to working

memory is not simply a byproduct of prefrontal contributions.

Working memory not only requires the maintenance of relevant information, but also the ability to ignore irrelevant information. In neurologically healthy individuals, the left putamen is more strongly activated when there is also information to ignore (McNab & Klingberg, 2008). Data from stroke patients with BG lesions reveal a similar result (Baier et al., 2010). In one condition of the Baier et al. study, patients were briefly presented with a circular array of spatial positions containing red circles, yellow circles, or nothing. After a 2 s delay, one of the locations was cued and patients had to respond yes if it corresponded to the position of a red circle and no otherwise. Thus, patients had to remember the positions of the red circles without confusing relevant (i.e., red circles) and irrelevant (i.e., yellow circles, empty positions) information. Fairly caudal regions of left putamen were strongly associated with the ability to ignore irrelevant information in this condition (as compared to a control condition with no irrelevant information). Interestingly, the right inferior frontal gyrus was associated with working memory capacity providing further support for differential contributions of prefrontal cortex and the putamen to working memory.

Studies combining the neuroimaging and neuropharmacological methods suggest that the contribution of the putamen to working memory may be related to dopaminergic function. For instance, individuals with low working memory span have been shown to have lower baseline dopamine levels in left putamen than individuals with high working memory span, with individual differences in span being positively (but not significantly) correlated with baseline dopamine levels (Cools, Gibbs, Miyakawa, Jagust, & D'Esposito, 2008). In addition, the D2 antagonist sulpiride predicted manipulation-related activity in bilateral putamen in a dose dependent manner such that higher plasma levels (presumably reflecting higher antagonism of D2 receptors) were associated with lower manipulation-related activity (Dodds et al., 2009). These studies are consistent in suggesting that increased dopaminergic activity in the putamen may improve working memory function.

Episodic Memory

Much of the research on episodic memory has focused on interactions between cortex and hippocampus (e.g., Paller & Wagner, 2002), but more recent research has revealed that the striatum may interact with the hippocampus during episodic memory formation (e.g., Shohamy & Wagner, 2008). The putamen appears to

make a contribution to episodic memory performance. For instance, the left putamen has been consistently implicated in the encoding of verbal episodic memories (Prince, Daselaar, & Cabeza, 2005; Sadeh, Shohamy, Levy, Reggev, & Maril, in press; Sperling et al., 2003; Ystad, Eichele, Lundervold, & Lundervold, 2010).

Studies of episodic memory are particularly interesting because they provide some of the strongest data implicating the putamen in nonmotor cognition as several studies have demonstrated that putamen activity during encoding predicts subsequent retrieval success. For example, left putamen activity during the encoding of face-name pairs is predictive of successful recognition (Sperling, et al., 2003). Similarly, Sadeh et al. (in press) observed bilateral putamen activity during the incidental encoding of self-generated words that was predictive of successful recognition performance and that the putamen activity was positively associated with hippocampal activity suggesting a cooperative interaction between these subcortical nuclei. The left putamen has even been shown to be more active for semantic (i.e., associations between same or different word pairs) than perceptual (i.e., associations between same word pairs printed in same or different fonts) episodic memory tasks (Prince, et al., 2005)

As is the case with most cognitive tasks, no single structure mediates task performance. Indeed, Sadeh et al. (in press) suggest that the putamen interacts cooperatively with the hippocampus during episodic memory encoding. Recent data from Ystad and colleagues (2010) suggest that the putamen contributes to episodic memory as part of a thalamostriatal network (i.e., the rostrocaudal extent of the superior putamen, the head of the caudate nucleus, and the mediodorsal nucleus of the thalamus). Based on an analysis of resting state functional connectivity, Ystad et al. (2010) found that greater functional connectivity in this thalamostriatal network was associated with worse episodic memory performance. Although a negative correlation between memory performance and connectivity may seem counterintuitive, it is consistent with recent work suggesting that desynchronization may be more optimal for network level function (e.g., Bergman et al., 2010; Nunez & Srinivasan, 2006).

