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The Role of the Basal Ganglia in Learning and Memory

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Textbooks in neuroscience generally discuss the basal ganglia as a component of the motor system. The strongest support for this idea comes from the study of patients with basal ganglia disorders, in which disorders of controlled movement are pronounced. Patients with Huntington's disease exhibit involuntary writhing and jerking movements, whereas patients with Parkinson's disease exhibit muscular rigidity, tremor, slowness, and difficulty initiating movement. However, the fact that these patients exhibit cognitive deficits as well suggests that the basal ganglia also play a role in abilities that are not directly motor.

The anatomical connections of the basal ganglia are consistent with a role in influencing the pyramidal motor system. The caudate and putamen receive projections from virtually all cortical regions. These projections are organized in an anterior-to-posterior fashion, with projections from the frontal cortex terminating in the head of the caudate and putamen (neostriatum), and projections from the occipital lobe terminating in the tail of the caudate. The primary output of the basal ganglia is through the internal globus pallidus, which projects to thalamic nuclei and brainstem motor nuclei. The thalamic target nuclei include the ventral anterior and ventrolateral nuclei, which project to the primary and supplementary motor cortices. Thus the basal ganglia are in a position to influence the pyramidal motor system, based on input from diverse cortical regions including the motor cortex itself. However, the mediodorsal nucleus of the thalamus is also targeted by the globus pallidus, and this nucleus projects to regions in the frontal lobe that play a role in cognitive functions that are nonmotor. The basal ganglia are thus intimately interconnected with almost all frontal lobe regions.

The relationship between the frontal lobes and the basal ganglia has been characterized in terms of loops from the frontal cortex to the striatum, the globus pallidus, and the thalamus, and then back to the frontal cortex. Five distinct loops have been identified, each appearing to be relatively anatomically segregated from the others at all levels of the circuit (Alexander, DeLong, & Strick, 1986). The motor circuit originates in the supplementary motor cortex, and the oculomotor circuit originates in the frontal eye fields. The other three circuits have been thought to be involved in cognition and emotion, and to originate

in the dorsolateral, orbitofrontal, and cingulate cortices (Mega & Cummings, 1994). Thus there is overwhelming evidence based on neuroanatomy alone that the basal ganglia play a role in cognition.

Findings from neuropsychological patients suggest that these cognitive circuits are functionally important. Patients with Huntington's disease or Parkinson's disease often exhibit deficits in executive function, as well as cognitive slowing and mood disorders consistent with frontal lobe involvement (Brandt & Butters, 1986; Brown & Marsden, 1988; Taylor, Saint-Cyr, & Lang, 1986). In Huntington's disease, degeneration occurs within the neostriatum; in Parkinson's disease, degeneration occurs in the substantia nigra, a major input to the neostriatum. Although patients with Huntington's disease exhibit more profound cognitive deficits (dementia is one clinical characteristic of the disease), and the two patient groups have quite different motor abnormalities, both groups show deficits on tests of frontal lobe function, such as the Wisconsin Card Sorting Test and measures of verbal fluency.

Patients with basal ganglia disorders also exhibit impairments in declarative memory that are consistent with frontal lobe dysfunction (Butters, Wolfe, Granholm, & Martone, 1986; Taylor, Saint-Cyr, & Lang, 1990). For example, these patients exhibit deficits in recall that are disproportionate to their recognition abilities, and they show decreased use of clustering strategies in recall. These patient groups have shown deficits in nondeclarative memory tasks as well. Early demonstrations of this occurred in the domain of motor skill learning. For example, patients with Huntington's disease were found to be impaired relative to control participants in the rotary-pursuit learning task (Gabrieli, Stebbins, Singh, Willingham, & Goetz, 1997; Heindel, Butters, & Salmon, 1988). Patients with Parkinson's disease have also been found to exhibit deficits in motor learning (Haaland, Harrington, O'Brien, & Hermanowicz, 1997; Schugens, Breitenstein, Ackermann, & Daum, 1998; Soliveri, Brown, Jahansahi, Caraceni, & Marsden, 1997). Plasticity in motor cortical regions appears to be a substrate for motor skill learning, so the basal ganglia may play a minor role in some cases when learning relies on cortical systems.

