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Chapter 13

CATEGORY LEARNING IN PARKINSON'S DISEASE

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ABSTRACT

An understanding of the early cognitive deficits in patients with Parkinson's disease (PD) could provide better insight into the nature of the disease as well as its future course. One area of study that holds considerable promise is the study of category learning. Much research has examined the neurobiological basis of category learning and it is now well-established that multiple cognitive and brain systems are involved in learning different types of categorization tasks. One broad class of category learning tasks that have been examined include those that are learned using an explicit, verbalizable strategy, whereas another broad class includes tasks that are learned using some form of implicit learning that occurs outside of conscious awareness. This chapter reviews past research examining both explicit and implicit category learning in nondemented patients with PD. It is demonstrated that PD patients can be impaired on both explicit and implicit category learning tasks, but for very different reasons: impairment on explicit tasks appears to be related to deficits in attentional processes, whereas impairments on implicit tasks occur when the rule theoretically requires a greater degree of representation within the striatum. It is also shown that PD patients' impairment on certain implicit tasks is highly predictive of future global cognitive decline, a finding that highlights the utility of studying category learning in this disease.

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INTRODUCTION

It is well accepted that, along with the classic motor symptoms (tremor, rigidity, bradykinesia, postural instability), cognitive deficits are highly prevalent in patients with Parkinson's disease (PD; Owen, 2004). Estimates of dementia range across studies, but a recent review suggests that 24-31% of patients with PD meet formal criteria for dementia at a given time (Aarsland, Zaccai, & Brayne, 2005), and other studies suggest that up to 78% of PD patients can become demented over an 8-year period (Aarsland, Andersen, Larsen, Lolk, & Kragh-Sorensen, 2003). It is also now well established that PD patients can experience significant cognitive impairment in the absence of a frank dementia. For example, relative to healthy controls, nondemented PD patients are impaired in a variety of cognitive areas, such as working memory (Gilbert, Belleville, Bherer, & Chouinard, 2005; Owen *et al.*, 1993; Owen, Iddon, Hodges, Summers, & Robbins, 1997; Postle, Jonides, Smith, Corkin, & Growdon, 1997), attention (R. G. Brown & Marsden, 1988; Filoteo & Maddox, 1999; Filoteo, Rilling, & Strayer, 2002; Sharpe, 1990), set shifting (Cools, Barker, Sahakian, & Robbins, 2001; Cronin-Golomb, Corkin, & Growdon, 1994; Hayes, Davidson, Keele, & Rafal, 1998; Owen, Roberts, Polkey, Sahakian, & Robbins, 1991), and procedural-based learning (Jackson, Jackson, Harrison, Henderson, & Kennard, 1995; Pascual-Leone *et al.*, 1993; Vakil & Herishanu-Naaman, 1998), to name a few. These deficits are often attributed to dysfunction within striatal-cortical circuits that are disrupted very early in the course of the disease (Dubois & Pillon, 1997; Muslimovic, Post, Speelman, & Schmand, 2005; Owen, 2004). Importantly, the understanding of the initial cognitive deficits in PD patients will provide a clearer picture of the nature and progression of future cognitive loss and possible dementia in this disease. Thus, the study of cognition in nondemented PD patients is crucial.

One research area that holds considerable promise in helping to better understand PD patients' early cognitive deficits is the study of category learning. Categorization is involved in learning to associate similar stimuli with one another to organize our world and help guide behavior, and as such, is highly important for our day to day activities. An important advancement over the last 10 years has been the increasing evidence for the existence of multiple category learning systems, each of which is best suited to learning a specific type of categorization problem (Ashby, Alfonso-Reese, Turken, & Waldron, 1998; Nosofsky, Palmeri, & McKinley, 1994; E. E. Smith & Sloman, 1994). Two forms of category learning that have been examined in PD are implicit and explicit category learning (see Figure 1). Past behavioral and functional neuroimaging work with normal participants and various patient populations provides extensive evidence for the distinction between implicit and explicit category learning (Ashby *et al.*, 1998; Filoteo, Maddox, Simmons *et al.*, 2005; Filoteo, Simmons, Zeithamova, Maddox, & Paulus, 2006; Knowlton & Squire, 1993; Maddox, Filoteo, Hejl, & Ing, 2004; Maddox, Filoteo, & Lauritzen, 2007; Maddox, Filoteo, Lauritzen, Connally, & Hejl, 2005; Maddox, O'Brien, Ashby, & Filoteo, 2007; Nomura *et al.*, 2007; E. E. Smith, Patalano, & Jonides, 1998; E. E. Smith & Sloman, 1994). Explicit category learning is dependent on hypothesis generation, logical reasoning, working memory and executive attention. Tasks that measure explicit category learning are often referred to as *rule-based* tasks, because there is typically a verbalizable "rule" that defines category membership. The learning of rule-based tasks is believed to be mediated within an anterior brain network that includes the dorsolateral frontal lobes and the anterior caudate nucleus (Ashby *et al.*, 1998), regions that are often impacted early in the course of PD.

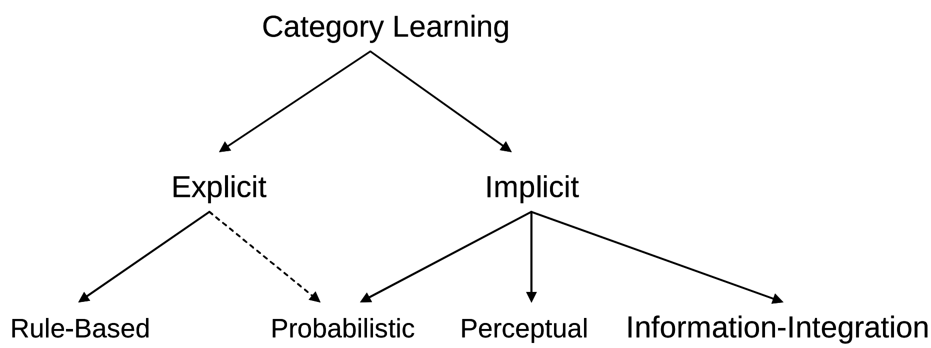

Figure 1. Classification of explicit and implicit category learning tasks.

In contrast, there are several forms of implicit category learning in which a participant can learn categories without having any conscious awareness of the category structures. Some of the tasks that have been used to examine implicit category learning in PD are *information-integration tasks*, *probabilistic learning tasks*, *prototype distortion tasks*, *and artificial grammar learning tasks*. Information-integration category learning tasks are thought to be learned via a procedural-based learning system that depends on a dopamine reward-mediated signal that associates a perceptual stimulus with a specific response (Wickens, 1990), and is thought to take place within a posterior brain network including the inferior temporal lobe and the posterior caudate nucleus (Ashby & Maddox, 2005; Nomura *et al.*, 2007). Probabilistic category learning tasks (e.g., the Weather Prediction Task) are also believed to depend on an implicit learning system in which information about the probability of category membership is learned across multiple trials. Prototype distortion tasks and artificial grammar learning tasks, on the other hand, are thought to be learned through a perceptual-based priming system that is mediated within posterior visual cortices (P. J. Reber & Squire, 1999; P. J. Reber, Stark, & Squire, 1998).

Given the nature and distribution of pathology in PD, it is not surprising that these patients are impaired on a variety of category learning tasks. For example, dopamine appears to be important in reward-mediated learning, so it might be expected that PD patients who, by definition, have a loss of dopamine-producing cells within the substantia nigra, would be impaired on tasks that are learned through feedback. Similarly, given the impact that PD has on striatal structures such as the caudate and putamen (via loss of dopamine input to these regions), it would not be surprising that these patients are impaired on any explicit or implicit category learning task that likely relies on those structures for learning. However, despite the finding that PD patients are impaired on a variety of category learning tasks, a number of important findings have been reported over the last 5 years that have enabled the nature of their deficits to be more clearly delineated, thus allowing one to describe in more specific terms why PD patients are impaired in some, but not all, aspects of category learning. This information has not only extended our knowledge regarding our understanding of this disease, but has also informed the cognitive neuroscience of normal category learning processes.

In this chapter, we review our previous work, and the work of other investigators, that has examined explicit and implicit category learning in nondemented patients with PD. In one section, we discuss previous studies in which explicit category learning was examined using both traditional clinical neuropsychological measures as well as experimental measures. In that section, we also address some conflicts in the literature regarding the potential underlying mechanism(s) of PD patients' explicit learning deficits. Next, we review the implicit category learning literature and address controversies regarding the conditions under which PD patients are impaired in learning implicitly based category structures. Finally, we discuss the potential clinical relevance of better understanding category learning deficits in PD.

PERCEPTUAL CATEGORIZATION TASK

In the majority of our category learning studies, we have used the perceptual categorization task first developed by Ashby and Gott (Ashby & Gott, 1988) in which individuals are presented with simple stimuli and asked to learn to categorize them into distinct groups. The stimuli often consist of lines that vary in length or orientation or Gabor patches that vary in orientation and spatial frequency (see Figures 2 and 3). In this task, participants are presented with a stimulus and are asked to categorize it into Category A or Category B. Once a response is made, the participant is given immediate corrective feedback. Prior to the experiment, a large number of stimuli are sampled randomly from specific underlying category distributions. Figure 2 displays an example of these category distributions from one of our studies in which the stimuli were Gabor patches that varied in orientation and spatial frequency. Each stimulus can be represented as a unique point in two-dimensional space. In Figure 2, the x-axis represents the spatial frequencies of the patch and the y-axis represents the orientation of the patch. Black squares represent Category A stimuli and open circles represent Category B stimuli. The arrows in Figure 2 link a sample stimulus with its representation in this two-dimensional stimulus space. In these studies, a single optimal categorization rule can be derived. The form of the rule is determined by the relationship between the two category distributions, and thus, the two stimulus attributes. The solid line in Figure 2 represents the optimal categorization rule. A participant who uses this rule will maximize long-run accuracy. Given the distribution of the Category A and B stimuli, and the optimal bound, the rule that best describes category membership in Figure 2 is a unidimensional rule in which Gabor patches with lower spatial frequencies (wider bars) are members of Category A, and patches with higher spatial frequencies (narrower bars) are members of Category B.