Cognitive Control

Cognitive control is a multifaceted construct that generally "... refers to the ability to perform task-relevant processing in the face of other distractions or other forms of interference, in the absence of strong

environmental support” (p. 257, O'Reilly, Herd, & Pauli, 2010). Research on cognitive control processes has historically focused on the prefrontal cortex (e.g., Badre & Wagner, 2007), but it is becoming increasingly clear that interactions between prefrontal cortex and the striatum are critical (e.g., Frank & Badre, 2011). Consistent with this claim, patients with combined caudate and putamen lesions are impaired on a variety of tasks tapping into cognitive control processes (Keri et al., 2002; Pickett, Kuniholm, Protopapas, Friedman, & Lieberman, 1998). Functional connectivity analyses suggest that the entire rostrocaudal extent of the inferior putamen participates in a number of networks (putamen-mediadorsal nucleus of the thalamus, putamen-superior parietal cortex) that mediate cognitive control processes (Ystad et al., 2011). Moreover, dopaminergic tone in the putamen may mediate the putamen's contribution to cognitive control given research demonstrating an association between fluoro-l-dopa uptake in the putamen and measures of cognitive control in individuals with Parkinson's disease (van Beilen & Leenders, 2006).

One of the hallmarks of cognitive control is the ability to flexibly update strategic processes in response to changing task demands. This ability has most commonly been studied using set-shifting paradigms in which participants must modify their decision strategy in response to the stimulus and/or feedback (Downes et al., 1989; Monsell, 2003). Neuroimaging data indicate that putamen activity increases on trials requiring a set shift (as compared to non-shift, control trials) (Rubia, et al., 2006). Such shift-related activity in the putamen may reflect strategic response updating as putamen activity increases when participants are required to select a response according to a new strategy as compared to selecting a response according to the current strategy (Monchi, Petrides, Petre, Worsley, & Dagher, 2001; Monchi, Petrides, Strafella, Worsley, & Doyon, 2006). Related studies investigating the necessity of the BG for the ability to reverse one's decision strategy have also implicated the putamen in performing stimulus-response (Bellebaum, et al., 2008) and stimulus-reward reversals (Cools, Ivry, & D'Esposito, 2006).

There is even some evidence to suggest that putamen lesions impair the ability to use task relevant information to guide behavior. Boyd and Winstein (2006; 2004) investigated the impact of providing explicit information on sequence learning. Explicit information improved the sequence learning performance of neurologically healthy participants whereas explicit information impaired the sequence learning performance of

individuals with putamen lesions. Taken together, these studies suggest that the putamen may be critical for cognitive control processes related to the top-down guidance of behavior.

Category Learning

Category learning is the process of establishing a memory trace that improves the efficiency of assigning novel objects to contrasting groups. While it is clear that the caudate nucleus is involved in category learning (Seger & Miller, 2010), only recently has there been data suggesting that the putamen is also involved. Single-cell recording data suggests that the putamen represents categorical information during (Williams & Eskandar, 2006) and after training (Merchant, Zainos, Hernandez, Salinas, & Romo, 1997). Moreover, neuroimaging data implicate the putamen in a variety of category learning tasks (Badre, Kayser, & D'Esposito, 2010; Cincotta & Seger, 2007; Seger & Cincotta, 2002; Waldschmidt & Ashby, in press), confidence ratings regarding categorization decisions (Seger, Dennison, Lopez-Paniagua, Peterson, & Roark, 2011), and even responses to cues that are predictive of the upcoming presentation of categorical information (Forstmann, Brown, Dutilh, Neumann, & Wagenmakers, 2010).

There is an immense literature, and considerable debate, on the cognitive processes underlying category learning. One of the more compelling ideas in the categorization literature is that the cognitive and neural substrates of category learning vary as a function of the particular categorization task (Ashby & Ell, 2001; Ashby & Maddox, 2005; Keri, 2003). Indeed, the idea that multiple systems mediate behavior is not new and its application in category learning is partly an extension of the large body of research supporting multiple memory systems (e.g., Cohen, Poldrack, & Eichenbaum, 1997; Squire, Knowlton, & Musen, 1993).

Although the multiple systems framework has proven to be quite successful for understanding the cognitive neuroscience of category learning in general, it is not currently detailed enough to provide an adequate account of the role of the putamen in category learning. For instance, multiple systems theories have traditionally focused on the contribution of the caudate nucleus to category learning (Ashby, Alfonso-Reese, Turken, & Waldron, 1998). More recent models suggest that the posterior putamen is capable of mediating category learning (Ashby & Crossley, 2011; Ashby, et al., 2007). In addition, recent neuroimaging data suggest that the contribution of the putamen may vary as a function of the category learning system that is recruited

(Helie, Roeder, & Ashby, 2010; Waldschmidt & Ashby, in press).