Motor skill learning is one of the classic preserved abilities both in amnesic patients and in patients with Alzheimer's disease (Dick, Nielson, Beth, Shankle, & Cotman, 1995; Tranel, Damasio, Damasio & Brandt, 1994). Thus the performance of patients with basal ganglia damage and patients with medial temporal lobe damage may be doubly dissociated from each other on measures of motor skill learning and recognition.

The interpretation of problems with motor skill learning in these patients is complicated by the fact that their motor performance is severely impaired relative to that of control subjects. Because baseline performance is often not equated, it can be difficult to compare learning for the two groups. However, deficits in these patients have also been observed in a number of other nondeclarative learning tasks that do not directly involve the performance of motor skills. In one study, patients with Huntington's disease were impaired at demonstrating the normal influence of recent stimuli when making weight judgments (Heindel, Salmon, & Butters, 1991). Normal subjects will tend to judge weights as being heavier if they have been previously exposed to lighter weights, and they will judge weights as lighter if they have previous experience with heavy weights. This biasing effect does not depend on declarative memory for lifting the biasing weights, because amnesic patients show this effect to the same extent as controls (Benzing & Squire, 1989). This biasing effect may be due to a mismatch between the actual weight and the motor program used to lift the weight that has been formulated based on recent experience with other weights. Patients with Huntington's disease may not incorporate this experience in reformulating the motor program used to lift the weights, and thus may be insensitive to biasing.

Patients with Huntington's disease also appear to have difficulty with perceptual-motor learning tasks that are learned normally by amnesic patients and patients with Alzheimer's disease. These include prism adaptation, in which subjects learn to decrease visually guided reaching error when wearing prism goggles (Paulsen, Butters, Salmon, Heindel, & Swenson, 1993). Learning this skill relies on the interface between the visual and motor systems. Other evidence suggests that patients with Huntington's disease or Parkinson's disease have difficulty learning to read mirror-reversed text (Koenig, Thomas-Anterion, & Laurent, 1999; Martone, Butters, Payne, Becker, & Sax, 1984). Although this skill probably depends on learning specific transformed letter identities, learning to scan the stimuli appropriately may also play a role.

One skill learning task that has been studied extensively with basal ganglia patients is the serial reaction time task. In this task, subjects see a stimulus move from location to location on a screen, and their task is to press a key corresponding to that location as quickly as possible. Unbeknownst to the subjects, the stimuli do not appear randomly, but rather appear according to a specific sequence. It can be shown that the reaction times of both normal subjects and amnesic patients benefit from the sequence, because if the stimuli are abruptly switched to a random sequence, there is a slowing of performance that is identical for the two groups (Nissen & Bullemer, 1987; Reber & Squire, 1994). Patients with Huntington's disease are impaired at this implicit sequence-learning task (Knopman & Nissen, 1991; Willingham & Koroshetz, 1993). Patients with Parkinson's disease have also been reported to show deficits, although these deficits may be apparent only when extensive training is used (see Figure 11.1) (Doyon et al., 1997; Ferraro, Balota, & Connor, 1993; Helmuth, Mayr, & Daum, 2000; Jackson, Jackson, Harrison, Henderson, & Kennard, 1995; Pascual-Leone et al., 1993; Sommer, Grafman, Clark, & Hallett, 1999).

Performance in the serial reaction time task is generally measured as the time required to press a key in response to a stimulus. In that sense, it is a motor learning task. However, it appears that the sequence information that is learned is more abstract than a series of movements. Instead, subjects learn a series of response locations, as indicated by the finding that there is excellent transfer of sequence learning to a new set of motor effectors, but poor transfer when new response locations are mapped onto the training sequence (Willingham, 1999; Willingham, Wells, Farrell, & Stemwedel, 2000). The fact that patients with basal ganglia disorders are impaired in sequence learning suggests that their impairment involves the implicit learning of information that is not specific to a motor response. The successive response locations gradually become associated with each other as a result of practice. Thus one important element of the type of learning that is dependent on the basal ganglia may be this gradual learning of associations. Deficits in motor skill learning in patients with basal ganglia disorders have also been interpreted in this way. Performance of motor actions depends on the learning of a sequence of components, and one component becomes associated with the subsequent component through practice. Fluid performance of the motor skill would result from a tight association between each component and its subsequent component through plasticity in the basal ganglia system (Graybiel, 1995). The contents of motor skill learning are quite inaccessible to declarative knowledge. Likewise, although the elements of a spatial sequence may be correctly recognized by some subjects, this knowledge is not necessary for improvement in performance as measured by reaction times.

