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LEARNING AND MEMORY FUNCTIONS OF THE BASAL GANGLIA

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Authors' note: In behavioral sections of the present review the term basal ganglia is often used to refer to the caudate nucleus and putmen (i.e., dorsal striatum). These structures are perhaps primary, but they are certainly not selective components of a group of subcortical structures that make up the basal ganglia. The broader term is used here simply in the interest of attracting the widest general readership of investigators interested in basal ganglia function.

■ **Abstract** Although the mammalian basal ganglia have long been implicated in motor behavior, it is generally recognized that the behavioral functions of this subcortical group of structures are not exclusively motoric in nature. Extensive evidence now indicates a role for the basal ganglia, in particular the dorsal striatum, in learning and memory. One prominent hypothesis is that this brain region mediates a form of learning in which stimulus-response (S-R) associations or habits are incrementally acquired. Support for this hypothesis is provided by numerous neurobehavioral studies in different mammalian species, including rats, monkeys, and humans. In rats and monkeys, localized brain lesion and pharmacological approaches have been used to examine the role of the basal ganglia in S-R learning. In humans, study of patients with neurodegenerative diseases that compromise the basal ganglia, as well as research using brain neuroimaging techniques, also provide evidence of a role for the basal ganglia in habit learning. Several of these studies have dissociated the role of the basal ganglia in S-R learning from those of a cognitive or declarative medial temporal lobe memory system that includes the hippocampus as a primary component. Evidence suggests that during learning, basal ganglia and medial temporal lobe memory systems are activated simultaneously and that in some learning situations competitive interference exists between these two systems.

INTRODUCTION

In the early 1900s, Kinnier Wilson coined the term extrapyramidal system to describe a mammalian basal ganglia system that interacts with brain-stem structures independently from the pyramidal tract to influence motor behavior. Wilson's emphasis on the role of the basal ganglia in motor behavior was driven by his early discoveries (1912, 1914) and those of Vogt (1911), revealing motor disorders in humans following damage to this brain region. The recognition that Parkinson's disease (a progressive neurodegenerative disease characterized by limb rigidity, tremors, and difficulty initiating movement) is fundamentally a disorder of basal ganglia function provided further evidence of the important role of this brain region in motor behavior. Decades of subsequent research on the behavioral functions of the mammalian basal ganglia have revealed a group of structures whose functions are diverse in nature, and it has long been recognized that behavioral classification of the basal ganglia strictly as a motor system is not tenable. Rather, evidence indicates that one nonmotor function of the basal ganglia involves participation in learning and memory. This view was partly espoused in early experimental research in animals investigating the effects of caudate nucleus lesions on performance of delayed response and alternation behavior (e.g., Battig et al. 1960; Butters & Rosvold 1968; Chorover & Gross 1963; Divac 1968, 1972; Divac & Oberg 1975; Gross et al. 1965; Kirkby 1969) and on performance of conditioned avoidance behavior (e.g., Allen & Davidson 1973, Kirkby & Polgar 1974, Neill & Grossman 1970, Prado-Alcala et al. 1975, Winocur 1974, Winocur & Mills 1969). The present review describes findings obtained primarily over the past decade supporting a role for the basal ganglia in mammalian learning and memory. Following a brief consideration of relevant anatomy and neurochemistry, the role of the basal ganglia in learning and memory is described based on findings from studies employing brain lesion and behavioral pharmacology approaches in experimental animals. It should be noted that there is also extensive research examining the role of the basal ganglia in learning and memory with electrophysiological techniques in behaving animals (e.g., Aosaki et al. 1994, Graybiel et al. 1994, Hikosaka et al. 1989, Jog et al. 1999, Mizumori et al. 2000, Rolls et al. 1983, Wiener 1993) and with neural computational modeling (e.g., Beiser et al. 1997, Berns & Sejnowski 1998, Gillies & Arbuthnott 2000). However, an adequate description of these two latter approaches is difficult given the prescribed limits of the present review, and therefore the reader is encouraged to examine this important additional literature. Following review of research in lower animals, the role of the basal ganglia in human learning and memory is described. This area of research involves neuropsychological studies of humans with neurological disorders that primarily compromise the basal ganglia (e.g., Parkinson's disease, Huntington's Chorea) and findings from experiments using brain neuroimaging techniques.

One description of the role of the basal ganglia in learning and memory in both lower animals and humans has been offered in the context of a multiple-systems

approach to memory organization (e.g., Knowlton et al. 1996a, Mishkin & Petri 1984, Packard et al. 1989). According to this idea, the basal ganglia mediate a form of learning and memory in which stimulus-response (S-R) associations or habits are incrementally acquired. In several studies in which a neuroscientific approach has been used, the putative S-R habit mnemonic function of the basal ganglia has been dissociated from that of a cognitive medial temporal lobe memory system in which the hippocampus is a major component (Packard 2001). Therefore, the present review also includes a consideration of how relatively independent basal ganglia and medial temporal lobe memory systems may interact in learning and memory.

BASAL GANGLIA: BRIEF ANATOMICAL CONSIDERATIONS

In 1664 anatomist Thomas Willis termed a prominent subcortical region of the telencephalon *corpus striatum*. Neuronal tracing techniques developed by Nauta and colleagues in the mid-1950s allowed for elucidation of connectivity of the broadly defined corpus striatal region, and the term basal ganglia was adopted to refer to a group of subcortical structures that included as primary components the caudate nucleus and putamen (the caudate-putamen are fairly undifferentiated in the rat but are separated by the internal capsule in primates), the globus pallidus, and the claustrum. Heimer and colleagues (e.g., Heimer & Van Hoesen 1979) subsequently adopted the term ventral striatum to delineate the most ventral aspects of the striatum (i.e., nucleus accumbens and portions of the olfactory tubercle) from more dorsal regions (i.e., caudate nucleus or dorsal striatum). Thus, the core structures of the mammalian basal ganglia include the dorsal striatum, ventral striatum, and globus pallidus. In addition, the substantia nigra, ventral tegmental area, and the subthalamic nucleus may be considered associated basal ganglia structures via their reciprocal connections with the core structures (for reviews see Ohye et al. 1996, Parent 1986).

The present review is restricted to addressing the role of the mammalian dorsal striatum (caudate nucleus and putamen) in learning and memory. However, it should be noted that several lines of evidence also suggest a role for the ventral striatum (e.g., nucleus accumbens) in learning and memory. This hypothesis was originally offered by Mogenson and colleagues (1980), who proposed that projections to the ventral striatum from limbic brain regions provide an interface between motivational states and behavioral action. Consistent with this idea, the mnemonic functions of the nucleus accumbens have been associated with forms of memory that are mediated by limbic structures that target the ventral striatum (i.e., hippocampus and amygdala) and, importantly, are unaffected by damage to the dorsal striatum (for reviews see Cador et al. 1989, Setlow 1997).