Ell and colleagues (2006; 2010) found that putamen lesions impaired the learning of categories dependent upon rule-guided behavior. The impairment was restricted to categorization tasks in which optimal performance requires participants to combine logical rules from multiple stimulus dimensions (e.g., if the stimulus is high on dimension 1 and low on dimension 2 it is a member of category A). An analysis of individual participant categorization strategies revealed that the impairment was driven by an inability to consistently apply task-appropriate strategies. More specifically, patients in Ell et al. (2006) were impaired on a four-category task because they were making large, frequent shifts between suboptimal categorization strategies. Patients in Ell et al. (2010), however, were impaired on a two-category task because they preferred to base their decisions on a single stimulus dimension. The reason for this subtle difference in explanation between the two studies likely stems from the fact that one-dimensional strategies were fairly successful in Ell et al. (2010), but not Ell et al. (2006). Indeed, putamen lesion patients tested in a separate one-dimensional category learning task performed similar to matched control participants (Ell, et al., 2010).

Neuroimaging data from Helie and colleagues (2010) suggest that the putamen may play a different role in categorization automaticity. Helie et al. trained neurologically healthy individuals to learn a one-dimensional task similar to that used by Ell et al. (2010) as well as a one-dimensional disjunctive task (i.e., if the stimulus is low on dimension 1 or high on dimension 1 it is a member of category A, if the stimulus is mid-range on dimension 1 it is a member of category B) for over 10,000 trials. While putamen activation increased with extensive training in both conditions (consistent with many other automaticity studies), the correlation between putamen activation and performance followed the opposite pattern (and became highly negative in the disjunctive condition). When considered in conjunction with the data of Ell et al. (2006; 2010), the Helie et al. (2010) data suggest that the role of the putamen in rule-based categorization may be transient and dependent on the amount of training.

Synthesis

There is little doubt that the putamen contributes to a wide variety of cognitive processes, but the specific nature of the contribution remains unclear. It has been known for some time that the putamen provides

a neural substrate for learning stimulus-response-outcome associations (e.g., Kimura, 1986). In contrast, there is also evidence that the contribution of the putamen is not necessarily dependent upon the need to associate a stimulus with a response. For example, putamen activity during incidental episodic encoding is predictive of subsequent retrieval accuracy (e.g., Sadeh, et al., in press). Similarly, Ell et al. (2006) compared categorization tasks with identical response requirements and equivalent task difficulty and found that putamen lesions only impaired learning on a task dependent upon rule-guided behavior.

The functional anatomy is also consistent with the putamen's involvement in cognitive functioning, but primarily in regions rostral to the anterior commissure (e.g., Postuma & Dagher, 2006). Thus, one question is whether or not the data reviewed in this chapter are consistent with the rostral-caudal division of the putamen. We investigated this question by plotting the centers of activation for imaging studies, and centers of lesion overlap for lesion studies, on a standardized brain (Figure 2; Table 1). As can be seen, the majority of the centers of activation/lesion are located in the rostral putamen (n=30) with a bias toward more ventral regions. Nevertheless, there are several studies where the center was posterior to the anterior commissure (n=16), suggesting that a strict rostrocaudal division of the putamen may not reflect all of the cognitive functionality of the putamen. Moreover, although we do not have a sufficient sample size to appropriately analyze the distribution by cognitive process, it is worth noting that the category learning (4/10) and cognitive control (8/12) studies had the highest proportion of data points posterior to the anterior commissure whereas stimulus-response-outcome learning (1/7), working memory (2/10), and episodic memory (1/7) had the lowest. Clearly more research will be necessary to fully understand the structure-function relationship in the putamen.