A major advantage in using the perceptual categorization task is that it allows us to examine different classes of categorization rules, such as implicit and explicit rules, by simply changing the distribution of the stimuli within the categories. Specifically, the rule depicted in Figure 2 is an explicit rule because the optimal rule that defines category membership (depicted as the sold line) can be easily verbalized. In essence, optimal performance requires that the participant learn to attend to only the spatial frequency of the stimuli and identify the cut-off width that best separates the two categories. This rule can be verbalized as "categorize stimuli with wide bars into Category A, and categorize stimuli with narrow bars into Category B". In contrast, Figure 3 depicts two examples of implicit rules-- a linear implicit rule (Figure 3A) and a nonlinear implicit rule (Figure 3B). In this example, the optimal rule that defines category membership is based on a relationship between the length and the orientation of the line stimuli (that is, information from the two dimensions must be integrated). Because these stimuli are in separate physical units (length and orientation), it is difficult to verbalize an optimal rule of this nature, and thus learning has to occur at an implicit level. In these examples, the rule depicted in Figure 3A is based on a linear combination of the two stimulus dimensions, whereas the rule depicted in Figure 3B is based on a nonlinear combination of the two dimensions.

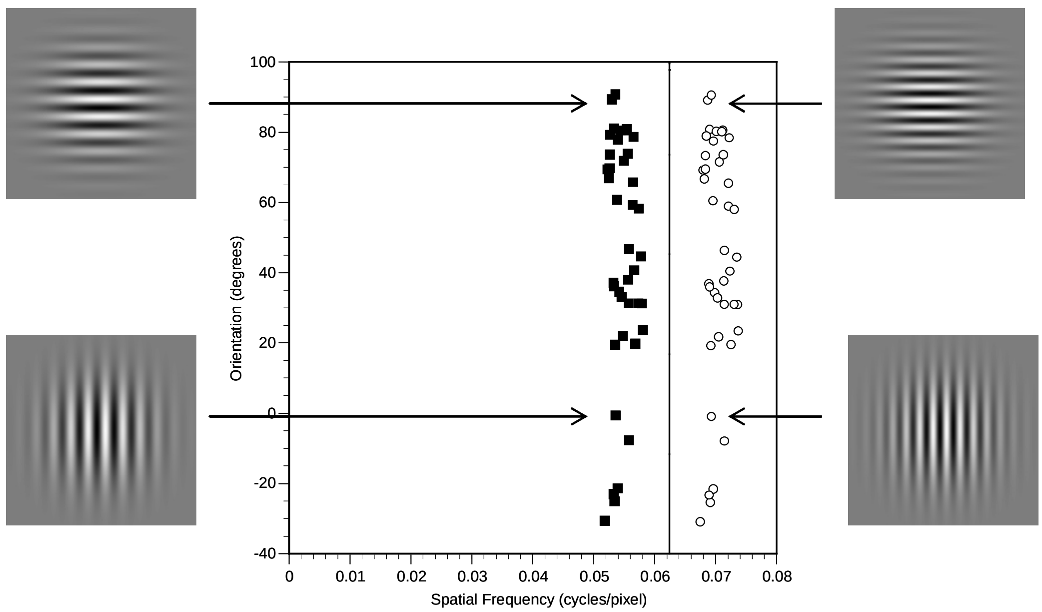

Figure 2. Stimulus distributions and sample stimuli used in the perceptual categorization task. Filled squares represent stimuli from Category A and open circles represent stimuli from Category B. The solid line represents the optimal unidimensional rule-based rule. Arrows point from specific stimulus exemplars to their location in the two-dimensional stimulus space.

Another major advantage in examining PD patients' performance on the perceptual categorization task is that it readily lends itself to the application of sophisticated quantitative models (Ashby & Waldron, 1999; Maddox, Ashby, & Bohil, 2003). These models enable one to identify the process a participant used to perform a given task (i.e., implicit vs. explicit). This is necessary because it is sometimes the case that a participant will attempt to use one approach to solve a task, such as an explicit approach, despite the fact that another approach, such as an implicit approach, is more optimal and would lead to greater levels of accuracy. Although the details of this modeling approach is beyond the scope of this chapter, we provide some discussion of how the application of these models has been invaluable in helping to better understand the nature of PD patients' category learning deficits. The interested reader is referred to other references for the details of this modeling approach (Ashby & Waldron, 1999; Ashby, Waldron, Lee, & Berkman, 2001; Maddox & Filoteo, 2007).

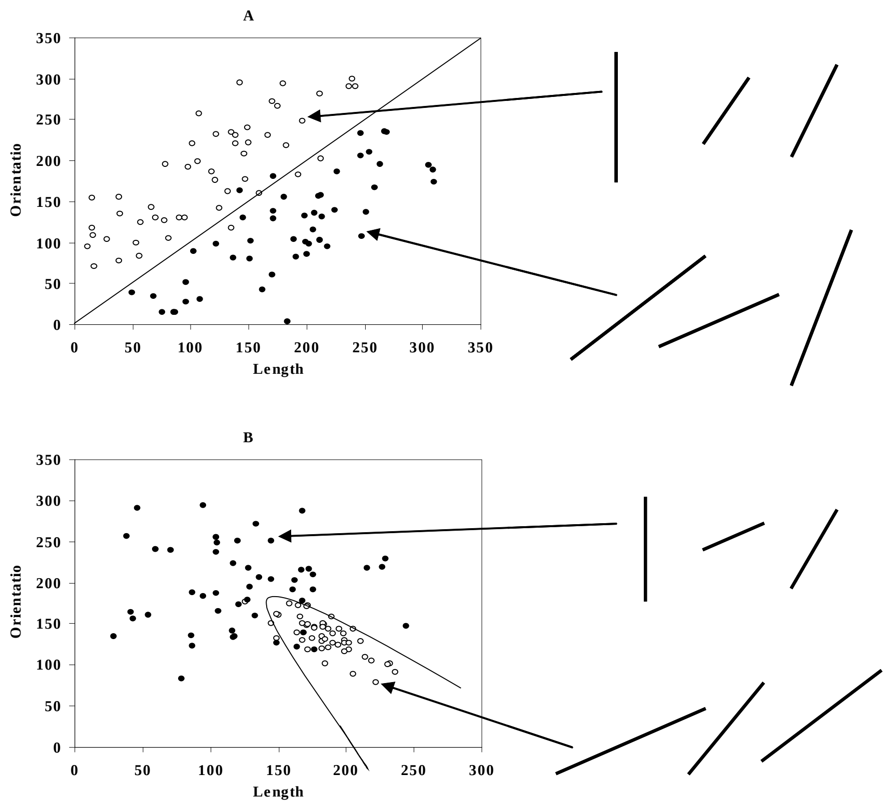

Figure 3. Sample stimuli and stimulus distributions for (A) the linear information-integration condition and (B) the nonlinear information-integration condition in which the stimuli were single lines that vary in length and orientation. Open circles represent stimuli from Category A and closed circles represent stimuli from Category B. The solid line and curve represent the optimal rules. Arrows point from specific stimulus exemplars to their location in the two-dimensional stimulus space.

EXPLICIT CATEGORY LEARNING IN PD

Rule-based measures of explicit category learning have been around since the 1920's (Weigl, 1927). The most popular rule-based clinical task that evaluates explicit category learning is the Wisconsin Card Sorting Test (WCST; Heaton, 1981). In performing the WCST, the participant has to learn a specific rule when matching cards of multiple dimensions (color, form, and number) to one of four key cards using trial-and-error feedback. Once the participant correctly classifies 10 cards in a row, the examiner changes the correct dimension (or rule) to which the participant must sort (e.g., from color to form) without informing the participant. The participant must then use the feedback to disengage from the previously correct rule in order to change to the new rule. Indices from the WCST include the number of trials it takes to achieve the first category sort, the number of categories achieved within 128 trials, the number of perseverative errors (i.e., the number of times a participant made a classification response to a previously correct dimension), and the number of set loss errors (i.e., the number of times a participant made at least 5 correct responses in a row but failed to achieve the criterion of 10 correct responses in a row). A number of studies have found that nondemented PD patients are impaired on the WCST (Azuma, Cruz, Bayles, Tomoeda, & Montgomery, 2003; Lees & Smith, 1983; Paolo, Axelrod, Troster, Blackwell, & Koller, 1996) and recent functional imaging research suggests that their deficit might be associated with decreased activation in the ventrolateral prefrontal cortex, particularly under task conditions in which the striatum is most involved (i.e., having to shift to a new dimension or rule; Monchi *et al.*, 2004; Monchi, Petrides, Mejia-Constain, & Strafella, 2007).

Despite these consistent findings of impairment on the WCST, one potential problem with establishing an explicit category learning deficit in patients with PD using this task is that the nature of their impairment does not appear to be in the *learning* of categories, but rather having to switch to a new category once a previous category has been learned. That is, nondemented PD patients tend not to be impaired in the number of trials it takes them to learn the first category on the WCST, but they tend to *perseverate* on the previously learned categorization rule when they are actually required to switch to a new rule (Paolo *et al.*, 1996). This deficit is highly consistent with PD patients' well-established impairment in set shifting (Cools *et al.*, 2001; Cronin-Golomb *et al.*, 1994; Hayes *et al.*, 1998; Owen *et al.*, 1991), particularly when having to shift from one stimulus dimension (e.g., shape) to another dimension (e.g., color; Downes *et al.*, 1989; Gauntlett-Gilbert, Roberts, & Brown, 1999). Thus, based on their performance on the WCST, nondemented PD patients do not appear to have an explicit category learning deficit *per se*, but rather their deficit on this measure appears to be more related to a deficit in set shifting.