The basal ganglia receive input from virtually all regions of the cerebral cortex, and these corticostriatal pathways are topographically organized (e.g., McGeorge & Faull 1989, Veening et al. 1980). The discovery of corticobasal ganglia loops delineates an important feature of the anatomical organization of the mammalian basal ganglia, and these pathways have been elegantly described in the monkey (for review see Alexander et al. 1986). Specific cortical regions project to the dorsal and ventral striatum, and pallidal output from the basal ganglia loops back into these same cortical regions via various thalamic nuclei. Evidence suggests that at least five parallel corticobasal ganglia loops exist (for review see Kimura & Graybiel 1995). With regards to learning and memory functions, one interesting recent hypothesis is that fronto-cortical-striatal loops are used by the basal ganglia to essentially train the cortex to produce learned motor responses in the presence of a particular pattern of sensory information (Wise et al. 1996). However, it is important to note that, although basal ganglia output is clearly looped via the globus pallidus and thalamus back to specific cortical sites, pallidal and nigral outputs also directly project to downstream brain-stem structures that allow for rapid access to spinal control of motor responses.

The basal ganglia also receive a prominent projection from the thalamus, and intralaminar thalamic nuclei are recognized as the primary origin of the thalamostriatal pathway. However, projections to the neostriatum originating in various other thalamic nuclei have also been identified. Overlapping territories exist between thalamic regions innervated by the output nuclei of the basal ganglia and thalamostriatal projection neurons, which suggests the presence of feedback circuitry between these two brain regions (for review see Mengual et al. 1999).

BASAL GANGLIA: BRIEF NEUROCHEMICAL CONSIDERATIONS

Neurochemically the basal ganglia is characterized by a prominent input from midbrain dopaminergic pathways originating in the substantia nigra and ventral tegmental area, primarily innervating the dorsal and ventral striatum, respectively (for reviews see Graybiel 1990, Gerfen & Wilson 1996). Corticostriatal, thalamostriatal, and afferent projections from limbic structures including the amygdala and hippocampus utilize excitatory amino acid neurotransmission and are predominantly glutamatergic (Fonnum et al. 1981). Medium spiny output neurons of the neostriatum, composing approximately 90% of striatal neurons, use gamma-amino butyric acid as a neurotransmitter. An additional prominent component of basal ganglia neurochemistry is a large population of cholinergic interneurons (Lynch et al. 1972). For each of these systems, the full complement of receptor subtype families that have been indented for each neurotransmitter are present in varying densities and distribution patterns in the basal ganglia. Finally, several neuropeptides are also localized in the basal ganglia, including various opioids, cholecystokinin, substance P, somatostatin, and neurotensin.

NEUROANATOMICAL AND NEUROCHEMICAL ORGANIZATION OF THE BASAL GANGLIA: PATCH AND MATRIX

In the mid-1980s, a series of important findings demonstrated the existence of two neural compartments in the mammalian neostriatum that are neurochemically and anatomically differentiated and are commonly termed the striatal patch and matrix (for review see Gerfen 1992). Neurochemically, the patch compartments of the striatum (also termed striosomes) are characterized by low levels of acetylcholine and high levels of various opiates and substance P. In contrast, the matrix compartment is characterized by cholinergic and somatostatin-containing neurons. Both striatal compartments receive dopaminergic input, although dopamine pathways originating in the ventral tegmental area and substantia nigra appear to primarily innervate the patch and matrix, respectively. Anatomically, corticostriatal and thalamostriatal projections are closely associated with the striatal matrix, while projections from limbic structures to the striatum (e.g., hippocampus, amygdala) appear to primarily innervate striatal patches. Investigation of the functional significance of the neurochemical and anatomical differentiation observed between these two striatal compartments represents an evolving area of basal-ganglia research. With regards to the role of the basal ganglia in learning and memory, one hypothesis is that the striatal matrix primarily mediates the mnemonic functions of the dorsal striatum (White 1989a).

ROLE OF THE BASAL GANGLIA IN LEARNING AND MEMORY: A THEORETICAL FORMULATION

As previously mentioned, one account of the role of the basal ganglia in learning and memory posits that the caudate nucleus mediates a form of learning and memory in which S-R associations or habits (e.g., Thorndike 1933, Hull 1943) are incrementally acquired (Knowlton et al. 1996a, Mishkin & Petri 1984, Packard et al. 1989; for a similar early proposal based on human studies see Phillips & Carr 1987). This hypothesis was originally proposed largely on the basis of evidence that lesions of the monkey putamen impair simultaneous visual discrimination learning (e.g., Buerger et al. 1974). In this task, animals are presented concurrently with two objects (i.e., stimuli), and selection of the same object within a given pair (i.e., response) is followed by food reward. According to S-R learning theory, the satisfying or annoying nature of the reinforcer simply serves to strengthen or weaken learning and is not itself represented in the associations formed (i.e., Thorndike's 1933 Law of Effect).

The hypothesis that the basal ganglia mediate S-R habit learning has gained support from studies in rats (e.g., Graybiel 1998; Jog et al. 1999; Kesner et al. 1993; McDonald & White 1993, 1994; Packard et al. 1989; Packard & McGaugh 1992, 1996; Packard & Teather 1997, 1998; White 1997), monkeys (e.g., Fernandez-Ruiz

et al. 2001, Kimura 1995; Teng et al. 2000), and humans (e.g., Butters et al. 1994; Heindel et al. 1988; Knowlton et al. 1996a; Martone et al. 1984). In particular, several of these studies have used dissociation methodology to provide support for the hypothesis that the basal ganglia and hippocampus are parts of independent memory systems that mediate the acquisition of S-R habits and cognitive (e.g., Tolman 1932) forms of memory, respectively.

ROLE OF THE BASAL GANGLIA IN LEARNING AND MEMORY: LESION STUDIES

Beginning in the early 1960s, numerous studies conducted in experimental animals used brain-lesion techniques to implicate the mammalian basal ganglia in performance of delayed alternation and response tasks (e.g., Battig et al. 1960; Butters & Rosvold 1968; Chorover & Gross 1963; Divac 1968, 1972; Divac & Oberg 1975; Gross et al. 1965; Kirkby 1969). Several investigators subsequently demonstrated that lesions of the basal ganglia impair acquisition of various types of conditioned avoidance behavior in rats (e.g., Allen & Davidson 1973, Kirkby & Polgar 1974, Neill & Grossman 1971, Prado-Alcala et al. 1975, Winocur 1974, Winocur & Mills 1969), providing further evidence of a potential mnemonic role for this brain region (for early reviews on putative learning and memory functions of the caudate nucleus see Chozick 1983, Oberg & Divac 1979). However, the conclusion that the effects of a pretraining lesion on task acquisition result from an impairment of learning and memory per se must always be offered cautiously, as such lesions may potentially disrupt nonmnemonic functions (e.g., sensory, motivational, and/or motoric) that contribute to task performance. One strategy for dissociating lesion effects on mnemonic versus nonmnemonic factors is to employ pairs of learning tasks that share the same motivational, sensory, and motoric characteristics. The first use of dissociation methodology to directly test the hypothesized selective role of the basal ganglia (dorsal striatum) in S-R habit learning involved a study in which two eight-arm radial maze tasks were used (Packard et al. 1989). In the standard win-shift version of the radial maze task introduced by Olton & Samuelson (1976), rats obtain food rewards by visiting each arm of the maze once within a daily training session, and re-entries into maze arms that were previously visited are scored as errors. In a newly developed win-stay version of the radial maze task, rats obtained food rewards by visiting four randomly selected and illuminated maze arms twice within a daily training session, and visits to unlit maze arms are scored as errors. Performance in the win-shift task requires rats to remember those arms that have been previously visited within a daily training session, and this task is essentially a prototypical test of spatial working memory (e.g., Olton & Papas 1979) and/or may involve the use of a Tolmanian (1932) cognitive mapping strategy (e.g., O'Keefe & Nadel 1978). In contrast, acquisition of the win-stay task requires rats to learn to approach lit maze arms, and this task is essentially a simultaneous visual discrimination that may involve acquisition of