The idea that patients with basal ganglia disorders may have an impairment in implicit associative learning has found support in work with experimental animals. Damage to the caudate nucleus in rats results in deficits in the "win-stay" radial-arm maze task, in which rats learn to traverse maze arms in which a cue is present in order to receive a food

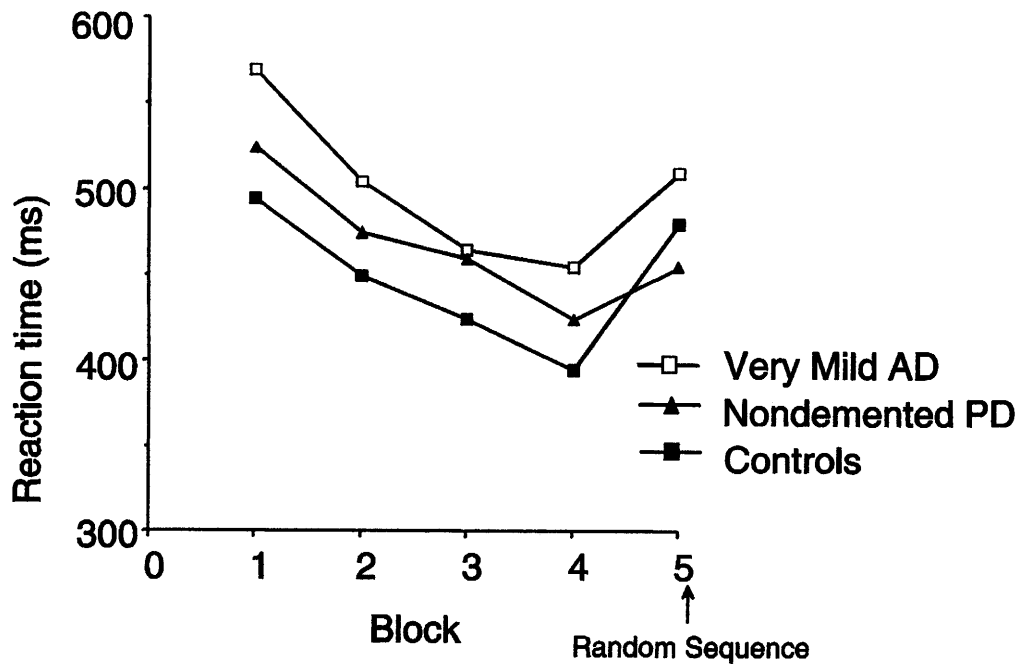


FIGURE 11.1. Patients with very mild Alzheimer's disease (AD), nondemented patients with Parkinson's disease (PD), and normal control subjects all showed improvement across blocks in the serial reaction time task when a fixed, 10-item sequence of locations was used. The PD patients appeared to have acquired less sequence-specific information than the other groups, because they showed a smaller reaction time increase when the sequence was switched to a random presentation of locations. Data from Ferraro, Balota, and Connor (1993).

reward (McDonald & White, 1994; Packard, Hirsh, & White, 1989). Performance on this same task is unaffected by lesions of the hippocampus or related structures. Rats appear to learn stimulus–response (S-R) associations in this task. That is, rather than learning an association between the cue and the food reinforcer, rats appear to learn to associate the cue with the arm entry response (Sage & Knowlton, 2000). The role of the food reinforcer is simply to strengthen this connection during training. This type of learning has historically been referred to as “habit learning” (see Mishkin & Petrie, 1984, for a review). Several researchers have suggested that other tasks that have been shown to be dependent on the caudate nucleus in experimental animals, such as some forms of discrimination learning, are also examples of habit learning (Battig, Rosvold, & Mishkin, 1962; Packard & McGaugh, 1992; Teng, Stefanacci, Squire, & Zola, 2000).