Using other tasks, recent studies have attempted to understand the specific processes underlying explicit category learning deficits in nondemented PD patients. For example, Price (2006) administered a rule-based task to a group of nondemented PD patients in which category membership was based on a weighting of the presence of different geometric shapes. Specifically, 1-3 geometric figures were presented on each trial and participants were required to categorize the stimulus configurations into 1 of 2 categories. Each geometric figure had a specific weight assigned and category membership depended on the combination of these weights. The rule was explicit in the sense that participants could learn these weights verbally as the task proceeded. Results indicated that PD patients were impaired relative to healthy controls in learning the rule across 160 trials. In addition, Price (2006) obtained verbal reports from participants regarding how they were attempting to solve the task. An analysis of these verbal reports indicated that PD patients were less likely to use more efficient strategies that would lead to better performance, such as the possibility that a specific geometric shape was associated more with a specific category or that there was a differential weighting associated with the various geometric figures. Thus, these results suggest that PD patients are impaired in generating specific hypotheses that could be used to learn categories.

In one of our first studies examining explicit category learning in PD patients (Maddox & Filoteo, 2001), we used the perceptual categorization task (described above) in which subjects were presented with horizontal and vertical lines that varied in length. Optimal responding required the participant to categorize the stimulus into one category if the horizontal line was longer than the vertical line or into the other category if the vertical line was longer than the horizontal line. Somewhat surprisingly, the patients learned the rule at the same rate and level as control participants. To further investigate explicit category learning, we conducted a follow-up study (Ashby, Noble, Filoteo, Waldron, & Ell, 2003) in which participants categorized single cards that varied along four different binary-valued dimensions (e.g., nature of shapes, number of shapes, filling of shapes, and color of card). In the explicit condition, category membership was defined by the value on a single dimension (e.g., the color of the card). In contrast to our original finding (Maddox & Filoteo, 2001), PD patients were impaired in learning this explicit categorization rule. This finding has also been replicated in another recent study (Maddox, Aparicio, Marchant, & Ivry, 2005).

At first glance the findings from these previous studies which demonstrated a rule-based deficit in PD patients (Ashby *et al.*, 2003; Maddox, Aparicio *et al.*, 2005) seem to contradict our original finding of no deficit (Maddox & Filoteo, 2001), but one potential explanation for these discrepant results has to do with the presence or absence of irrelevant dimensional variation in the tasks used in the studies. That is, in our original study (Maddox & Filoteo, 2001), both of the stimulus dimensions (i.e., the length of the horizontal and vertical lines) were relevant to category membership, so there was no irrelevant dimensional variation. In contrast, in the other studies (Ashby *et al.*, 2003; Maddox, Aparicio *et al.*, 2005), one dimension of the stimulus was relevant and three dimensions could vary randomly from trial-to-trial. Thus, the task in the more recent studies required greater selective attention than our original study, suggesting that attentional deficits might contribute to PD patients' explicit category learning deficits.

We examined this hypothesis more directly in a follow-up study (Filoteo, Maddox, Ing, Zizak, & Song, 2005) where we systematically manipulated the selective attention requirements during the learning of an explicit task. Specifically, participants were administered a task in which they were presented with stimuli that had four binary-valued dimensions in four different conditions. Examples of representative stimuli from one stimulus set used in this study are shown in Figure 4A. For these “castle” stimuli, the potential relevant dimensions could be the shape of the foundation (diamond or square), location of the ramparts (above walls or sunken into walls), number of rings surrounding the castle (1 or 2), or the color of the drawbridge (yellow or green). In each of the four conditions, one of the binary-valued dimensions determined category membership, and zero, one, two, or three irrelevant dimensions varied from trial-to-trial. Thus, there was a systematic difference among the four conditions in terms of the degree of irrelevant dimensional variation, and thus, the amount of selective attention required. Figure 4B displays the number of trials-to-criterion (i.e., the number of trials it took subjects to obtain ten correct responses in a row correct with a greater number of trials indicative of poorer performance) for the four experimental conditions for the PD patients, a group of age-matched controls, and a group of younger controls. As can be seen, PD patients demonstrated a dramatic increase in trials-to-criterion relative to the age-matched controls when there were two irrelevant dimensions that varied across trials. Overall, these results indicated that PD patients' ability to learn the explicit categories was impacted to a much greater extent than controls as the number of varying irrelevant dimensions increased, suggesting that deficits in selective attention might contribute to the PD patients' impairment in explicit category learning. This finding is consistent with a previous study that demonstrated that PD patients are only impaired in discrimination learning when there is increased irrelevant dimensional variation (Channon, Jones, & Stephenson, 1993).

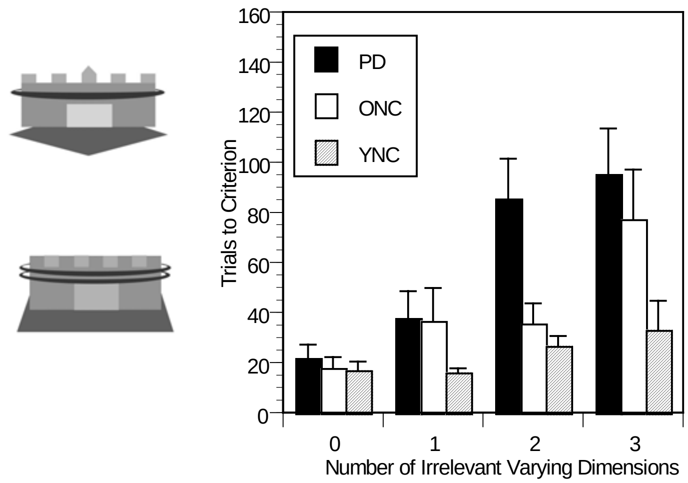

Figure 4. (A) Sample “castle” stimuli, and (B) trials-to-criterion for the PD patients, older normal controls (ONC), and younger normal controls (YNC).

Although this work supports the notion that deficits in selective attention processes might underlie the explicit category learning impairment in patients with PD, the specificity of such a deficit had not been demonstrated. In particular, PD patients had not been examined on more complex explicit category learning tasks in which other cognitive processes are also emphasized. Indeed, most past studies of explicit category learning in PD have used tasks in which only a single dimension is relevant, such as those studies that have used the WCST (Ashby *et al.*, 2003; Paolo *et al.*, 1996). Such tasks emphasize selective attention processes that are often found to be impaired in nondemented patients with PD (Filoteo & Maddox, 1999; Maddox, Filoteo, Delis, & Salmon, 1996; Sharpe, 1990). However, it is well known that PD patients are impaired in other cognitive processes that also likely contribute to explicit category learning. Specifically, working memory deficits have often been reported in these patients (Gilbert *et al.*, 2005; Owen *et al.*, 1993; Owen *et al.*, 1997; Postle *et al.*, 1997), and this cognitive process is likely involved in explicit category learning. For example, in learning explicit rules, participants must generate hypotheses regarding the possible rule, test such hypotheses using feedback, switch to a new hypothesis if the one currently in use is not correct, and keep track of those hypotheses that either did not work or are currently working. Thus, it is possible that deficits in working memory might also contribute to PD patients' impairment in learning explicit categorization rules.

To examine this issue, we conducted another study in which participants were asked to learn three explicit category structures (Filoteo, Maddox, Ing, & Song, 2007). One of the conditions required participants to learn the rule depicted in Figure 2, and the other two conditions required participants to learn the rules depicted in Figure 5. The stimuli in this study consisted of Gabor patches that varied from trial-to-trial in orientation and the width of the bars. In the *unidimensional* explicit condition (Figure 2), optimal responding required that the subject set a criterion on the spatial frequency dimension and respond "A" if the bars were wide or "B" if the bars were narrow. Orientation was irrelevant in this condition although it varied from trial-to-trial. Thus, participants had to attend selectively to one stimulus dimension (the width of the bars) and ignore the other, irrelevant varying dimension (orientation). Note, as in previous studies (Ashby *et al.*, 2003; Maddox, Aparicio *et al.*, 2005), this rule required participants to learn a rule in the presence of an irrelevant dimension that varied from trial-to-trial. In the *conjunctive* explicit condition, optimal responding required the subject to respond "A" if the stimulus was more vertical *and* had narrow bars, or respond "B" if otherwise. This approach represents an explicit combination of the two features and the rule is highly verbalizable. As such, this task is considered to be explicit. The optimal rule is depicted by the solid horizontal and vertical lines in Figure 5A. In the *disjunctive* condition, the optimal rule required that the subject respond "A" if the stimulus was more vertical and had narrow bars *or* if the stimulus was more horizontal and had wide bars, or to respond "B" if the stimulus was more vertical and had wide bars *or* if the stimulus was more horizontal and had narrow bars. The optimal rule is depicted by the solid horizontal and vertical lines in Figure 5B.

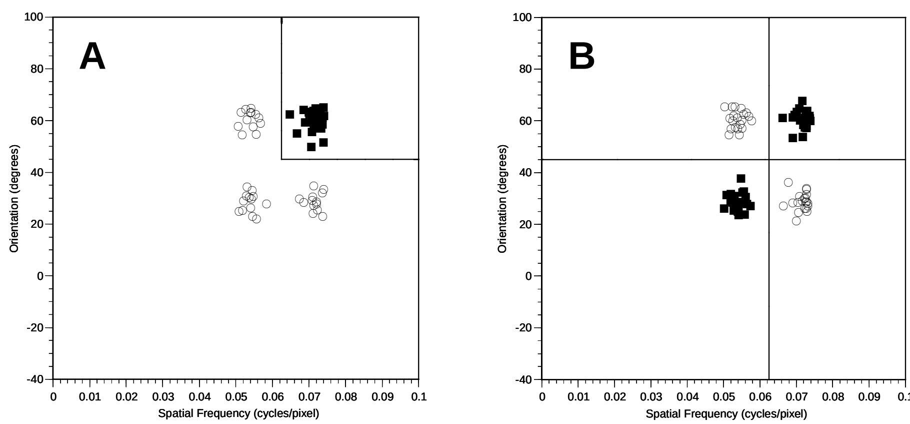

Figure 5. Stimulus distributions for (A) conjunctive, and (B) disjunctive rule-based category learning conditions. Filled squares represent stimuli from Category A and open circles represent stimuli from Category B. Solid lines represent the optimal bounds for each condition.