a Hullian (1943) S-R habit. When rats are trained on these two tasks following electrolytic lesions of the dorsal striatum, a dissociation is observed; dorsal striatal lesions impair acquisition of the win-stay task and do not affect acquisition of the win-shift task. Interestingly, lesions of the hippocampal system (fimbria-fornix) produce the opposite pattern of results, providing evidence of a double dissociation of the mnemonic functions of the dorsal striatum and hippocampal system (Packard et al. 1989). These findings were subsequently replicated in a study employing neurotoxic dorsal striatal and hippocampal lesions (McDonald & White 1993). Importantly, when rats are well trained in the win-stay radial maze task and subsequently exposed to reinforcer devaluation (via pairing of the food reward with nauseating lithium chloride injections), they continue to approach illuminated maze arms (Sage & Knowlton 2000). This finding suggests that representation of the food reward is not guiding learned behavior in this task; rather, performance of the caudate-dependent win-stay task involves acquisition of an S-R (light-approach) and not a stimulus-stimulus (light-food) association.

An additional study utilized two water maze tasks to investigate the selective role of the basal ganglia in S-R memory (Packard & McGaugh 1992). In these tasks, analogous to those originally introduced by Morris (1984), two rubber balls protruding above the water surface served as cues. One ball (correct) was located on top of a platform that could be used to escape the water, and the other ball (incorrect) was located on top of a thin rod and thus did not provide escape. The two balls also differed in visual appearance (i.e., vertical versus horizontal, black versus white stripes). In a cognitive version of the task, the correct platform was located in the same spatial location on every trial, but the visual appearance of the ball varied. Therefore, this version of the task requires rats to learn to approach the correct ball on the basis of spatial location, and not visual pattern. In an S-R habit version of the task, the correct platform was located in different spatial locations across trials, but the visual pattern was consistent. Therefore, this task could be acquired by learning an approach response to the visual cue. Lesions of the dorsal striatum impair acquisition of the S-R habit task, without affecting acquisition of the spatial task (Packard & McGaugh 1992). In another version of the water maze task, rats were trained to swim to a visibly cued escape platform located in a constant spatial location (McDonald & White 1994). Following acquisition of the task, the nature of the learned behavior was probed by moving the visible platform to a novel spatial location. On the probe trial, half of the control rats swam to the old platform location (indicating the use of spatial memory), and half swam to the visibly cued platform in the new location (indicating the use of S-R memory). In contrast, all of the rats with dorsal striatal lesions swam to the old spatial location, indicating an impairment in S-R learning. Again, it is of interest to note that, in both of the water maze studies described above, lesions of the hippocampal system (fimbria-fornix) produced the opposite pattern of results (i.e., a selective impairment of spatial memory).

Numerous other studies have used irreversible pretraining lesions of the basal ganglia to demonstrate impairments in the acquisition of learning tasks that

theoretically could be acquired by an S-R habit memory system. For example, in rats, caudate nucleus lesions impair the acquisition of two-way active avoidance behavior (e.g., Green et al. 1967, Kirkby & Kimble 1968, Neill & Grossman 1971), simultaneous tactile discriminations (Colombo et al. 1989), simple straight-alley runway behavior (Kirkby et al. 1981, Salinas et al. 1998), invariant reference memory in a four-arms baited, four-arms unbaited radial maze task (Colombo et al. 1989, Packard & White 1990), conditional visual (Reading et al. 1991, Winocur & Estes 1998), and auditory (Adams et al. 2001) discrimination learning.

In addition to studies employing irreversible brain lesions, recent research using intracaudate infusion of drugs that produce temporary neural inactivation (i.e., tetrodotoxin or lidocaine) also reveal a role for the basal ganglia in learning and memory (Lorenzi et al. 1995, Packard & McGaugh 1996). In one study (Packard & McGaugh 1996), a plus-maze task that figured prominently in the historic debate between S-R and cognitive learning theorists (for review see Restle 1957) was used to examine the role of the caudate nucleus in response learning. Potegal (1972) originally proposed that the caudate nucleus mediates egocentric response learning, and several experimental findings support this idea (e.g., Abraham et al. 1983, Brasted et al. 1997, Cook & Kesner 1988, Kesner et al. 1993, Mitchell & Hall 1988, Robbins & Brown 1990, Thompson et al. 1980). In the aforementioned plus-maze study (Packard & McGaugh 1996), rats were trained in a daily session to obtain food from a consistently baited goal box (west) and were trained to approach this maze arm from the same start box on each trial (south). Following seven days of training (i.e., on day eight), rats were given a probe trial in which they were placed in the start box opposite to that used during training (north). On the probe trial, rats that entered the west arm (i.e., the spatial location where food was located during training) were designated place learners, and rats that entered the east arm (i.e., made the same body turn response that had been reinforced during training) were designated response learners. Prior to the probe trial, rats received intradorsolateral caudate injections of the local anesthetic lidocaine, in order to examine the role of this brain region in the expression of previously learned behavior. On the day-eight probe trial, rats receiving vehicle or lidocaine injections into the dorsolateral caudate were predominantly place learners, providing further evidence that the functional integrity of the dorsolateral caudate is not necessary for expression of spatial or place learning. However, with extended training in the cross-maze, intact rats switch from the use of place learning to a response-learning tendency (Hicks 1964, Ritchie et al. 1950). Therefore, the rats were trained for an additional seven days, given a second probe trial on day 16, and again received intracerebral injections of lidocaine prior to the probe trial. On this second probe trial, rats receiving vehicle injections into the dorsolateral caudate were predominantly response learners, revealing a switch from the use of place to response learning with extended training. In contrast, rats receiving intradorsolateral caudate injections of lidocaine prior to the second probe trial exhibited place learning, demonstrating a blockade of the expression of response learning. This finding also indicates that when the shift from the use of place to response

learning occurs the place representation can be brought back into use by blockade of the caudate nucleus response-learning system. Consistent with the double dissociations between basal ganglia and hippocampal mnemonic function observed in studies using irreversible lesions, intradorsal hippocampal infusions of lidocaine selectively impaired the expression of place learning (Packard & McGaugh 1996).

Finally, recent evidence also indicates that pretraining neurotoxic lesions of monkey basal ganglia (i.e., ventrocaudal neostriatum) impair concurrent visual-discrimination learning and leave visual-recognition memory intact (Fernandez-Ruiz et al. 2001). Similarly, conjoint damage to the hippocampus and ventrocaudal neostriatum (but not hippocampus alone) impairs concurrent and pattern-discrimination learning (Teng et al. 2000). Therefore, the selective impairment of S-R habit learning that has been revealed following lesion damage to the basal ganglia in rats is also observed following neostriatal damage in monkeys. Taken together, these findings suggest that the mnemonic functions of the basal ganglia generalize across mammalian species, an idea that is also supported by research on humans (e.g., Knowlton et al. 1996a).