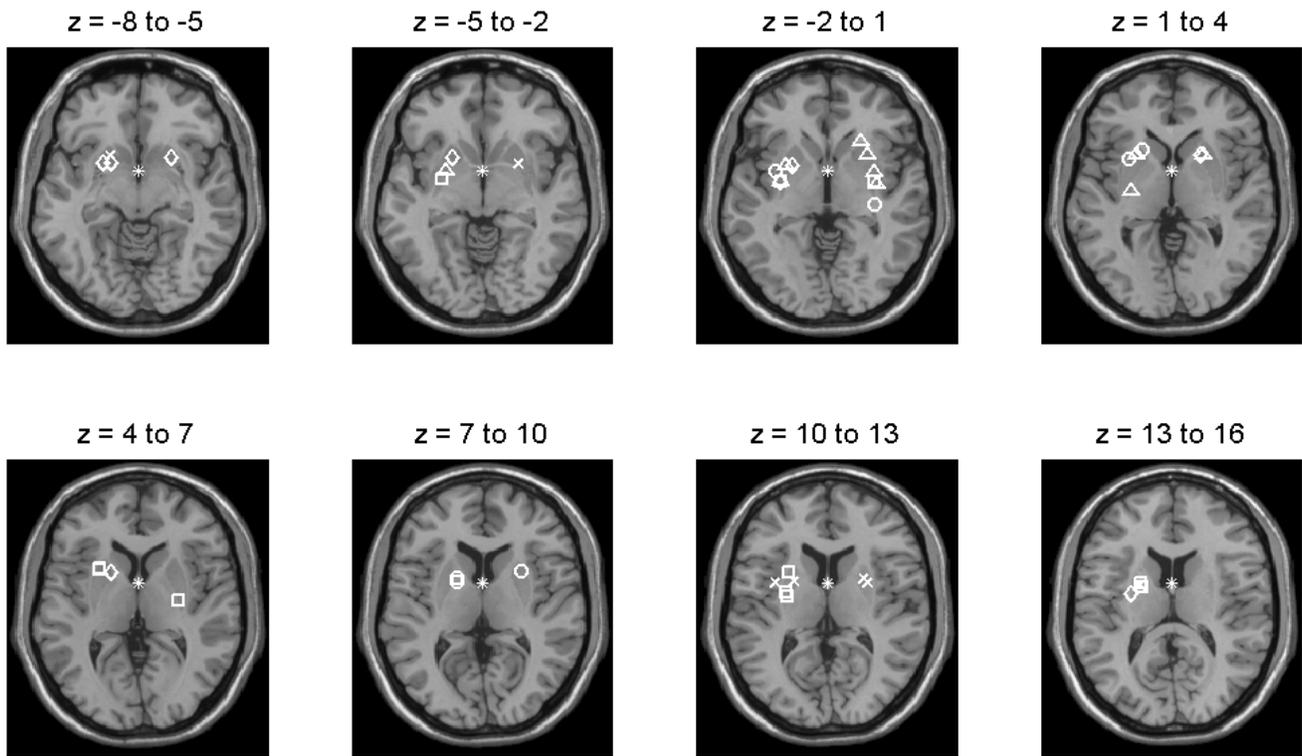


Figure 2. Centers of neuroimaging activation or lesion location associated with studies of stimulus-response-outcome learning (o), working memory (◇), episodic memory (x), cognitive control (□), and category learning (Δ) plotted in standardized (MNI) space. The rostrocaudal location of the anterior commissure is plotted for reference (white asterisk). Only data from studies where putamen coordinates were reported or could be easily estimated from figures are plotted. See Table 1 for the MNI coordinates and references.

Table 1. Coordinates used for generating Figure 2.

Cognitive Process	MNI Coordinates	Lesion/Neuroimaging	Reference
SRO Associations	-30, 9, 3	Neuroimaging	Brovelli et al. (2011)
	-36, 0, 0		
	27, 9, 9		
	-20, 16, 2	Neuroimaging	Haruno & Kawato (2006)
	-18, 4, 8	Neuroimaging	McClure et al. (2003)
	-18, 1, 8		
	33, -24, 0	Neuroimaging	Tricomi et al. (2009)
Working Memory	-28, -8, 13	Lesion	Baier et al. (2010)
	-24, 4, 0	Neuroimaging	Cairo et al. (2004)
	20, 12, 1		
	-24, 13, -9		
	-18, 8, 4	Neuroimaging	Chang et al. (2007)
	-20, 10, -4		
	-24, 6, -6	Neuroimaging	Dodds et al. (2009)
	24, 10, -8		
-18, 6, -6	Neuroimaging	McNab & Klingberg (2008)	
-32, -8, -1	Lesion	Voytek and Knight (2010)*	

Episodic Memory	-19, 11, -8	Neuroimaging	Prince et al. (2005)
	-23, 1, 11		
	-22, -2, 14	Neuroimaging	Sadeh et al. (in press)
	28, 0, 10		
	-36, 0, 12	Neuroimaging	Sperling et al. (2003)
Cognitive Control	25, 3, 12	Neuroimaging	Ystad et al. (2010)
	25, 5, -5		
	-28, -7, 11	Lesion	Bellebaum et al. (2008) ⁺
	-27, -10, 12		
Category Learning	-26, 8, 12		
	21, 0, 13	Lesion	Boyd & Winstein (2004)
	-32, -8, -1	Lesion	Cools et al. (2006) [*]
	33, -8, -1		
	-26, 11, 6	Neuroimaging	Monchi et al. (2001)
	28, -13, 4		
	-26, 10, 5		
	-20, -3, 13	Neuroimaging	Monchi et al. (2006)
	-28, -6, -5		
	20, -1, 16	Neuroimaging	Rubia et al. (2006)
Episodic Memory	-25, 2, -4	Neuroimaging	Badre et al. (2010)
	22, 12, 2		
	-32, -8, -1	Lesion	Ell et al. (2006; 2010) [*]
	33, -1, -1		
	35, -10, 1	Neuroimaging	Forstmann et al. (2010)
	-28, -15, 2		
	28, 12, -2	Neuroimaging	Seger & Cincotta (2002)
	-28, 4, 0		
	24, 22, -2		
-24, 12, 2			