Note, although optimal responding in both the conjunctive and disjunctive tasks required participants to use a verbalizable combination of the two stimulus dimensions, the two tasks likely emphasize working memory to a different degree. Specifically, the logical expression associated with the disjunctive rule is much longer than the logical expression associated with the conjunctive rule, and therefore should require greater working memory. Thus, a comparison of PD patients' performances in the conjunctive and disjunctive conditions could help determine whether working memory deficits might also contribute to PD patients' explicit category learning deficits. In addition, because the conjunctive and disjunctive conditions require the participant to base their decision on both stimulus dimensions, these conditions served as an important test to determine if PD patients are impaired in all explicit tasks, or if they are impaired in only those tasks where there is irrelevant dimensional variation, such as in the unidimensional task.

Figure 6 displays the results from the three conditions. As can be seen, PD patients demonstrated a large impairment on the unidimensional explicit condition (Figure 6A), replicating previous findings (Ashby *et al.*, 2003; Maddox, Aparicio *et al.*, 2005). In contrast, the patients were not impaired in the conjunctive condition (Figure 6B) or the disjunctive condition (Figure 6C). Importantly, both groups displayed less learning in the disjunctive condition than the conjunctive condition, which was likely due to the greater working memory requirements of the former task. The pattern of PD patients' performance suggests that the explicit deficit exhibited by these patients in past studies is likely related to an impairment in selective attention. That is, the unidimensional condition placed a greater emphasis on selective attention processes because optimal responding required that the participant ignore the irrelevant variation on the orientation dimension, whereas selective attention requirements were less in the conjunctive and disjunctive conditions because optimal responding required that the participant attend to both the spatial frequency and orientation dimensions. In contrast, working memory deficits do not appear to account for their explicit category learning deficits, a view that has also been supported by previous studies (Price, 2006).

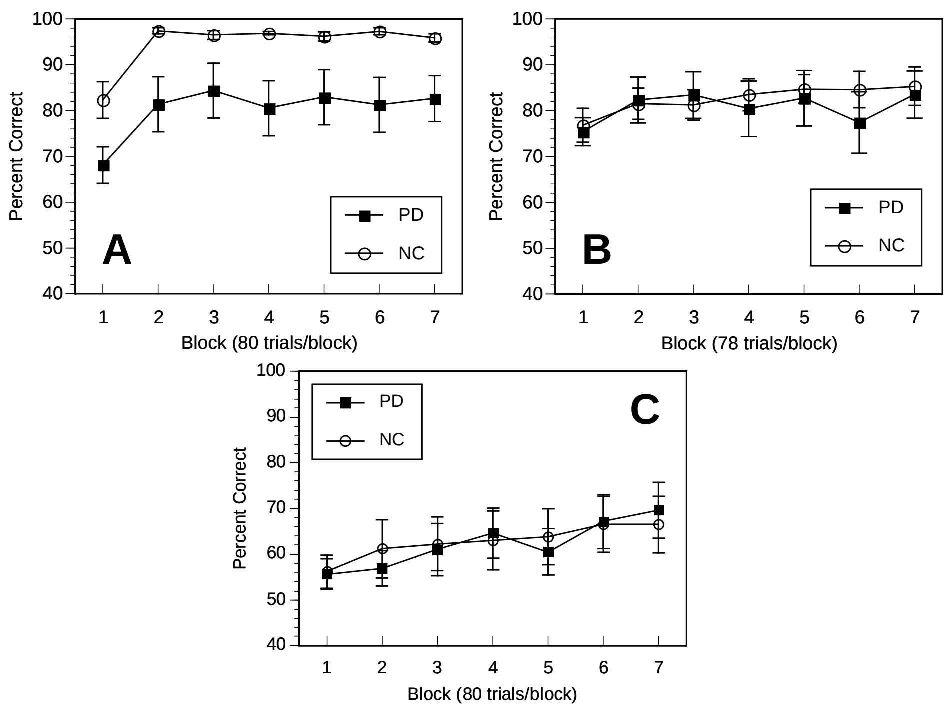

Figure 6. Accuracy for PD patients and NC subjects for (A) unidimensional, (B) conjunctive, and (C) disjunctive rule-based category learning conditions.

Taken together, previous work suggests that nondemented PD patients' impairments on traditional clinical rule-based tasks may be due to a deficit in shifting attentional set, whereas more recent studies that have used experimental measures suggest that their rule-based deficit may be associated with impairments in hypothesis generation and/or selective attention.

IMPLICIT CATEGORY LEARNING

As described above, three different classes of tasks have been used to investigate implicit category learning in PD patients: prototype distortion tasks and artificial grammar learning tasks; probabilistic learning tasks; and information-integration tasks. The results of studies using these three classes of tasks are discussed below.

Prototype Distortion Learning and Artificial Grammar Learning Tasks

The first implicit tasks to be discussed are the artificial grammar task and the prototype learning task (Posner & Keele, 1968; A. S. Reber, 1967). In the artificial grammar learning task, participants are presented strings of letters that conform to a particular grammatical structure and are asked to attend to these stimuli. After having been exposed to those stimuli, participants are told that the letter strings they were shown all conformed to a particular grammatical structure and that they are now going to be shown new stimuli, with some of those conforming to the grammatical structure and the others not conforming. The participants' task is to categorize these new stimuli as either conforming or not conforming to the grammatical structure. The prototype distortion learning task is somewhat similar to the artificial grammar learning task. Specifically, participants are typically exposed to 9-dot stimuli from a single category, where the stimuli are “high distortions” of a prototype display. Participants are not required to make a response during training, but are simply told to study each of the stimuli that are presented. After their exposure to the stimuli, participants are presented with the prototype, low distortions of the prototype, high distortions of the prototype (not seen during training), and "random" stimuli (consisting of a 9-dot display that are randomly organized). The participants task is to categorize the new stimuli and decide whether each item 'is' or 'is not' a member of the previously studied category.

To our knowledge, all studies that have examined PD patients on either the artificial grammar learning or the prototype distortion learning tasks using the above methods have shown normal performances in patients relative to controls (P. J. Reber & Squire, 1999; J. Smith, Siegert, McDowall, & Abernethy, 2001; Witt, Nuhsman, & Deuschl, 2002b), although one study did report that patients were impaired after a second exposure to the test stimuli in an artificial grammar learning task (Peigneux, Meulemans, Van der Linden, Salmon, & Petit, 1999).

The finding of relatively spared performance on these tasks is consistent with the notion that learning under these conditions is primarily dependent on a perceptual priming system mediated by posterior visual cortices, including the occipital lobes and fusiform gyrus (P. J. Reber, Gitelman, Parrish, & Mesulam, 2003; Skosnik *et al.*, 2002), brain regions that are relatively spared early in the course of PD. Such learning is believed to reflect a perceptual form of learning that is not dependent on the striatum, and thus it may not be surprising that PD patients are unimpaired on such tasks. This is especially the case when there is only one structured category and the participant's task is to state during transfer whether the test item is a member or not a member of that category (often referred to as an A/not A task) (Ashby & Maddox, 2005).

A related explanation why PD patients may not be impaired on these tasks is that they use "observational" training in that participants are not given any information regarding category membership when the stimuli are presented during training. Indeed, a recent study demonstrated that PD patients are impaired on an artificial grammar learning task when learning is based on trial-by-trial feedback, but they are not impaired after simply observing the stimuli during training (J. G. Smith & McDowall, 2006). This issue will be discussed in greater detail below.

Probabilistic Category Learning

Another form of category learning that has been studied in patients with PD is probabilistic learning, in which a set of stimuli are probabilistically related to one of two outcomes. The most popular task that has been used with PD patients is the Weather Prediction Task (WPT), which requires subjects to learn to categorize stimuli (consisting of various cue combinations) that are probabilistically associated with one of two categorical outcomes-- 'rain' or 'sunshine' (Gluck, Oliver, & Myers, 1996). Previous studies using the WPT in PD patients have yielded mixed results. For example, the first study to examine PD patients on the WPT found a deficit in these patients early in training (the first 50 trials), whereas patients were normal later in training (Knowlton, Mangels, & Squire, 1996), a finding that was later replicated by other investigators (Witt, Nuhsman, & Deuschl, 2002a). In contrast, using a slightly modified version of the WPT, another study found that PD patients were impaired both early in training (the first 50 trials) as well as later in training (trials 100-150) (Shohamy, Myers, Grossman *et al.*, 2004). Still, other studies have only identified deficits in PD patients after extensive training (>200 trials) (Shohamy, Myers, Onlaor, & Gluck, 2004). Finally, at least two studies have found that PD patients are not impaired on the WPT (Moody, Bookheimer, Vanek, & Knowlton, 2004; Price, 2005).

One potential explanation as to these discrepant results is the recent finding of important individual differences as to how a participant might solve the WPT. To examine this issue, Gluck and colleagues (Gluck, Shohamy, & Myers, 2002) instantiated several different strategic approaches one could use when performing the WPT and applied this strategy analysis to PD patients' performances on this task (Shohamy, Myers, Grossman *et al.*, 2004; Shohamy, Myers, Onlaor *et al.*, 2004). The results were very interesting in that both PD patients and control participants tended to learn the WPT early on by memorizing stimuli with only a single cue present (referred to as a singleton strategy). As learning progressed, however, the majority of control participants tended to switch to 'multi-cue' strategy that required the integration of multiple cues within the display. In contrast, the PD patients tended to continue to use a singleton strategy that they had adopted during the early part of learning and failed to switch away to the more advantageous multi-cue approach.