BASAL GANGLIA, LEARNING, AND MEMORY: FUNCTIONAL HETEROGENEITY

Several early studies on the role of the basal ganglia in learning and memory were guided in part by anatomical evidence demonstrating the existence of the corticostriatal pathways. One hypothesis that has continued to garner support is that the mnemonic function of the caudate nucleus is organized based on the nature of the topographical cortical input this structure receives. For example, in experimental animals lesions of either the frontal cortex or the medial region of the caudate nucleus to which it projects produce similar impairments in performance of delayed alternation and response tasks (e.g., Divac 1972; Kolb 1977; Rosvold 1968, 1972). Moreover, lesions of regions of the caudate nucleus that receive visual or olfactory input selectively impair conditioned emotional responding based on visual or olfactory stimuli, respectively (Viaud & White, 1989; see Pisa & Cyr 1990, Winocur 1974 for additional examples of regional specificity of the dorsal striatum in learning).

One suggestion with regard to functional heterogeneity of the mnemonic role of the basal ganglia is that S-R habit learning may selectively involve lateral regions of the dorsal striatum, whereas the medial dorsal striatum may mediate a cognitive form of memory that appears similar to that typically associated with the hippocampus. This idea is based in part on evidence that lesions of the medial, but not lateral, dorsal striatum, impair the use of spatial navigation in a hidden-platform water maze task (e.g., Devan & White 1999, Furtado & Mazurek 1996, Whishaw et al. 1987) and bias rats toward the use of S-R memory in a water maze task in which competing place- and cue-learning preferences are simultaneously assessed (Devan et al. 1999, Devan & White 1999). It should be noted that in

some of these water maze studies, medial dorsal striatal lesions did not completely prevent spatial learning (Devan et al. 1999, Devan & White 1999, Whishaw et al. 1987). Moreover, there is behavioral evidence that appears inconsistent with the idea that medial dorsal striatal lesions produce mnemonic deficits identical to those produced by hippocampal system lesions. For example, large lesions of the dorsal striatum that include lateral and medial regions (Packard et al. 1989, 1992), as well as lesions restricted to the medial dorsal striatum (Sakamoto & Okaichi 2001), do not impair acquisition of hippocampus-dependent win-shift behavior in the radial maze. Moreover, in the previously described spatial and S-R visual-discrimination water maze tasks (Packard & McGaugh 1992), medial dorsal striatal lesions selectively impaired acquisition of the S-R task, whereas fimbria-fornix lesions produced the opposite effect. Similarly, lesions of the medial caudate impair the S-R component of a sequential learning task, without affecting the use of spatial information, whereas hippocampal lesions produce the opposite effect in this task (DeCoteau & Kesner 2000). Finally, recent evidence suggests that separate lesions of the medial or lateral dorsal striatum each impair acquisition of an S-R auditory conditional-response association task (Adams et al. 2001). In sum, findings of a number of studies suggest the existence of functional heterogeneity within the dorsal striatum in learning. However, further research is clearly necessary to determine whether such heterogeneity is limited to modality-specific S-R memory, or whether medial regions of dorsal striatum may in part mediate more cognitive forms of information processing.

ROLE OF THE BASAL GANGLIA IN LEARNING AND MEMORY: POSTTRAINING DRUG STUDIES

An additional experimental approach that has been used to assess the mnemonic functions of the basal ganglia involves posttraining manipulations of this structure. Studies using localized intracerebral posttraining treatments have contributed significantly to our understanding of the neuroanatomical and neurochemical bases of memory. Early experimental findings (Breen & McGaugh 1961, Burnham 1904, Duncan 1949, Zubin & Barrera 1941) supported the hypothesis (Hebb 1949, Muller & Pilzecker 1900) that memory is in a labile state immediately following a training experience, and over time the information is consolidated into a more permanent state. Consistent with consolidation theory, a critical feature of these treatments is that they are time dependent, that is, they are most effective when administered shortly after training and lose effectiveness as the training-treatment interval is increased. The time-dependent nature of posttraining treatments also indicates that the effects on retention are not due to a proactive influence on motivational, sensory, or motoric processes (for reviews see McGaugh 1966, 1989, 2000).

Early research utilized posttraining electrical stimulation to implicate the basal ganglia in memory processes (for review see Kesner & Wilburn 1974). Subsequent

research using posttraining pharmacological treatments has implicated dopaminergic, cholinergic, and glutamatergic neurotransmission in dorsal striatal memory processes. With regard to dopamine, studies employing 6-hydroxydopamine lesions to deplete striatal dopamine initially suggested a role for the nigrostriatal dopamine pathway in the mnemonic functions of the basal ganglia (e.g., Neill et al. 1974, White 1988, Zis et al. 1974; see also Major & White 1978).

Memory enhancement produced by posttraining intracaudate infusion of the indirect catecholamine agonist amphetamine in conditioned emotional-response tasks provides direct evidence of a role for striatal dopamine in memory consolidation (Carr & White 1984, Viaud & White 1989). Posttraining intracaudate injections of various dopamine receptor agonists (i.e., amphetamine, D1 receptor, and D2 receptor agents) also enhance memory in the win-stay radial maze task and have no effect in the win-shift task (Packard & White 1991). Similarly, posttraining intracaudate amphetamine injections enhance memory in an S-R visible platform water maze task, but they have no effect on memory in a hidden platform (spatial) task in the same apparatus (Packard et al. 1994, Packard & Teather 1998). In both of these latter studies, posttraining intradorsal hippocampal infusions of dopamine agonists produced the opposite pattern, a selective enhancement spatial memory.

In addition to evidence indicating a role for striatal dopamine in memory, extensive evidence from rats trained in various conditioned avoidance behaviors indicates a role for cholinergic mechanisms within the basal ganglia in memory consolidation (e.g., Deadwyler et al. 1972; Haycock et al. 1973; Neill & Grossman 1971; Packard et al. 1996; Prado-Alcala et al. 1972, 1981; Prado-Alcala & Cobos-Zapian 1977, 1979). Specifically, posttraining intradorsal striatal infusions of muscarinic cholinergic receptor agonist and antagonist drugs typically enhance and impair memory, respectively. Recent studies have also implicated glutamatergic function in dorsal striatal memory processes. Posttraining intracaudate infusions of glutamate and the NMDA receptor antagonist AP5 enhance and impair memory in an S-R visible platform water maze task, respectively (Packard & Teather 1997, 1999). Evidence also suggests a role for metabotropic glutamate receptors in caudate-dependent memory in the visible platform task (Packard et al. 2001). As observed following administration of dopaminergic drugs, the effects of posttraining intracaudate infusion administration of glutamate, AP5, and mGluR agents are task dependent; similar infusions have no effect on memory in a hidden platform water maze task. Finally, a potential role for GABAergic transmission in basal ganglia memory processes was initially suggested by findings indicating that posttraining infusions of the GABA receptor antagonist picrotoxin into the substantia nigra impairs memory (Kim & Routtenberg 1976), and recent research has demonstrated memory-impairing effects of picrotoxin infused directly into the dorsal striatum (Salado-Castillo et al. 1996).