These studies of habit learning in experimental animals raise the question of whether there is a similar learning system in humans that is also dependent on the basal ganglia. This question cannot be answered in the obvious way of giving the same tests to humans that have been used with experimental animals, because humans appear to learn most discrimination tasks in a few trials using declarative memory, and not in the gradual manner that is typical in animals (Squire, Zola-Morgan, & Chen, 1988). One area in which the habit-learning system may be operating in humans is in the learning of categories in which the membership rules are not easy to verbalize, and thus are not easy to discern through

hypothesis testing or memory for specific trials. One example is a task in which the subject must classify intersecting lines into two categories (Figure 11.2). Category membership can be defined by a linear (and thus easily verbalizable) relationship between the horizontal and vertical lines. Learning this type of classification problem appears to be intact in patients with Parkinson's disease, and may depend on the integrity of frontal lobe function (Maddox & Filoteo, in press). In contrast, when category membership is defined by a nonlinear relationship between horizontal and vertical line lengths, amnesic patients appear to learn to categorize these stimuli as well as normal subjects do, whereas patients with Parkinson's disease exhibit impaired performance (Filoteo, Maddox, & Davis, 2001; Maddox & Filoteo, in press).

It is important to note that patients with Parkinson's disease and Huntington's disease do not have a global deficit in implicit category learning. These patients appear to perform normally on tasks in which subjects are presented with a set of stimuli that belong

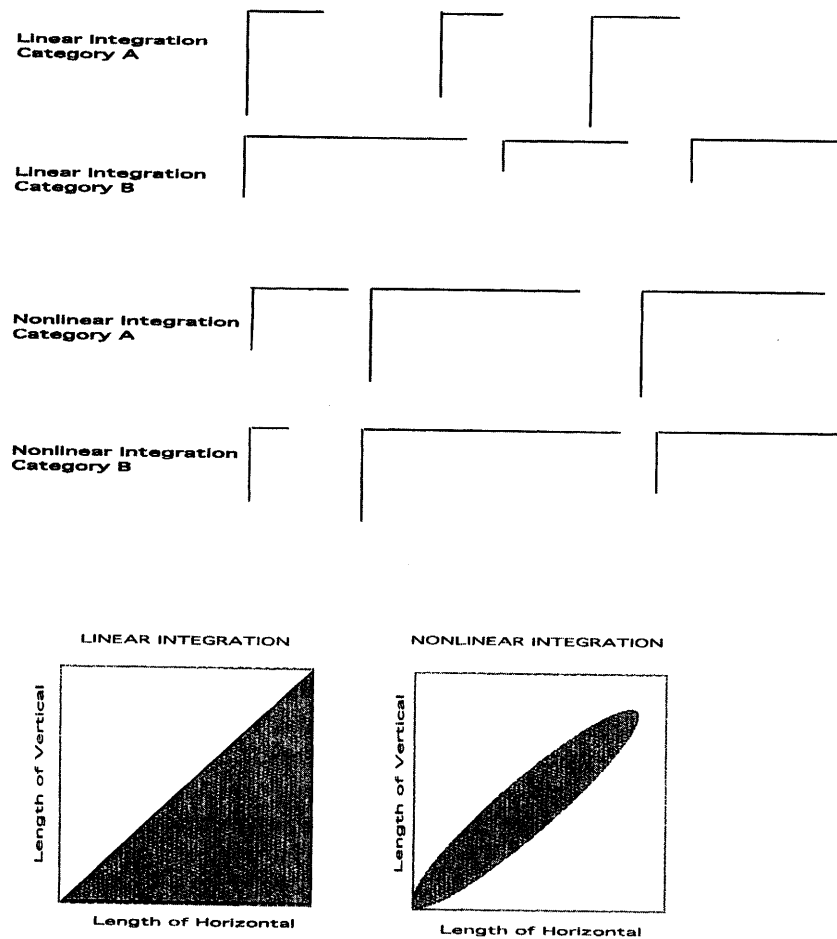


FIGURE 11.2. Category structures from Maddox and Filoteo (in press). Examples of categories defined by a linear categorization rule (vertical length greater or less than horizontal length; diagram on the left) and a nonlinear categorization rule (diagram on the right). In both cases, the shaded area in the diagrams refers to members of category A.

in one category (such as dot patterns or letter strings), and then are asked to classify whether or not new stimuli are part of the same category or not (Knowlton et al., 1996; Reber & Squire, 1999). In these tasks, the subjects receive no feedback during training and do not classify the items into two different categories. Thus subjects do not need to learn associations in these tasks; rather, they can respond based on the fact that items similar to the trained category can be processed more efficiently than dissimilar items, due to perceptual fluency's resulting from exposure to items during training. This type of learning may have a locus in cortical areas involved in perception, and thus should not be greatly affected by disorders of the basal ganglia. Neuroimaging data support a cortical locus for this type of category learning (Reber, Stark, & Squire, 1998).