Interestingly, in one study (Shohamy, Myers, Onlaor *et al.*, 2004), PD patients and controls who switched to a multi-cue strategy did not differ on the WPT, suggesting that when patients can change to a more efficient strategy, they are able to apply it just as accurately as controls.

The finding that PD patients are impaired on the WPT because of a failure to switch strategies is reminiscent of their deficit described above on the WCST. In fact, these results are in line with the finding that PD patients' deficits on the WPT have been associated with the number of perseverative errors on the WCST (Knowlton *et al.*, 1996; Price, 2005). This observation again supports the notion that PD patients' impairment on the WPT may be more a failure to switch cognitive set than to learn probabilistic categorization rules.

Another potentially important finding with the WPT comes from functional imaging data. In particular, functional imaging studies with normal participants indicate that learning the WPT is associated with activity in the striatum, medial temporal lobes, midbrain dopamine regions (i.e., the substantia nigra and ventral tegmentum), and the ventral striatum. In fact, Poldrack and colleagues (Poldrack *et al.*, 2001; Poldrack, Prabhakaran, Seger, & Gabrieli, 1999; Rodriguez, Aron, & Poldrack, 2006) demonstrated an important dynamic when normal participants learn the WPT in that, as the task is performed across time, there is a shift from greater activation of medial temporal lobe regions (which are involved in explicit memory processes) to greater activation in the striatum.

Importantly, a recent functional imaging study with PD patients performing the WPT demonstrated increased activation within the medial temporal lobe relative to controls, as well as decreased activation of the striatum (Moody *et al.*, 2004). These findings, along with the results from those studies that examined strategic approaches in learning the WPT, suggest the possibility that, early in learning, PD patients may engage an explicit approach to solving the task that is mediated within the medial temporal lobe memory system, and fail to disengage that system in order to switch to a more optimal approach that is mediated within the striatum.

Information-Integration Category Learning

As described in the previous section, past studies that have attempted to examine implicit category learning in PD patients using the WPT tasks have yielded mixed results. However, even when PD patients have been shown to be impaired on such tasks as the WPT, a more detailed analysis of their deficits suggests that they may be impaired in switching away from an explicit rule in order to adopt an implicit rule, and not in implicit learning *per se*. In our studies of category learning, the use of the perceptual categorization task has allowed us to construct the categories in a manner where we are more certain that participants use either an implicit or explicit approach, but not both. In addition, the application of quantitative models has allowed us to further determine what approach a participant takes when learning the task.

The results from one of our first category learning studies in PD indicated that nondemented patients are impaired in learning an implicit categorization rule, such as the one shown in Figure 3B (Maddox & Filoteo, 2001). However, in a subsequent study (Ashby *et al.*, 2003), we found that PD patients were normal in learning an implicit information-integration rule. One important difference between the two studies was that in the Maddox & Filoteo (2001) study, the optimal rule that defined category membership was defined by a nonlinear relationship between the stimulus dimensions. In contrast, the optimal rule that defined category membership in the Ashby et al. (2003) study was based on a linear relationship between the relevant stimulus dimensions. Thus, the linearity of the rule might account for the discrepant findings in these two studies.

To address this possibility, we conducted a third study in which implicit category learning in PD patients was examined using both a linear and a nonlinear rule to determine whether differences in the linearity of the categories would impact learning (Filoteo, Maddox, Salmon, & Song, 2005). In this study, we used single lines that varied in length and orientation (See Figure 3). In the nonlinear implicit condition, the optimal rule was defined by a nonlinear relationship between the length and the orientation of the line (Figure 3A), whereas in the linear implicit condition, the optimal rule was defined by a linear relationship between the two dimensions (Figure 3B). Although optimal learning for both the linear and the nonlinear categorization rules require implicit processes, it has been suggested that the nonlinear rule does so to a greater extent (Ashby *et al.*, 2001). In particular, quantitative modeling of normal participants' performance suggests that nonlinear rules might theoretically require greater involvement of the striatum than linear rules. Thus, it was anticipated that PD patients would be more impaired on the nonlinear rule than the linear rule.

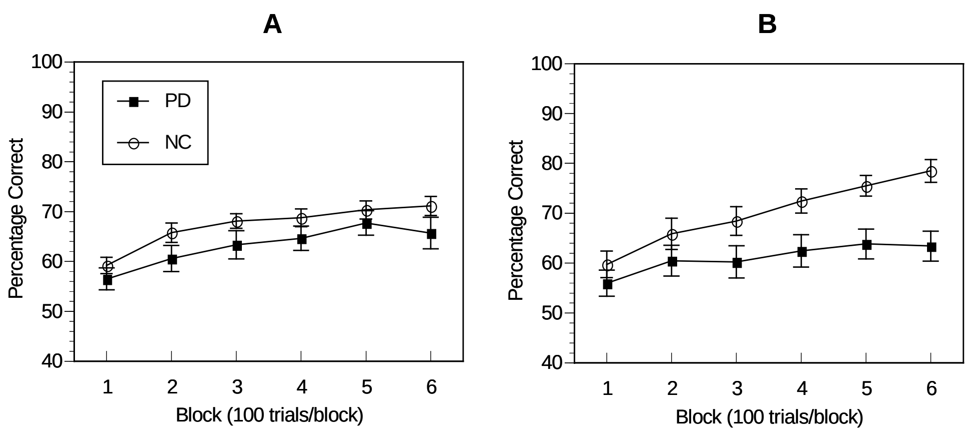

Figure 7. Percentage correct for PD patients and normal controls on (A) the linear information-integration condition and (B) the nonlinear information-integration condition.

The results from the two conditions are shown in Figure 7 and indicated that PD patients were impaired in the nonlinear condition (Figure 7B), but were normal in the linear condition (Figure 7A). These findings replicated our original study (Maddox & Filoteo, 2001) by identifying a deficit in PD patients in nonlinear implicit category learning. In addition, we also applied quantitative models to the participants' data in the linear and nonlinear condition to identify what approach (implicit or explicit) individuals used when learning these rules. Interestingly, only a fairly small percentage of the PD patients (55%) and control participants (65%) used an implicit approach in learning the linear rule, whereas the other participants in the two groups used an explicit approach. In contrast, most of the PD patients (80%) and the control participants (80%) used an implicit approach in learning the nonlinear rule. Importantly, when we compared the PD patients and control participants who actually used an implicit approach in the nonlinear condition, we continued to observe a deficit in the patients, whereas the two subgroups in the linear condition did not differ. Thus, unlike PD patients' past performances on the WPT, the deficits we observed on measures of information-integration category learning do indeed suggest that PD patients are impaired in learning some implicit categorization rules. This especially seems to be the case when the rule is defined by a complex (i.e., nonlinear) relationship among the stimulus attributes, and such deficits may be related to the integrity of the striatum.

Although the results of our previous studies suggest that nondemented PD patients are primarily impaired in learning nonlinear implicit categorization rules but not linear rules, two recent studies have not supported this observation. Price (Price, 2005) found that PD patients were impaired in learning a linear implicit rule, a finding that is not consistent with that of Ashby et al. (2003). Price (2005) argued that the different findings in her study and those in Ashby et al. might be due to the categories in her study being less complex as compared to the other two studies. However, this explanation does not account for the results of our studies (Filoteo, Maddox, Salmon *et al.*, 2005; Maddox & Filoteo, 2001) in which the categories were more complex than those in Price's (2005) study. As such, the nature of this discrepancy awaits further study.

Other studies have also found somewhat conflicting results. Schmitt-Eliassen and colleagues (Schmitt-Eliassen, Ferstl, Wiesner, Deuschl, & Witt, 2007) administered a nonlinear information-integration task similar to the one used by Maddox and Filoteo (2001) but, in contrast to our results, these authors did not find any differences between PD patients and controls. However, it is important to point out that neither the PD patients nor controls in the Schmitt-Eliassen et al. study displayed a large amount of learning; likely owing to the design of the study in that the task alternated blocks of trials in which feedback was either given or not give following a participant's response. This floor effect could have made it more difficult to detect differences between the PD patients and normal control participants.

The majority of the studies to date that have examined PD patients on information-integration category learning tasks have demonstrated that these patients are impaired when the rule is nonlinear. In theory, such rules likely place more demands on the striatum relative to linear rules because the former rules require a greater degree of representation, and this could explain why PD patients are primarily impaired in nonlinear learning.

Impact of Feedback on Implicit Category Learning in PD

The studies described above suggest some inconsistencies in the literature regarding whether PD patients are impaired in implicit category learning. Specifically, several studies have shown that PD patients are not impaired on prototype distortion or artificial grammar learning tasks, whereas most studies have suggested that PD patients are impaired on probabilistic and information-integration category learning tasks. One explanation that has been put forward to account for these discrepant findings is that PD patients are primarily impaired on category learning tasks in which feedback is necessary for learning (P. J. Reber & Squire, 1999). That is, tasks such as the prototype distortion or artificial grammar learning tasks do not require participants to learn based on trial-by-trial feedback, but rather participants learn under observational training conditions in which they simply view the stimuli and often perform an orienting task. In contrast, the probabilistic and information-integration category learning tasks used in past studies almost exclusively relied on trial-by-trial feedback during the acquisition of the categories. Because a dopamine reinforcement signal is believed to underlie trial-by-trial learning, and PD patients have decreased levels of dopamine, the differences in how participants are trained on these various tasks might account for these discrepant findings.

In support of this possibility, recent studies have shown that PD patients are primarily impaired on certain category learning tasks under trial-by-trial learning conditions but not under observational training conditions. For example, Shohamy and colleagues (Shohamy, Myers, Grossman *et al.*, 2004) demonstrated that PD patients are impaired on a version of the WPT when training was done through trial-by-trial feedback, whereas their patients were normal when they observed the stimulus cues with the associated category label and were asked to explicitly remember the associations. Similarly, a recent study by Schmitt-Eliassen et al. (2007) identified normal observational learning in a PD group using the same implicit category structure as in one of our previous studies (Maddox & Filoteo, 2001). As described above, although Schmitt-Eliassen et al. did not identify any substantial learning in patients or controls using trial-by-trial feedback, our previous study demonstrated that PD patients were impaired under feedback conditions. Taken together, these studies provide support for the possibility that PD patients are primarily impaired when the acquisition of the categories is based on feedback following each response, but not when it is based on simply observing the stimuli and the associated category labels, and that these differences may be related to alterations in the dopamine system in PD.