In view of the evidence implicating dopamine, acetylcholine, glutamate, and GABA in the mnemonic functions of the basal ganglia, important questions remain concerning the neural mechanisms that integrate the action of these neurotransmitters. According to one hypothesis (White 1989a, White et al. 1994),

glutamatergic corticostriatal projections provide the dorsal striatum with sensory information underlying the formation of S-R associations, whereas GABAergic output to the globus pallidus mediates the motor or response element of habit memory. Dopaminergic input to dorsal striatum is hypothesized to provide a reinforcing signal that effectively stamps together S-R associations. Evidence indicating that 6-hydroxydopamine lesions of the nigrostriatal dopamine pathway block the memory-enhancing effects of posttraining intracaudate infusion of cholinergic agents suggests the existence of acetylcholine-dopamine interactions in striatal memory processes (White et al. 1994).

It is important to note that the putative reinforcing action of dopamine on the formation of S-R habits in the dorsal striatum is differentiated from the rewarding properties of this neurotransmitter. Extensive evidence suggests that affective or rewarding properties of dopamine are mediated by release of this transmitter in the ventral striatum (e.g., via ventral tegmental area projections to the nucleus accumbens). The proposed role of the ventral tegmental-accumbens dopamine pathway in stimulus-reward learning (e.g., Shultz et al. 1997, Sutton & Beninger 1999, Wickens 1990), in which affective information may be represented in memory, may be different than the reinforcing action of this neurotransmitter in S-R habit learning, in which affective information is not represented in the underlying associative structure (for a discussion of theoretical distinctions between the concepts of reward and reinforcement see White 1989b). This suggestion is consistent with evidence indicating that 6-hydroxydopamine lesions of the dorsal striatum do not block the primary rewarding affective properties of dopamine agonists as measured in conditioned place preference behavior or impair the acquisition of conditioned reinforcement tasks that putatively involve stimulus-reward learning (e.g., Cador et al. 1989).

Further research is necessary to elucidate the synaptic and cellular mechanisms by which dopamine, acetylcholine, and glutamate influence dorsal striatal memory processes. Interestingly, each of these transmitter systems has been implicated in various forms of synaptic plasticity [i.e., long-term potentiation (LTP) and long-term depression (LTD)] that have been identified in the basal ganglia (e.g., Calabresi et al. 1992, Centonze et al. 1999, Charpier & Deniau 1997, Garcia-Munoz et al. 1992, Lovinger et al. 1993, Kerr & Wickens 2001), although the relationship between neostriatal LTP and/or LTD and the mnemonic functions of this brain region is currently unknown.

ROLE OF THE BASAL GANGLIA IN HUMAN LEARNING AND MEMORY

Investigation of the role of the basal ganglia in human learning and memory has provided some convergence with data from experimental animals. The fact that the cerebral cortex is highly developed in humans (especially frontal lobe) suggests that corticostriatal loops may subserve even more complex functions in humans. Patients with basal ganglia disorders exhibit impairments in a number of cognitive

tasks (for review see Glosser 2001). Cognitive impairment is a primary feature of Huntington's disease, which involves cell loss in the caudate and putamen. Patients with Parkinson's disease also exhibit a variety of cognitive deficits, though not typically as severe. In Parkinson's disease, cell death in the substantia nigra leads to a loss of dopaminergic input to the caudate and putamen. In both of these patient groups, motor deficits are the most obvious consequences of basal ganglia disease. However, as has been described in experimental animals, the demonstration of nonmotor deficits following basal ganglia dysfunction also suggests a broader role for this brain region in human behavior, one that clearly includes learning and memory functions.

PROBABILISTIC CLASSIFICATION LEARNING

The deficits in habit learning that have been demonstrated in experimental animals with damage or dysfunction in the caudate nucleus appear to have an analog in humans with basal ganglia dysfunction. However, the maze tasks that have been used with rats may not readily lend themselves to studies of human learning and memory. For instance, although the caudate-dependent win-stay radial maze task is learned gradually and incrementally across many trials in rats (McDonald & White 1993, Packard et al. 1989), it seems likely that humans would surmise that the illuminated maze arms are selectively baited within a few trials. In order to tap into a human habit learning system, it may be necessary to circumvent the use of explicit or declarative memory. For example, by using a learning task in which cues and outcomes are probabilistically related, explicit memory for what has occurred on each particular trial is not as useful as a general sense of the relationship between cues and outcomes gleaned across numerous training trials.

One version of a probabilistic classification task involves a weather prediction game (Knowlton et al. 1994). There are four cues in the task (i.e., cards with geometric shapes), and these cues predict one of the outcomes approximately 60–85% of the time. Subjects are told that on each trial they will be seeing a set of cues on a computer screen and that their task is to guess whether the cues predict sun or rain. If the subjects make a correct response, they hear a high tone and see a smiling face on the screen, and if their response is incorrect they hear a low tone and see a frowning face on the screen. Although subjects often feel as if they are simply guessing, they nevertheless generally exhibit learning in this task over 50–100 trials, as evidenced by a tendency to choose the more highly associated outcome. Evidence suggests that damage to the basal ganglia results in a deficit in this probabilistic classification task, as patients with Huntington's disease and Parkinson's disease are impaired in task acquisition (Knowlton et al. 1996a). Although the locus of cell loss is different in the two diseases—Parkinson's disease affects the dopaminergic input to the striatum and Huntington's disease affects cells in the striatum itself—it appears that in either disorder the circuitry that is required for learning the stimulus outcome associations is disrupted. The deficit is particularly noteworthy in patients with Parkinson's disease because these

patients are able to show evidence of normal declarative memory for the training episode.

It is important to note that in various caudate-dependent learning tasks, rats with lesions of the hippocampal system exhibit intact (or in some cases facilitated) acquisition. Therefore, if learning underlying the probabilistic classification task is analogous to caudate-dependent S-R learning, then it should be acquired normally by patients with damage to structures in the medial temporal lobe that are critical for declarative memory. In fact, it does appear that temporal lobe amnesic patients perform normally on this task (Knowlton et al. 1994, Reber et al. 1996). Thus, a double dissociation between declarative memory and habit learning is observed when patients with Parkinson's disease are compared to amnesic patients. This double dissociation parallels the findings with experimental animals, which suggests that habit learning may be a mnemonic function of the basal ganglia that is conserved across species.

MOTOR SKILL AND PERCEPTUAL-MOTOR LEARNING

In addition to the probabilistic classification task, patients with basal ganglia dysfunction are impaired on other tasks in which procedures or habits may be acquired. Patients with basal ganglia dysfunction exhibit deficits in motor skill learning, primarily for open loop motor skills that are not under the direct control of visual feedback (Gabrieli et al. 1997, Harrington et al. 1990). Although the existence of motor performance deficits can complicate the interpretation of these findings, impaired acquisition has been reported in learning paradigms in which motor performance problems are unlikely to be the primary cause of a failure to show learning. For example, patients with Huntington's disease exhibit reduced weight–biasing effects (Heindel et al. 1991). In this study, subjects lifted a set of weights and then later judged the heaviness of a new set of weights. Subjects' prior experience with the weights affected their judgments; if they had initially lifted heavier weights, they judged the test weight to be lighter than if they had initially lifted lighter weights. This biasing effect may occur because the motor program for lifting the target weight is influenced by previous experience (i.e., if the subject has just been lifting heavy weights, the motor system may be prepared to lift heavy weights). Therefore, a test weight may appear lighter if the motor system is prepared to lift heavy weights, whereas the same weight may seem heavier if the motor system has been prepared to lift lighter weights. This biasing effect does not require declarative memory for experience with the weights because patients with Alzheimer's disease exhibit bias to the same extent as control subjects. The deficit exhibited by patients with Huntington's disease may occur because of a difficulty adapting motor programs based on experience.