Another strategy for developing habit-learning tasks in humans has been to use probabilistic associations between cues and correct responses. In such a task, declarative memory for each individual trial is not useful. Rather, correct responding can result from gradually building up an association across multiple trials. This gradual associative learning is thought to be characteristic of the caudate-dependent habit-learning tasks studied in animals. In a "weather prediction" version of the probabilistic classification task, the stimuli are cards with geometric shapes. On each trial, one to three cards appear, and the subject must guess whether the outcome will be sunny or rainy weather. Each card is associated with one of the two outcomes 60–85% of the time. Although subjects often feel as if they are guessing, they gradually learn to select the most associated outcome for each combination across trials. Amnesic patients perform as well as controls on this task, demonstrating that declarative memory of the cue–outcome associations is not necessary for normal performance (Knowlton, Squire, & Gluck, 1994). In contrast, patients with Huntington's disease and Parkinson's disease exhibit impaired learning on this task (Knowlton, Mangels, & Squire, 1996; Knowlton et al., 1996). The contrasting performance of patients with medial temporal lobe damage and patients with basal ganglia disorders on this task is reminiscent of the findings in habit-learning tasks used in animals. Moreover, the double dissociation between the performance of amnesic patients and patients with Parkinson's disease on the probabilistic classification task and a declarative memory questionnaire about the study episode establishes that these two forms of learning are dependent on distinct systems.

In the probabilistic classification task, it is not the case that the cue–outcome associations are fundamentally inaccessible to declarative memory. In fact, with extended training, individuals with intact memory are able to acquire declarative, flexible knowledge of the structure of the task (Reber, Knowlton, & Squire, 1996). The pattern of neuropsychological data is consistent with the finding that declarative learning can eventually influence performance on this task. With more than about 100 trials of training, control subjects begin to outperform amnesic patients, and patients with Parkinson's disease who have intact declarative memory begin to catch up to the level of control subjects.

Evidence from functional neuroimaging is consistent with neostriatal involvement in skill-learning and habit-learning tasks. The neostriatum is generally activated during performance of the serial reaction time task when there is an implicitly learned sequence, compared to blocks of trials in which locations are presented randomly (Peigneux et al., 2000; Rauch et al., 1997). Learning in the probabilistic classification task is also associated with activation in the caudate nucleus (Poldrack, Prabhakaran, Seger, & Gabrieli, 1999). This activation occurs early in training, and is accompanied by a decrease in medial temporal lobe activation. These findings suggest the intriguing possibility that the declarative and habit-learning systems may be mutually inhibitory. The medial temporal lobe memory system appears to be specialized for rapid learning of information about individual trials,

whereas the neostriatal habit system appears to be specialized for gradual learning across many trials. Thus the two systems may occasionally be in conflict, if the response based on an implicitly learned habit differs from a response based on declarative learning about a recent episode. (See Ashby, Alfonso-Reese, Turken, & Waldron, 1998, for a computational model of basal ganglia function in which competition between implicit and declarative rule learning is a critical feature.)

A clear example of such conflict has been demonstrated in rats tested in a plus-shaped maze. Animals start from one arm of the maze and food is placed at the end of an arm 90 degrees from the start arm. Rats quickly learn the location of the reward in the maze. On transfer trials from the opposite start arm, they enter the same arm that had been reinforced (thus turning in the direction opposite from the direction they had turned during training). However, with extended training, the rats appear to respond based on an S-R habit. That is, when starting from the opposite end of the maze, they continue to make a turn in the same direction as they had during training. If a local anesthetic is injected into the caudate nucleus after extended training, rats will again respond based on memory for location and will turn in the opposite direction when started from the opposite end of the maze (Packard & McGaugh, 1996). Thus, with extended training, the S-R habit appears to overwhelm the more rapidly learned spatial memory, but the spatial memory can be "unmasked" if neostriatal function is compromised.