Additional evidence suggesting a role of dopamine in feedback-based learning comes from Frank and colleagues (Frank, Seeberger, & O'Reilly R, 2004). In their study, PD patients were tested 'on' dopaminergic medication or 'off' dopaminergic medication on a probabilistic category learning task using trial-by-trial feedback. Three different pairs of individual stimuli were presented to participants during training and participants had to select one of the two stimuli as being correct. Each of the stimuli had different probabilities associated with the correct response-- importantly, for stimulus pair A-B, stimulus A was associated with the correct response 80% of the time, whereas stimulus B was associated with the correct response 20% of the time. Because of the probabilistic nature of the task, participants could potentially learn to choose stimulus A over stimulus B for the A-B pairings either because they learned from positive feedback when selecting stimulus A, or they learned from negative feedback when selecting stimulus B. To differentiate these two possibilities, the investigators presented a transfer phase in which no feedback was given and participants were shown novel pairings of stimuli in which the A and B stimuli were never presented together. If participants learned about the task during acquisition based more on the positive feedback after having selected the A stimulus, they should be more likely to select the A stimulus in the pairings presented during transfer, whereas if they learned about the task during acquisition based more on negative feedback after having selected the B stimulus, they should avoid the B stimulus during transfer and select the other stimuli that were paired with the B stimulus. Interestingly, the results of that study indicated that PD patients 'on' medication were more likely to select the A stimulus during transfer, suggesting that they learned the task during acquisition based on positive feedback. In contrast, PD patients 'off' medication were more likely to avoid the B stimulus, suggesting that they learned the task during acquisition based more on negative feedback. These results have important implications for not only understanding the potential impact that dopamine might play on various forms of category learning in PD, but also provide some insight into the complexity of the nature of feedback in category learning. Certainly, this study raises the question as to whether the category learning results described above are dependent on whether PD patients were tested when 'on' medication.

CLINICAL APPLICATIONS OF CATEGORY LEARNING TASKS IN PD

A highly important goal in determining the clinical utility of category learning in PD is to identify whether such measures are sensitive to current cognitive deficits and predictive of future cognitive decline in nondemented PD patients. Predicting the rate of cognitive decline in patients with PD can have important implications for both clinical management and treatment strategies. Most past studies have attempted to predict the rate of cognitive decline in patients with PD using a variety of symptom and disease variables including older age at disease onset, predominant rigidity/akinesia motor symptoms, and psychiatric symptoms (Aarsland *et al.*, 2001; Hobson & Meara, 2004; Levy *et al.*, 2000). Some success has been achieved in predicting cognitive decline in patients with PD on the basis of their current level of cognitive functioning. In particular, a number of studies have shown that poor performance on traditional clinical measures of executive function predicts subsequent global cognitive decline in these patients. This predictive relationship has been shown using such executive function measures as the Stroop test and measures of verbal fluency (Dujardin *et al.*, 2004; Jacobs *et al.*, 1995; Janvin, Aarsland, & Larsen, 2005; Levy *et al.*, 2002; Mahieux *et al.*, 1998). In addition, previous studies have shown that indices from the WCST can be predictive of future dementia in PD (Woods & Troster, 2003), suggesting the possibility that category learning task may be sensitive to cognitive decline in these patients.

To further determine the potential clinical utility of PD patients' category learning deficits, we re-examined their nonlinear implicit category learning deficit described above by computing the percentage of patients who were at least 1.5 standard deviations below the mean of the controls (representing at least a mild impairment) and compared this percentage to the percentage of patients who were at least 1.5 standard deviations below the standardization sample on more traditional clinical executive-function measures, such as the WCST and verbal fluency tests. As noted above, past work has shown that these measures are the best predictors of future cognitive decline and dementia in PD. The results indicated that 60% of the nondemented PD patients were at least mildly impaired on the nonlinear implicit category learning task, whereas only 6% were impaired on the WCST (perseverative errors), 0% on the letter fluency test, and 0% on the category fluency test. For the nonlinear implicit task, there was a .91 positive predictive value (i.e., the probability that an individual has PD given they are impaired on the task), and a .74 negative predictive value (i.e., the probability that an individual does not have PD given they were not impaired on the task). These findings suggest that measures of implicit category learning hold great promise for detecting subtle cognitive deficits early in the course of the PD and may be more sensitive than traditional neuropsychological measures.

At the time of our first evaluation of the PD patients on the nonlinear implicit task, we also administered the Mattis Dementia Rating Scale (MDRS; Mattis, 1988), which is a measure of global cognitive functioning that has been used successfully in this population in both clinical and research settings (G. G. Brown *et al.*, 1999). At that time, the PD patients did not differ from controls on the MDRS, despite their impairment in the nonlinear condition. To further examine the potential clinical utility of PD patients' implicit category learning deficit, we conducted a follow-up study (Filoteo, Maddox, Song, & Salmon, 2007) in which re-administered the MDRS to 85% of the patients who participated in our previous study (mean time between evaluations = 1.6 years) and examined whether performances in the nonlinear and linear conditions predicted future cognitive decline. At the time of our first evaluation, the PD patients' mean MDRS total score was 139.0 and at the time of the second evaluation, their mean score was 134.2. The results were very striking in that performance in the final block of the nonlinear condition was highly predictive (r=-.78; 61% of the variance) of future decline on the MDRS, whereas poorer performance on the WCST was less predictive of decline (r=.42; 18% of the variance). Importantly, none of the patients were considered to be demented at the time of their second evaluation and accuracy performance in the nonlinear condition did not correlate with patients' initial MDRS scores.

In a follow-up regression analysis, we also determined that performance on the nonlinear implicit task still predicted subsequent cognitive decline even after age, gender, motor impairment, mood, baseline performance on the MDRS, and performance on the WCST were taken into account. The finding that performance on the nonlinear implicit task predicted future cognitive decline above that predicted by baseline MDRS scores is important because it suggests that implicit category learning provides additional predictive value above and beyond baseline neuropsychological evaluations.

We also examined whether our quantitative analyses would provide any additional predictive information regarding global cognitive decline. We found that PD patients whose data on the nonlinear task were best fit by one of the implicit models declined less on the MDRS than those whose data were best fit by an explicit model. This difference is depicted in Figure 8. Most importantly, we determined whether the inclusion of the model-based analyses could help predict decline on the MDRS above and beyond what was predicted by accuracy performance alone. As noted above, final block accuracy in the nonlinear condition predicted 61% of the variance associated with future decline on the MDRS. To examine this issue, we conducted a stepwise regression analysis in which we predicted change on the MDRS by first entering final block accuracy and then in the next step entering whether a patient's performance was best fit by an implicit or an explicit model. The inclusion of this latter variable predicted a significant additional 15% of the variance above and beyond the 61% predicted by accuracy level alone. Thus, using a single category learning task, we were able to predict 76% of the total variance associated with future cognitive decline in a nondemented PD sample after a mean follow-up of just 1.6 years. These results clearly establish the clinical utility for the use of quantitative modeling for a better prediction of global cognitive decline in nondemented PD patients.

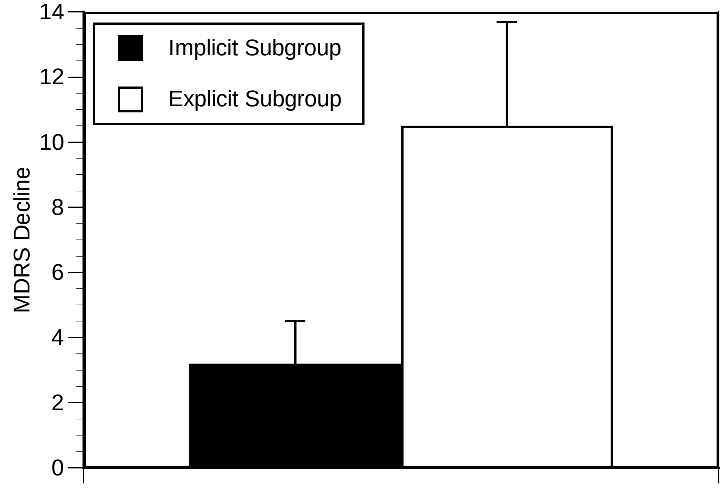

Figure 8. Decline on the Mattis Dementia Rating Scale in PD patient subgroups whose data were best fit by an implicit model or an explicit model.

Overall, these results are promising and indicate that the nonlinear implicit task is more sensitive to current and future cognitive impairment in nondemented PD patients than traditional neuropsychological tests, and that performance on at least one implicit task appears to offer unique predictive information above and beyond that which is provided by more traditional measures.

CONCLUSIONS

Our understanding of the nature of category learning deficits in patients with PD has not only taught us a great deal about the conditions under which these patients are impaired on such tasks, but has also informed us as to the role of various brain regions that are likely involved in normal category learning. Based on the understanding of the pathology associated with PD, it appears that the striatum plays an important role in various forms of category learning. In addition, we are now at a point where our understanding of these deficits is also starting to help us to predict future cognitive decline (and likely dementia), suggesting that a deeper understanding of the category learning impairments in these patients will likely have important clinical utility.

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REFERENCES

Aarsland, D., Andersen, K., Larsen, J. P., Lolk, A., & Kragh-Sorensen, P. (2003). Prevalence and characteristics of dementia in Parkinson disease: an 8-year prospective study. *Arch Neurol, 60*(3), 387-392.