Patients with Huntington's disease also exhibit deficits in perceptual-motor skill learning. For example, in the prism adaptation task, subjects wear prism goggles that effectively shift their visual world. Subjects initially make reaching errors while wearing prism goggles, but with practice, they are able to reduce the error.

When subjects remove the goggles there is even a transient error in reaching as the perceptual-motor system readapts to the normal visual world. Patients with Huntington's disease do not adapt as well as control subjects, while patients with Alzheimer's disease are able to adapt normally despite their declarative memory problems (Paulsen et al. 1993). Thus, it appears that changes in motor behavior based on perceptual input depend on the neostriatum, and not on cortical and medial temporal lobe regions affected in Alzheimer's disease.

An additional set of tasks that appear to tap into basal ganglia mnemonic processing involves sequence learning (e.g., Laforce & Doyon 2001, Willingham et al. 1996). In the serial reaction-time task (Nissen & Bullemer 1987), for instance, subjects see a series of stimuli such as asterisks appearing on a computer screen, and their task is to press the key directly below each asterisk as it appears. Unbeknownst to the subject, the asterisks appear according to a fixed sequence. As subjects practice the task, their reaction times decrease (i.e., they press the keys faster in response to the asterisks). In normal subjects, much of this learning is specific to the sequence, and this can be demonstrated by switching from the fixed sequence to randomly appearing asterisks. Although this change is not readily apparent to subjects, their reaction times slow down significantly when this shift occurs. Subjects are not generally able to recognize the sequence after training and may deny that there was a fixed sequence, even though they exhibit sensitivity to the sequence through their performance. There are several reports of poor performance by patients with basal ganglia disorders on the serial reaction-time task. Patients with Huntington's disease, for instance, do not exhibit decreases in reaction time when the fixed sequence is switched to one that is random (Willingham & Koroshetz 1993). One complicating factor is that the movement disorder exhibited by these patients results in their initial performance being much slower and variable than that of controls. Although the slower performance of the patients with Huntington's disease could on the one hand give them more room to improve, it may also be the case that their difficulty with simply performing the task overwhelms any sequence-specific learning that might be present. Nevertheless, the data are consistent with the idea that the basal ganglia are important for learning a visuomotor sequence. In contrast, as is the case with other implicit learning tasks, amnesic patients show normal sequence learning (Nissen & Bullemer 1987, Reber & Squire 1994).

The data from patients with Parkinson's disease on sequence learning are less clear. Although several studies have observed impaired sequence learning in Parkinson's patients, other studies have not (Helmuth et al. 2000, Smith et al. 2001, Sommer et al. 1999). There are several factors that may contribute to this inconsistent pattern of results. First, subjects in the patient groups appear to have differed in the severity of the disease. As Parkinson's disease primarily involves degeneration of projections to the putamen (Morrish et al. 1996), it is possible that patients with early Parkinson's disease may not exhibit a deficit if sequence learning depends on the integrity of the caudate nucleus. Second, the sequences used in different experiments may differ in important ways. For example, some sequences are not balanced for first-order dependencies. If A, B, C, and D represent the four

locations in which asterisks appear, the sequence DCBACBDCAB is formed such that position D is always followed by position C. In contrast, the sequence DCBACADABCDB does not have this property. For each position, all other positions are equally likely to follow. Sequence-specific speed up would thus indicate that subjects are learning more than just the dependencies of single items. Sequences can be constructed that are even more complex, with second-order dependencies balanced for all groups. Given that there are several aspects of the sequence that can be learned, it may be that patients with Parkinson's disease are impaired on only some types of sequence learning. If so, it would help investigators focus on the type of information processing mediated by the basal ganglia. For example, although the serial reaction-time task measures motor response speed, it appears that learning is more abstract than a sequence of movements. Subjects exhibit good transfer when switched to another effector (such as the other hand) or if the locations are mapped onto a different set of keys. However, if the locations are changed, performance suffers greatly, even if the same pattern of movements occurs that had occurred during training (Willingham et al. 2000). Thus, it appears that what may be acquired is a sequence of locations that one should respond to, rather than a motor sequence.

ROLE OF BASAL GANGLIA IN LEARNING AND MEMORY: HUMAN NEUROIMAGING STUDIES

In addition to neuropsychological studies, there are several human neuroimaging studies indicating that the basal ganglia is involved in learning skills and habits. Activation in the caudate nucleus has been observed while subjects are learning the skill of reading mirror-reversed text (Dong et al. 2000). Interestingly, the striatal involvement may only be present during learning, with highly skilled performance primarily activating cortical circuitry (Poldrack & Gabrieli 2001). Several neuroimaging studies also have demonstrated activation of the basal ganglia during learning of the serial reaction-time task (Doyon et al. 1996, Rauch et al. 1997). In these studies, activation in the caudate nucleus is observed while subjects are performing the serial reaction-time task with a fixed sequence, compared to blocks of trials for which locations occur randomly. Moreover, activation in the caudate nucleus is associated with performance of an implicitly learned sequence, but not when subjects are explicitly told the sequence beforehand and can therefore consciously anticipate the location of the upcoming stimulus. In another study, positron emission tomography (PET) was used to measure dopamine release while participants played a video game (Koepp et al. 1998). As subjects played the game and improved their performance, there was decreased binding of radiolabeled raclopride (a dopamine antagonist) in dorsal and ventral striatum in comparison to a control condition. These data suggest that endogenous dopamine release increased in the neostriatum during practice, consistent with research in lower animals demonstrating a role for striatal dopamine in S-R habit learning (e.g., Packard & White 1991).

INTERACTIONS BETWEEN BASAL GANGLIA AND MEDIAL TEMPORAL LOBE MEMORY SYSTEMS: TEMPORAL ASPECTS

As previously described, numerous studies have dissociated the S-R habit memory function of the basal ganglia from those of a declarative medial temporal lobe memory system that includes the hippocampus as a primary component. Within the context of a multiple-systems approach to memory organization, one important question concerns the nature of potential interactions between different memory systems. In considering this issue, one can start with the observation that during learning basal ganglia and hippocampal memory systems appear to be activated simultaneously and in parallel (McDonald & White 1994, Packard & McGaugh 1996). Recall that, with extended training in a plus maze, expression of response-learning tendencies comes to overshadow previously dominant place learning (Hicks 1964, Packard & McGaugh 1996, Ritchie et al. 1950). This shift indicates that in a learning task for which both memory systems can provide an adequate solution, the hippocampal system mediates a rapid form of learning that initially controls behavior but that eventually cedes behavioral control to a caudate memory system mediating a more slowly developing S-R form of learning. Consistent with this suggestion, rats that are overtrained in the caudate-dependent win-stay radial maze task appear to perform based on S-R associations because reinforcer devaluation does not alter response accuracy or latency (Sage & Knowlton 2000). However, early in training before asymptotic performance has been reached, rats do show longer latencies to run down cued arms if the reinforcer has been devalued, which suggests that a representation of the food is present at early stages of learning. In view of evidence that performance on the hippocampus-dependent win-shift radial arm maze task is affected by reinforcer devaluation (Sage & Knowlton 2000), it appears that the reinforcer is represented in what has been learned by the hippocampus about which arms have been visited.