It is important to note that there are significant differences between the probabilistic classification task and the maze tasks used to measure habit learning in rats. In the case of the tasks used in animals, habit learning is evident only after many trials, and its control over behavior increases with extended training. However, for the probabilistic classification task, extended training appears to allow subjects to develop declarative representations that exert some control over behavior. This may be due to the way human subjects approach the task; subjects are likely to be motivated to acquire conscious knowledge of the task structure, and the probabilistic task structure makes this more difficult until later in training.

Another potential difference between the habit-learning tasks used in experimental animals and the probabilistic learning task studied with humans is the extent to which learning consists of an S-R association. In the win-stay task, for example, rats appear to learn an association between a cue and a motor response (running down an arm). In the probabilistic classification task, what is learned is not a specific motor response, but rather a tendency to react in a particular way to a cue. Subjects may still be learning S-R associations, but the response is a more abstract tendency to make a particular choice given a cue, independently of the motor response selected.

Another cognitive domain in which patients with Parkinson's disease have deficits is in switching between tasks. For example, these patients have difficulty with the Wisconsin Card Sorting Test, in which the subject must shift from sorting cards along one dimension (i.e., color) to another (i.e., shape). One study showed that patients with Parkinson's disease had greater difficulty shifting set when subjects were switched to sorting along a dimension that had been present previously (and thus was subject to learned irrelevance; Owen et al., 1993). For example, they had difficulty shifting from sorting to color to sorting to shape if differences in shape had been present in the previous sorting trials. Medicated patients with Parkinson's disease performed much better if the irrelevant dimension in the previous sorting trials was not present after the switch. Thus there was no impairment if the stimuli that were being sorted according to color differed in terms of number and not shape, and then differed in terms of shape and color after the switch to the shape-sorting task.

In another study, patients and control subjects were asked to switch between a color-naming and a shape-naming task. Reaction time suffered more for the patients than it did for controls when they switched tasks than when they performed the same task a second time. The presence of an irrelevant dimension (such as differences in color during the shape-naming task or differences in shape during the color-naming task) also slowed their performance compared to controls (Hayes, Davidson, Keele, & Rafal, 1998).

These deficits in set shifting may be related to the deficits in habit formation discussed previously. Sorting or naming based on a given dimension could be viewed as performance of an S-R habit. Putting a card with yellow circles into the "yellow" pile, or saying "yellow" in response to a stimulus, is based on an association between the cue and the appropriate response. These associations may be maintained in short-term memory, and thus they differ from skills and habits that are stored in long-term memory and are later retrieved. Nevertheless, the basal ganglia may be important in the online production of these S-R behaviors. If the links between the stimulus and the response are tenuous, switching between them may be more difficult. Although these behaviors may be produced by cortical systems, the basal ganglia may allow these S-R associations to be produced more fluently in an automatic fashion.

This question naturally arises: To what extent do deficits in habit learning or implicit category learning have a negative impact on the everyday lives of patients with basal ganglia disorders? The types of tasks that have been used in the laboratory to demonstrate deficits in these patients are generally quite unlike anything encountered in daily life. However, it seems likely that these implicit learning deficits are clinically significant. Although rigidity, tremor, and slowness of movement are the most debilitating symptoms of Parkinson's disease, these patients also exhibit bradyphrenia, or slowness of thought, under many circumstances (Hanes, Pantelis, Andrewes, & Chiu, 1996; Pate & Margolin, 1994). This slowness may arise because the basal ganglia are important for performing tasks automatically. Patients must therefore perform in a deliberate fashion tasks that would ordinarily be performed by habit.