Aarsland, D., Andersen, K., Larsen, J. P., Lolk, A., Nielsen, H., & Kragh-Sorensen, P. (2001). Risk of dementia in Parkinson's disease: a community-based, prospective study. *Neurology, 56*(6), 730-736.

Aarsland, D., Zaccai, J., & Brayne, C. (2005). A systematic review of prevalence studies of dementia in Parkinson's disease. *Mov Disord, 20*(10), 1255-1263.

Ashby, F. G., Alfonso-Reese, L. A., Turken, A. U., & Waldron, E. M. (1998). A neuropsychological theory of multiple systems in category learning. *Psychological Review, 105*(3), 442-481.

Ashby, F. G., & Gott, R. E. (1988). Decision rules in the perception and categorization of multidimensional stimuli. *J Exp Psychol Learn Mem Cogn, 14*(1), 33-53.

Ashby, F. G., & Maddox, W. T. (2005). Human category learning. *Annu Rev Psychol, 56*, 149-178.

Ashby, F. G., Noble, S., Filoteo, J. V., Waldron, E. M., & Ell, S. W. (2003). Category learning deficits in Parkinson's disease. *Neuropsychology, 17*(1), 115-124.

Ashby, F. G., & Waldron, E. M. (1999). On the nature of implicit categorization. *Psychon Bull Rev, 6*(3), 363-378.

Ashby, F. G., Waldron, E. M., Lee, W. W., & Berkman, A. (2001). Suboptimality in human categorization and identification. *Journal of Experimental Psychology: General, 130*(1), 77-96.

Azuma, T., Cruz, R. F., Bayles, K. A., Tomoeda, C. K., & Montgomery, E. B., Jr. (2003). A longitudinal study of neuropsychological change in individuals with Parkinson's disease. *Int J Geriatr Psychiatry, 18*(12), 1115-1120.

Brown, G. G., Rahill, A. A., Gorell, J. M., McDonald, C., Brown, S. J., Sillanpaa, M., & Shults, C. (1999). Validity of the Dementia Rating Scale in assessing cognitive function in Parkinson's disease. *J Geriatr Psychiatry Neurol, 12*(4), 180-188.

Brown, R. G., & Marsden, C. D. (1988). Internal versus external cues and the control of attention in Parkinson's disease. *Brain, 111 (Pt 2)*, 323-345.

Channon, S., Jones, M. C., & Stephenson, S. (1993). Cognitive strategies and hypothesis testing during discrimination learning in Parkinson's disease. *Neuropsychologia, 31*(1), 75-82.

Cools, R., Barker, R. A., Sahakian, B. J., & Robbins, T. W. (2001). Mechanisms of cognitive set flexibility in Parkinson's disease. *Brain, 124*(Pt 12), 2503-2512.

Cronin-Golomb, A., Corkin, S., & Growdon, J. H. (1994). Impaired problem solving in Parkinson's disease: impact of a set-shifting deficit. *Neuropsychologia, 32*(5), 579-593.

Downes, J. J., Roberts, A. C., Sahakian, B. J., Evenden, J. L., Morris, R. G., & Robbins, T. W. (1989). Impaired extra-dimensional shift performance in medicated and unmedicated Parkinson's disease: evidence for a specific attentional dysfunction. *Neuropsychologia, 27*(11-12), 1329-1343.

Dubois, B., & Pillon, B. (1997). Cognitive deficits in Parkinson's disease. *J Neurol, 244*(1), 2-8.

Dujardin, K., Defebvre, L., Duhamel, A., Lecouffe, P., Rogelet, P., Steinling, M., & Destee, A. (2004). Cognitive and SPECT characteristics predict progression of Parkinson's disease in newly diagnosed patients. *Journal of Neurology, 251*(11), 1383-1392.

Filoteo, J. V., & Maddox, W. T. (1999). Quantitative modeling of visual attention processes in patients with Parkinson's disease: effects of stimulus integrality on selective attention and dimensional integration. *Neuropsychology, 13*(2), 206-222.

Filoteo, J. V., Maddox, W. T., Ing, A. D., & Song, D. D. (2007). Characterizing rule-based category learning deficits in patients with Parkinson's disease. *Neuropsychologia, 45*(2), 305-320.

Filoteo, J. V., Maddox, W. T., Ing, A. D., Zizak, V., & Song, D. D. (2005). The impact of irrelevant dimensional variation on rule-based category learning in patients with Parkinson's disease. *J Int Neuropsychol Soc, 11*(5), 503-513.

Filoteo, J. V., Maddox, W. T., Salmon, D. P., & Song, D. D. (2005). Information-integration category learning in patients with striatal dysfunction. *Neuropsychology, 19*(2), 212-222.

Filoteo, J. V., Maddox, W. T., Simmons, A. N., Ing, A. D., Cagigas, X. E., Matthews, S., & Paulus, M. P. (2005). Cortical and subcortical brain regions involved in rule-based category learning. *Neuroreport, 16*(2), 111-115.

Filoteo, J. V., Maddox, W. T., Song, D., & Salmon, D. P. (2007). Implicit category learning performance predicts rate of cognitive decline in nondemented patients with Parkinson's disease. *Neuropsychology,*

Filoteo, J. V., Rilling, L. M., & Strayer, D. L. (2002). Negative priming in patients with Parkinson's disease: evidence for a role of the striatum in inhibitory attentional processes. *Neuropsychology, 16*(2), 230-241.

Filoteo, J. V., Simmons, A. N., Zeithamova, D., Maddox, W. T., & Paulus, M. P. (2006). *Change in patterns of brain activity related to early and later learning of information-integration category structures.* Paper presented at the Cognitive Neuroscience Society, San Francisco.

Frank, M. J., Seeberger, L. C., & O'Reilly R, C. (2004). By carrot or by stick: cognitive reinforcement learning in parkinsonism. *Science, 306*(5703), 1940-1943.

Gauntlett-Gilbert, J., Roberts, R. C., & Brown, V. J. (1999). Mechanisms underlying attentional set-shifting in Parkinson's disease. *Neuropsychologia, 37*(5), 605-616.

Gilbert, B., Belleville, S., Bherer, L., & Chouinard, S. (2005). Study of verbal working memory in patients with Parkinson's disease. *Neuropsychology, 19*(1), 106-114.

Gluck, M. A., Oliver, L. M., & Myers, C. E. (1996). Late-training amnesic deficits in probabilistic category learning: a neurocomputational analysis. *Learn Mem, 3*(4), 326-340.

Gluck, M. A., Shohamy, D., & Myers, C. (2002). How do people solve the "weather prediction" task?: individual variability in strategies for probabilistic category learning. *Learn Mem, 9*(6), 408-418.

Hayes, A. E., Davidson, M. C., Keele, S. W., & Rafal, R. D. (1998). Toward a functional analysis of the basal ganglia. *J Cogn Neurosci, 10*(2), 178-198.

Heaton, R. K. (1981). *Wisconsin Card Sorting Test*. Odessa, FL: Psychological Assessment Resources.

Hobson, P., & Meara, J. (2004). Risk and incidence of dementia in a cohort of older subjects with Parkinson's disease in the United Kingdom. *Movement Disorders, 19*(9), 1043-1049.

Jackson, G. M., Jackson, S. R., Harrison, J., Henderson, L., & Kennard, C. (1995). Serial reaction time learning and Parkinson's disease: evidence for a procedural learning deficit. *Neuropsychologia, 33*(5), 577-593.

Jacobs, D. M., Marder, K., Cote, L. J., Sano, M., Stern, Y., & Mayeux, R. (1995). Neuropsychological characteristics of preclinical dementia in Parkinson's disease. *Neurology, 45*(9), 1691-1696.

Janvin, C. C., Aarsland, D., & Larsen, J. P. (2005). Cognitive predictors of dementia in Parkinson's disease: a community-based, 4-year longitudinal study. *Journal of Geriatric Psychiatry and Neurology, 18*(3), 149-154.

Knowlton, B. J., Mangels, J. A., & Squire, L. R. (1996). A neostriatal habit learning system in humans. *Science, 273*(5280), 1399-1402.

Knowlton, B. J., & Squire, L. R. (1993). The learning of categories: parallel brain systems for item memory and category knowledge. *Science, 262*(5140), 1747-1749.

Lees, A. J., & Smith, E. (1983). Cognitive deficits in the early stages of Parkinson's disease. *Brain, 106 (Pt 2)*, 257-270.

Levy, G., Jacobs, D. M., Tang, M. X., Cote, L. J., Louis, E. D., Alfaro, B., Mejia, H., Stern, Y., & Marder, K. (2002). Memory and executive function impairment predict dementia in Parkinson's disease. *Movement Disorders, 17*(6), 1221-1226.

Levy, G., Tang, M. X., Cote, L. J., Louis, E. D., Alfaro, B., Mejia, H., Stern, Y., & Marder, K. (2000). Motor impairment in PD: relationship to incident dementia and age. *Neurology, 55*(4), 539-544.

Maddox, W. T., Aparicio, P., Marchant, N. L., & Ivry, R. B. (2005). Rule-based category learning is impaired in patients with Parkinson's disease but not in patients with cerebellar disorders. *J Cogn Neurosci, 17*(5), 707-723.

Maddox, W. T., Ashby, F. G., & Bohil, C. J. (2003). Delayed feedback effects on rule-based and information-integration category learning. *J Exp Psychol Learn Mem Cogn, 29*(4), 650-662.

Maddox, W. T., & Filoteo, J. V. (2001). Striatal contributions to category learning: quantitative modeling of simple linear and complex nonlinear rule learning in patients with Parkinson's disease. *Journal of the International Neuropsychological Society, 7*(6), 710-727.

Maddox, W. T., & Filoteo, J. V. (2007). Modeling visual attention and category learning in amnesiacs, striatal-damaged patients, and normal aging. In R. W. J. Neufeld (Ed.), *Advances in Clinical Cognitive Science: Formal Modeling and Assessment of Processes and Symptoms* (pp. 113-145): American Psychological Association.