Taken together, these findings raise the possibility that postposttraining injections of a memory-enhancing agent into the dorsal striatum or hippocampus during early training might influence the time course of the shift in the use of these two structures to guide learned behavior. In an experiment designed to address this implication, rats received postposttraining intradorsal hippocampal or intradorsolateral caudate infusion of glutamate during early time points (on days 3–5) of plus-maze training (Packard 1999). Rats receiving vehicle injections predominantly displayed place learning on an early (day 8) probe trial and response learning on a later (day 16) probe trial. However, rats receiving postposttraining intrahippocampal infusions of glutamate predominantly displayed place learning on both the early and late probe trials, which suggests that infusion of glutamate into the hippocampus strengthened a spatial representation, effectively blocking the shift to response learning that occurs with extended training. In contrast, rats given postposttraining glutamate infusions into the caudate-putamen predominantly displayed response learning on both the early and late probe trials, which suggests that

infusion of glutamate into the caudate-putamen accelerated the shift to response learning that occurs in control rats only following extended training. Therefore, manipulation of a neurotransmitter system relevant to the mnemonic processes mediated by both the basal ganglia and hippocampus can bias animals toward the use of a specific memory system.

Although plus-maze studies in experimental animals clearly demonstrate that with extended training there is a shift from the use of cognitive to habit memory, this phenomenon has been observed in animals in which both memory systems are functional at the initiation of training. However, it is of interest to note that in patients with Parkinson's disease, deficits on a probabilistic classification task are most apparent early in training. After extended training (more than about 150 trials), Parkinson's patients do tend to approach the performance of control subjects. It is likely that in this situation, subjects are eventually able to gain sufficient declarative knowledge of the task structure to further improve their performance and may begin to make optimal choices for some cue patterns rather than simply probability match. Patients with Parkinson's disease would presumably gain declarative knowledge of the task along with control subjects. Patients with amnesia, as well as control subjects, would not be able to acquire this declarative knowledge and thus would be relatively impaired later in training. Indeed, this pattern has been observed when amnesic patients are given extended training on this task (Knowlton et al. 1994).

INTERACTIONS BETWEEN BASAL GANGLIA AND MEDIAL TEMPORAL LOBE MEMORY SYSTEMS: COMPETITIVE ASPECTS

As simultaneous and parallel activation of basal ganglia and medial temporal lobe memory systems occurs during learning, one form of interaction between these systems appears to be competitive or interfering in nature. Sherry & Schacter (1987) hypothesized that the presence of functional incompatibility, in which an existing memory system is unable to provide an adequate solution in a situation involving novel information or task demands, may have driven natural selection processes that ultimately resulted in the evolution of multiple memory systems. One can envision a type of racehorse model in which both systems undergo learning-related changes, with the system that comes up with the most valid and reinforced response enjoying a strengthening of its control on behavior.

In experimental settings, competitive interference between different memory systems may be potentially revealed in studies in which pretraining lesions of a given system result in enhanced acquisition of a task relative to brain-intact animals. For example, in the caudate-dependent win-stay radial maze task, it is conceivable that spatial information processed by the hippocampal system, which provides the rat with information concerning those maze arms in which food has already been retrieved, may interfere with the task requirement of revisiting maze

arms in which food was recently removed. Consistent with this hypothesis, lesions of the hippocampal system facilitate acquisition of caudate-dependent win-stay radial maze behavior (Packard et al. 1989, McDonald & White 1993). In addition, pretraining hippocampal system lesions (Matthews & Best 1995) and postposttraining neural inactivation of the dorsal hippocampus (Schroeder et al. 2002) facilitate acquisition of caudate-dependent response learning. The enhancing effect of hippocampal lesions on acquisition of caudate-dependent two-way active avoidance behavior has also been interpreted as resulting from the removal of spatial information processing that would tend to interfere with the task requirement of returning to a spatial location in which electrical shock has recently been administered (O'Keefe & Nadel 1978). In some learning situations, interference with hippocampal memory processes by the caudate nucleus may also occur. Consistent with this suggestion, lesions of the caudate nucleus facilitate acquisition of a spatial Y-maze discrimination task (Mitchell & Hall 1988), perhaps by disrupting the use of a potentially interfering response-learning strategy.

Investigation of potential neurochemical mechanisms that mediate the interaction between basal ganglia and temporal lobe memory systems is at an early stage (Gold et al. 2001, Packard 1999). As previously described, in a plus-maze task that can be acquired using either caudate-dependent response learning or hippocampus-dependent place learning, postposttraining intracerebral infusions of glutamate can bias animals toward the use of a particular memory system (Packard 1999). Other findings suggest that dorsal striatal cholinergic function may also influence the relative efficiency and use of hippocampal and caudate memory systems. For example, increases in acetylcholinetransferase activity in the dorsolateral caudate are negatively correlated with accuracy in a hippocampus-dependent working memory task (Colombo & Gallagher 1998). In addition, in vivo microdialysis reveals that during acquisition of a plus-maze task, a higher ratio of acetylcholine release in the hippocampus relative to the dorsal striatum is associated with the use of place learning on a subsequent probe trial (C. McIntyre, C. K. Marriot, P.E. Gold, submitted). Remarkably, the ratio of acetylcholine release in the hippocampus relative to the dorsal striatum prior to initial training predicts whether rats will later employ place or response learning in the plus maze, which suggests that relative levels of cholinergic activity may in part determine individual differences in the use of these two memory systems (C. McIntyre, C. K. Marriot, P. E. Gold, submitted).

Consideration of memory processes that may be active in the probabilistic classification task suggests that interference between basal ganglia and medial temporal lobe memory systems is also likely to occur in humans. For example, in the probabilistic classification task, episodic memory for a particular trial in which a lower probability outcome occurs would contradict the response based on an S-R habit that has developed across training. For the very first few responses, the subject may select an outcome based on their declarative memory of the reinforcement received when one of the cues present had appeared shortly before. However, as the cue-response habit strengthens, the striatal memory system could guide behavior more accurately with potentially less effort. With extended training, there may

be enough exposure to individual trials to allow declarative knowledge of the task structure to be acquired. At this point, subjects may begin to choose the most associated outcome and begin to probability maximize. Consistent with this suggestion is evidence indicating that patients with medial temporal lobe damage are relatively impaired following extended training in this task (Knowlton et al. 1994). In addition, in some cases of caudate-dependent sequence learning, explicit knowledge of the sequence can impair acquisition as measured by reaction time, which suggests that effortful retrieval of explicit knowledge can interfere with the performance of the implicitly learned sequence.