To put memory systems in an evolutionary context, it has been argued that the pressures arising from managing increasingly complex social networks have played the primary role in shaping human cognition (Dunbar, 2000; Tomasello, 2000). The everyday cognitive problem that the basal ganglia learning system may be specialized to solve is the acquisition of the ability to use nonverbal information to make automatic social inferences. Nonverbal communication has been shown to have a major influence on one's inferences about social situations. Our knowledge and ability to decode and generate nonverbal social cues are implicit, for the most part. For example, we are almost totally unaware of the information that leads us to feel that other people do or do not like us, based on their verbal tone and "body language." Learning to read (and perhaps produce) these cues presumably arises gradually from social experience throughout life. The basal ganglia may be the site where these nonverbal cues become linked with appropriate responses (Lieberman, 2000). There are several studies suggesting that patients with Parkinson's disease are impaired in decoding nonverbal communication, such as prosody (Benke, Bosch, & Andree, 1998; Speedie, Brake, Folstein, Bowers, & Heilman, 1990). Indeed, the depression that commonly occurs with basal ganglia disorders may even be exacerbated by the impaired processing of the positive regard shown by others.

The study of the basal ganglia in implicit learning may prove to be an area of convergence among neuropsychology, behavioral neuroscience, and the emerging field of social-cognitive neuroscience. Links have already been made between the effects of basal ganglia damage in humans and experimental animals. The suggestion that the cognitive processes

that depend on the basal ganglia are critical in the domain of social behavior is an intriguing possibility. The basal ganglia may turn out to play a much greater role in human mental activity than previously thought.

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In another study, patients and control subjects were asked to switch between a color-naming and a shape-naming task. Reaction time suffered more for the patients than it did for controls when they switched tasks than when they performed the same task a second time. The presence of an irrelevant dimension (such as differences in color during the shape-naming task or differences in shape during the color-naming task) also slowed their performance compared to controls (Hayes, Davidson, Keele, & Rafal, 1998).

These deficits in set shifting may be related to the deficits in habit formation discussed previously. Sorting or naming based on a given dimension could be viewed as performance of an S-R habit. Putting a card with yellow circles into the "yellow" pile, or saying "yellow" in response to a stimulus, is based on an association between the cue and the appropriate response. These associations may be maintained in short-term memory, and thus they differ from skills and habits that are stored in long-term memory and are later retrieved. Nevertheless, the basal ganglia may be important in the online production of these S-R behaviors. If the links between the stimulus and the response are tenuous, switching between them may be more difficult. Although these behaviors may be produced by cortical systems, the basal ganglia may allow these S-R associations to be produced more fluently in an automatic fashion.

This question naturally arises: To what extent do deficits in habit learning or implicit category learning have a negative impact on the everyday lives of patients with basal ganglia disorders? The types of tasks that have been used in the laboratory to demonstrate deficits in these patients are generally quite unlike anything encountered in daily life. However, it seems likely that these implicit learning deficits are clinically significant. Although rigidity, tremor, and slowness of movement are the most debilitating symptoms of Parkinson's disease, these patients also exhibit bradyphrenia, or slowness of thought, under many circumstances (Hanes, Pantelis, Andrewes, & Chiu, 1996; Pate & Margolin, 1994). This slowness may arise because the basal ganglia are important for performing tasks automatically. Patients must therefore perform in a deliberate fashion tasks that would ordinarily be performed by habit.

To put memory systems in an evolutionary context, it has been argued that the pressures arising from managing increasingly complex social networks have played the primary role in shaping human cognition (Dunbar, 2000; Tomasello, 2000). The everyday cognitive problem that the basal ganglia learning system may be specialized to solve is the acquisition of the ability to use nonverbal information to make automatic social inferences. Nonverbal communication has been shown to have a major influence on one's inferences about social situations. Our knowledge and ability to decode and generate nonverbal social cues are implicit, for the most part. For example, we are almost totally unaware of the information that leads us to feel that other people do or do not like us, based on their verbal tone and "body language." Learning to read (and perhaps produce) these cues presumably arises gradually from social experience throughout life. The basal ganglia may be the site where these nonverbal cues become linked with appropriate responses (Lieberman, 2000). There are several studies suggesting that patients with Parkinson's disease are impaired in decoding nonverbal communication, such as prosody (Benke, Bosch, & Andree, 1998; Speedie, Brake, Folstein, Bowers, & Heilman, 1990). Indeed, the depression that commonly occurs with basal ganglia disorders may even be exacerbated by the impaired processing of the positive regard shown by others.

The study of the basal ganglia in implicit learning may prove to be an area of convergence among neuropsychology, behavioral neuroscience, and the emerging field of social-cognitive neuroscience. Links have already been made between the effects of basal ganglia damage in humans and experimental animals. The suggestion that the cognitive processes