Maddox, W. T., Filoteo, J. V., Delis, D. C., & Salmon, D. P. (1996). Visual selective attention deficits in patients with Parkinson's disease: A quantitative model-based approach. *Neuropsychology, 10*(2), 197-218.

Maddox, W. T., Filoteo, J. V., Hejl, K. D., & Ing, A. D. (2004). Category number impacts rule-based but not information-integration category learning: further evidence for dissociable category-learning systems. *J Exp Psychol Learn Mem Cogn, 30*(1), 227-245.

Maddox, W. T., Filoteo, J. V., & Lauritzen, J. S. (2007). Within-category discontinuity interacts with verbal rule complexity in perceptual category learning. *J Exp Psychol Learn Mem Cogn, 33*(1), 197-218.

Maddox, W. T., Filoteo, J. V., Lauritzen, J. S., Connally, E., & Hejl, K. D. (2005). Discontinuous categories affect information-integration but not rule-based category learning. *J Exp Psychol Learn Mem Cogn, 31*(4), 654-669.

Maddox, W. T., O'Brien, J. B., Ashby, F. G., & Filoteo, J. V. (2007). Dissociating stages of information-integration category learning. *Submitted for publication*.

Mahieux, F., Fenelon, G., Flahault, A., Manifacier, M. J., Michelet, D., & Boller, F. (1998). Neuropsychological prediction of dementia in Parkinson's disease. *Journal of Neurology, Neurosurgery and Psychiatry, 64*(2), 178-183.

Mattis, S. (1988). *Dementia Rating Scale*. Odessa, FL: Psychological Assessment Resources.

Monchi, O., Petrides, M., Doyon, J., Postuma, R. B., Worsley, K., & Dagher, A. (2004). Neural bases of set-shifting deficits in Parkinson's disease. *J Neurosci, 24*(3), 702-710.

Monchi, O., Petrides, M., Mejia-Constain, B., & Strafella, A. P. (2007). Cortical activity in Parkinson's disease during executive processing depends on striatal involvement. *Brain, 130*(Pt 1), 233-244.

Moody, T. D., Bookheimer, S. Y., Vanek, Z., & Knowlton, B. J. (2004). An implicit learning task activates medial temporal lobe in patients with Parkinson's disease. *Behav Neurosci, 118*(2), 438-442.

Muslimovic, D., Post, B., Speelman, J. D., & Schmand, B. (2005). Cognitive profile of patients with newly diagnosed Parkinson disease. *Neurology, 65*(8), 1239-1245.

Nomura, E. M., Maddox, W. T., Filoteo, J. V., Ing, A. D., Gitelman, D. R., Parrish, T. B., Mesulam, M. M., & Reber, P. J. (2007). Neural correlates of rule-based and information-integration visual category learning. *Cereb Cortex, 17*(1), 37-43.

Nosofsky, R. M., Palmeri, T. J., & McKinley, S. C. (1994). Rule-plus-exception model of classification learning. *Psychol Rev, 101*(1), 53-79.

Owen, A. M. (2004). Cognitive dysfunction in Parkinson's disease: the role of frontostriatal circuitry. *Neuroscientist, 10*(6), 525-537.

Owen, A. M., Beksinska, M., James, M., Leigh, P. N., Summers, B. A., Marsden, C. D., Quinn, N. P., Sahakian, B. J., & Robbins, T. W. (1993). Visuospatial memory deficits at different stages of Parkinson's disease. *Neuropsychologia, 31*(7), 627-644.

Owen, A. M., Iddon, J. L., Hodges, J. R., Summers, B. A., & Robbins, T. W. (1997). Spatial and non-spatial working memory at different stages of Parkinson's disease. *Neuropsychologia, 35*(4), 519-532.

Owen, A. M., Roberts, A. C., Polkey, C. E., Sahakian, B. J., & Robbins, T. W. (1991). Extra-dimensional versus intra-dimensional set shifting performance following frontal lobe excisions, temporal lobe excisions or amygdalo-hippocampectomy in man. *Neuropsychologia, 29*(10), 993-1006.

Paolo, A. M., Axelrod, B. N., Troster, A. I., Blackwell, K. T., & Koller, W. C. (1996). Utility of a Wisconsin Card Sorting Test short form in persons with Alzheimer's and Parkinson's disease. *Journal of Clinical and Experimental Neuropsychology, 18*(6), 892-897.

Pascual-Leone, A., Grafman, J., Clark, K., Stewart, M., Massaquoi, S., Lou, J. S., & Hallett, M. (1993). Procedural learning in Parkinson's disease and cerebellar degeneration. *Ann Neurol, 34*(4), 594-602.

Peigneux, P., Meulemans, T., Van der Linden, M., Salmon, E., & Petit, H. (1999). Exploration of implicit artificial grammar learning in Parkinson's disease. *Acta Neurol Belg, 99*(2), 107-117.

Poldrack, R. A., Clark, J., Pare-Blagoev, E. J., Shohamy, D., Creso Moyano, J., Myers, C., & Gluck, M. A. (2001). Interactive memory systems in the human brain. *Nature, 414*(6863), 546-550.

Poldrack, R. A., Prabhakaran, V., Seger, C. A., & Gabrieli, J. D. (1999). Striatal activation during acquisition of a cognitive skill. *Neuropsychology, 13*(4), 564-574.

Posner, M. I., & Keele, S. W. (1968). On the genesis of abstract ideas. *J Exp Psychol, 77*(3), 353-363.

Postle, B. R., Jonides, J., Smith, E. E., Corkin, S., & Growdon, J. H. (1997). Spatial, but not object, delayed response is impaired in early Parkinson's disease. *Neuropsychology, 11*(2), 171-179.

Price, A. L. (2005). Cortico-striatal contributions to category learning: dissociating the verbal and implicit systems. *Behav Neurosci, 119*(6), 1438-1447.

Price, A. L. (2006). Explicit category learning in Parkinson's disease: deficits related to impaired rule generation and selection processes. *Neuropsychology, 20*(2), 249-257.

Reber, A. S. (1967). Implicit learning of artificial grammars. *Journal of Verbal Learning and Verbal Behavior, 6*, 855-863.

Reber, P. J., Gitelman, D. R., Parrish, T. B., & Mesulam, M. M. (2003). Dissociating explicit and implicit category knowledge with fMRI. *J Cogn Neurosci, 15*(4), 574-583.

Reber, P. J., & Squire, L. R. (1999). Intact learning of artificial grammars and intact category learning by patients with Parkinson's disease. *Behav Neurosci, 113*(2), 235-242.

Reber, P. J., Stark, C. E., & Squire, L. R. (1998). Contrasting cortical activity associated with category memory and recognition memory. *Learn Mem, 5*(6), 420-428.

Rodriguez, P. F., Aron, A. R., & Poldrack, R. A. (2006). Ventral-striatal/nucleus-accumbens sensitivity to prediction errors during classification learning. *Hum Brain Mapp, 27*(4), 306-313.

Schmitt-Eliassen, J., Ferstl, R., Wiesner, C., Deuschl, G., & Witt, K. (2007). Feedback-based versus observational classification learning in healthy aging and Parkinson's disease. *Brain Res*.

Sharpe, M. H. (1990). Distractibility in early Parkinson's disease. *Cortex, 26*(2), 239-246.

Shohamy, D., Myers, C. E., Grossman, S., Sage, J., Gluck, M. A., & Poldrack, R. A. (2004). Cortico-striatal contributions to feedback-based learning: converging data from neuroimaging and neuropsychology. *Brain, 127*(Pt 4), 851-859.

Shohamy, D., Myers, C. E., Onlaor, S., & Gluck, M. A. (2004). Role of the basal ganglia in category learning: how do patients with Parkinson's disease learn? *Behav Neurosci, 118*(4), 676-686.

Skosnik, P. D., Mirza, F., Gitelman, D. R., Parrish, T. B., Mesulam, M. M., & Reber, P. J. (2002). Neural correlates of artificial grammar learning. *Neuroimage, 17*(3), 1306-1314.

Smith, E. E., Patalano, A. L., & Jonides, J. (1998). Alternative strategies of categorization. *Cognition, 65*(2-3), 167-196.

Smith, E. E., & Sloman, S. A. (1994). Similarity- versus rule-based categorization. *Mem Cognit, 22*(4), 377-386.

Smith, J., Siegert, R. J., McDowall, J., & Abernethy, D. (2001). Preserved implicit learning on both the serial reaction time task and artificial grammar in patients with Parkinson's disease. *Brain Cogn, 45*(3), 378-391.

Smith, J. G., & McDowall, J. (2006). When artificial grammar acquisition in Parkinson's disease is impaired: the case of learning via trial-by-trial feedback. *Brain Res, 1067*(1), 216-228.

Vakil, E., & Herishanu-Naaman, S. (1998). Declarative and procedural learning in Parkinson's disease patients having tremor or bradykinesia as the predominant symptom. *Cortex, 34*(4), 611-620.

Weigl, E. (1927). Zur Psychologie Sogenannter Abstrakionsprozesse [Translated in Journal of Abnormal Social Psychology, 36, 3-33]. *z. Psychol, 103,* 2-45.

Wickens, J. (1990). Striatal dopamine in motor activation and reward-mediated learning: steps towards a unifying model. *J Neural Transm Gen Sect, 80*(1), 9-31.

Witt, K., Nuhsman, A., & Deuschl, G. (2002a). Dissociation of habit-learning in Parkinson's and cerebellar disease. *J Cogn Neurosci, 14*(3), 493-499.

Witt, K., Nuhsman, A., & Deuschl, G. (2002b). Intact artificial grammar learning in patients with cerebellar degeneration and advanced Parkinson's disease. *Neuropsychologia, 40*(9), 1534-1540.

Woods, S. P., & Troster, A. I. (2003). Prodromal frontal/executive dysfunction predicts incident dementia in Parkinson's disease. *Journal of the International Neuropsychological Society, 9*(1), 17-24.