Direct evidence for the idea that basal ganglia and medial temporal lobe memory systems may compete in some learning situations is provided by human neuroimaging studies employing the probabilistic classification task. During learning of the weather prediction task, activation is present in the caudate nucleus, and there is a concomitant decrease in medial temporal lobe activation relative to the activation present when the subject performs a low-level baseline task such as indicating if more than two cards are present (Poldrack et al. 1999). Furthermore, a recent fMRI study using a design in which activation can be measured on individual trials has shown that activation in the caudate nucleus and medial temporal lobe is negatively correlated within subjects (Poldrack et al. 2001). This study also demonstrates that at the beginning of learning it appears that subjects rely on medial temporal lobe structures; this dependence rapidly declines with training and with an increase in dependence on the striatum.

At present, the factors that may influence the interaction between basal ganglia and medial temporal lobe memory systems are not well understood. The use of various reinforcement/training parameters (e.g., correction versus noncorrection, spaced versus massed trials) has been shown to influence the relative use of hippocampus-dependent place learning and caudate-dependent response learning in the plus-maze task (for review see Restle 1957), and these parameters might affect the interaction between these two memory systems in other situations as well. The nature of the visual environment (e.g., heterogenous versus homogenous surrounds) also influences the type of learning observed in various maze tasks and appears to bias the brain toward the use of hippocampus-dependent or caudate-dependent learning. In the caudate-dependent win-stay radial maze task, for instance, the removal of extra-maze cues enhances task acquisition in brain-intact rats, an effect that is strikingly similar to the effects of damaging the hippocampal system and training rats in this task in the presence of abundant extra-maze cues (Packard & White 1987).

In addition to experimental factors, the neural basis of competitive interference between basal ganglia and medial temporal lobe memory systems is unknown. There are reportedly direct connections between the entorhinal cortex and the neostriatum in the rat that, when stimulated, have been shown to mediate a long phase of inhibition after initial excitation (Finch et al. 1995). Interestingly, there is a report that neuronal activity in the human caudate nucleus shows a similar phenomenon while the subject is performing a declarative memory task. In this study,

patients with Parkinson's disease who had been implanted with depth electrodes in the head of the caudate for therapeutic reasons performed a yes/no recognition task for words that had been studied a few minutes before (Abdullaev & Melnichuk 1997). There was a small initial increase in firing as each test word was presented, followed by 800–1400 msec of a decrease in firing relative to baseline. Communication between the basal ganglia and medial temporal lobe memory systems may occur via output projections to frontal cortical regions that in turn project to the medial temporal lobe. However, there are also direct connections between the basal ganglia and thalamic nuclei projecting to area TE in the inferior temporal lobe, which in turn sends heavy projections to the medial temporal lobe (Middleton & Strick 1996). Although this projection is far smaller than the output to frontal lobe, it could conceivably play a role in mediating the competition between these two systems for behavioral output during performance.

Finally, recent evidence suggests that in some learning situations the amygdaloid complex may influence the relative use of basal ganglia and medial temporal lobe memory systems. Posttraining intrabasolateral amygdala infusions of amphetamine appear to activate efferent amygdala pathways that modulate both caudate-dependent and hippocampus-dependent memory processes (Packard et al. 1994, Packard & Cahill 2001, Packard & Teather 1998). The memory modulatory role of the basolateral amygdala is related in part to the actions of various stress hormones and concomitant emotional arousal (for reviews see Cahill & McGaugh 1998, Packard et al. 1995). Recent evidence indicates that amygdala lesions block the impairing effects of acute stress on spatial memory in the water maze and enhance the use of caudate-dependent S-R memory in a water maze task that can be simultaneously acquired by basal ganglia and hippocampal memory systems (Kim et al. 2001). In addition, in a water plus-maze task, pretraining intrabasolateral amygdala infusions of anxiogenic drugs result in the predominant use of caudate-dependent response learning on a later drug-free probe trial (J.C. Wingard & M.G. Packard, submitted). Taken together, these findings suggest that affective state can influence the relative use of basal ganglia and hippocampal memory systems and that the basolateral amygdala may mediate this modulatory effect of emotion on memory.

BASAL GANGLIA AND TASK SWITCHING

In addition to being a potential site of storage of learned habits or procedures, the basal ganglia also appears to be able to "switch" between various tasks depending on the demands present. This process is also known as the ability to shift cognitive set in response to the environment. Patients with damage to basal ganglia circuitry exhibit performance costs that are greater than controls when switching from one task to another. For example, patients with Huntington's disease were impaired on a match-to-sample task in which they needed to choose the sample from among three distracters (Lawrence et al. 2000). These distracters included items that were

identical to the sample along one dimension (e.g., color or form). The patients made significantly more errors than controls, chiefly because they picked these similar distracters. This deficit was even present when there was no delay between the sample and the choice phase, which suggests that it is not due to a general memory problem. Rather, it seems that patients with Huntington's disease have difficulty shifting attention between dimensions and may simply respond based on matching along a single dimension. In addition, neuroimaging evidence suggests that frontal corticostriatal loops are activated when subjects must select between many possible responses (Desmond et al. 1998). In this study, subjects were required to complete three letter word stems (e.g., STR—) with the first word that came to mind. On blocks in which there were many possible responses, there was greater activation in the left middle frontal gyrus and left caudate nucleus than on blocks in which there was only one valid response. Thus, corticostriatal loops may play a role in selection between alternative responses.

The ability to readily switch between learned stimulus response associations or procedures would seem to be a necessary component of many complex executive tasks such as planning, problem solving, and strategizing. Because these executive functions rely on prefrontal cortex, the task-switching functions of the basal ganglia may make a critical contribution to executive abilities via corticostriatal loops. Patients with Parkinson's and Huntington's diseases generally exhibit deficits in executive function; these deficits are more pronounced in Huntington's disease. Although direct involvement of prefrontal cortex may contribute to these deficits in both patient groups, it appears that striatal dennervation in Parkinson's disease is highly predictive of set-shifting impairments (Marie et al. 1999).

CONCLUSIONS

Decades of research on the anatomy, neurochemistry, and neurophysiology of the basal ganglia have refined our understanding of the role of this brain region in motor behavior. However, the idea that the basal ganglia function strictly as a motor system is no longer supported by neurobehavioral research. Extensive evidence now indicates that one behavioral function of the basal ganglia involves participation in learning and memory processes. In particular, several lines of evidence are consistent with the hypothesis that the basal ganglia (specifically the dorsal striatum) mediate a form of learning in which associations between stimuli and responses (i.e., S-R habits) are acquired. Studies employing brain-lesion techniques in experimental animals have dissociated the S-R mnemonic role of the basal ganglia from those of a cognitive medial temporal lobe memory system in which the hippocampus is a primary component. Behavioral pharmacology experiments indicate a role for dopaminergic, cholinergic, and glutamatergic neurotransmission in the mnemonic functions of the basal ganglia, and various forms of long-term synaptic plasticity (i.e., LTD, LTP) have been identified in this brain region. Neuropsychological studies of humans with Parkinson's and Huntington's

disease, as well as human neuroimaging studies, have provided some support for the role of the basal ganglia in S-R habit learning. Finally, evidence suggests that in a given learning situation basal ganglia and medial temporal lobe systems are activated simultaneously, and recent studies have begun to examine the nature of the interaction between these brain regions in learning and memory.

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