Note. Coordinates were reported in the cited studies unless otherwise noted. ^{*} Coordinates estimated from region of maximal overlap of lesion reconstructions across patients. ⁺ Coordinates estimated from figure plotting individual patient lesion locations for patients with a reversal learning impairment (patients 1, 4, and 11, respectively). SRO – stimulus-response-outcome; MNI – Montreal Neurological Institute

CONCLUSION

Although it is well established that the putamen is critical for many aspects of motor learning, relatively little research has addressed the cognitive functions of the putamen. In this chapter, we provide a selective review of data from studies focusing on stimulus-response-outcome learning, working memory, episodic memory, cognitive control, and category learning. These studies utilized a diversity of methodological approaches including anatomical, electrophysiological, human/nonhuman lesion, neuroimaging, and neuropharmacological techniques. Despite this diversity, the studies provide converging evidence in support of the cognitive functions of the putamen.

Many of the studies reviewed in this chapter have demonstrated that the putamen is associated with various cognitive functions. This is an important first step toward the goal of understanding the role of the

putamen in cognition. One challenge, however, is the lack of independence among various cognitive processes. For example, working memory manipulation could be thought of as a form of cognitive control. Similarly, different category learning systems depend upon stimulus-response-outcome learning, working memory, episodic memory, and cognitive control to varying degrees. Unfortunately, there is no easy solution to this problem. Perhaps the best approach is to be detailed in the specification of the cognitive process of interest and, whenever possible, make the process concrete (e.g., by using computational modeling).

Another challenge is to understand if (and how) the contribution of the putamen to cognition differs from the caudate. Many researchers would argue that there is a significant difference in the functional contributions of these striatal nuclei. This view, we argue, is due in large part to the success of the classic loop model of the BG, which assigns striatal nuclei to a number of functionally distinct networks (Alexander, et al., 1986). The results of recent anatomical work suggest, however, that it may be more appropriate to think of the striatum as comprising a number of functional zones that span striatal nuclei (Haber, 2010; Parent & Hazrati, 1995; Postuma & Dagher, 2006). In this framework, for example, the caudate and the putamen both contribute to motor and cognitive functioning. The specific striatal regions important for cognitive or motor processing depend to some degree on the cortical structures that are involved. However, given the integrative nature of information processing within the BG, and between the BG, thalamus, and cortex, it will be challenging to assign strict functional labels to regions of the putamen.

Ultimately, what is necessary is to develop a more thorough understating of the role of the putamen at the neural systems level. The recent surge in functional connectivity analyses in neuroimaging studies provides a promising tool. For example, Seger and colleagues (Lopez-Paniagua & Seger, 2011; Seger, et al., 2011; Seger, Peterson, Cincotta, Lopez-Paniagua, & Anderson, 2010) used granger causality mapping to measure the influence exerted on/by the putamen during category learning. These studies suggest that the contribution of the putamen to category learning is at least in part due to its position within a subcortical network that is functionally associated with the caudate nucleus, hippocampus, and midbrain dopaminergic neurons. The specific anatomical pathways mediating such functional connectivity networks are unclear at this point, but such network-level techniques will be critical for the development of more detailed neurobiological theories.

Neurocomputational modeling will also continue to be an essential tool in testing hypotheses regarding the network-level involvement of the putamen in cognition. Consistent with modern functional views of BG anatomy, the vast majority of neurocomputational models focusing on the contributions of the BG to cognition model the striatum rather than focusing on the caudate or putamen (e.g., Frank & Badre, 2011). A focus on the putamen is often implied, however, when modeling tasks that depend upon the learning of context-dependent stimulus-response associations (Ashby & Crossley, 2011; Ashby, et al., 2007; Waldschmidt & Ashby, in press). For example, Ashby and Crossley (2011) developed a model that describes how thalamic neurons in the centromedian-parafascicular complex interact with tonically active cholinergic interneurons and medium spiny neurons in the putamen during the course of category learning. The continued development of such neurocomputational models will be critical for generating and testing hypotheses regarding the functional connectivity and role of the putamen in cognition.

In sum, the evidence reviewed in this chapter strongly implicates the putamen in various cognitive processes. In select cases, the data are strong enough to rule out the alternative hypothesis that putamen involvement is simply a byproduct of the motor demands of the task. Research that integrates across methodological approaches and cognitive processes will prove critical to advancing our understanding of the role of the putamen in cognition.

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