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Rule Based Category Learning in Patients with Parkinson's Disease

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Abstract

Measures of explicit rule-based category learning are commonly used in neuropsychological evaluation of individuals with Parkinson's disease (PD) and the pattern of PD performance on these measures tends to be highly varied. We review the neuropsychological literature to clarify the manner in which PD affects the component processes of rule-based category learning and work to identify and resolve discrepancies within this literature. In particular, we address the manner in which PD and its common treatments affect the processes of rule generation, maintenance, shifting and selection. We then integrate the neuropsychological research with relevant neuroimaging and computational modeling evidence to clarify the neurobiological impact of PD on each process. Current evidence indicates that neurochemical changes associated with PD primarily disrupt rule shifting, and may disturb feedback-mediated learning processes that guide rule selection. Although surgical and pharmacological therapies remediate this deficit, it appears that the same treatments may contribute to impaired rule generation, maintenance and selection processes. These data emphasize the importance of distinguishing between the impact of PD and its common treatments when considering the neuropsychological profile of the disease.

Keywords

PARKINSON'S DISEASE; STRIATUM; CATEGORY LEARNING; DOPAMINE; EXECUTIVE FUNCTION

As a fundamental aspect of human cognition, categorization enables appropriate responses to a variety of familiar and novel stimuli. The same categorization processes that govern decisions of dire importance, such as whether or not the street sign ahead signals a road hazard, also govern more mundane behaviors such as filing papers or sorting laundry. The ubiquitous nature

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²We use the general abbreviation PD when discussing research that did not specifically examine the impact of PD medication. When addressing research that specifically examined the impact of medication, we distinguish between PD patients on and off medication.

³The present discussion focuses specifically on rule shifting within category learning tasks and does not address the substantial literature related to task switching. Task switching differs from rule shifting in that it does not emphasize learning and involves changing stimulus-response mappings. In addition, task switching is more consistently affected by DA withdrawal than rule shifting, which suggests the two processes are sufficiently different to not be discussed as relying on the same mechanisms.

of categorization has led to extensive examination of the cognitive and, more recently, neurobiological processes underlying its performance.

Much work in the area of categorization has focused on the processes underlying the acquisition of new categories and it is generally accepted that multiple learning systems operate in parallel to support such learning (Ashby, Alfonso-Reese, Turken & Waldron, 1998; Ashby & Valentin, 2005; Erickson & Kruschke, 1998; Maddox & Ashby 2004; Reber & Squire, 1994; Smith & Grossman, 2008; Smith, Patalano, & Jonides, 1998; but see Nosofsky & Johansen, 2000 for discussion of a unitary system of categorization). At least one of these systems supports implicit category learning, which develops gradually with little intention, and at least one other system supports explicit category learning, which requires effortful hypothesis testing and memorization processes (Ashby et al., 1998; Maddox & Ashby, 2004; Poldrack et al., 2001; Poldrack & Packard, 2003; Smith & Grossman, 2008; Smith et al., 1998).

In this review, we focus specifically on the neurobiological aspects of explicit, rule-based category learning as a detailed examination of both implicit and explicit systems is outside the scope of the present article (for details on the neural mechanisms of implicit category learning, see Ashby & Ennis, 2006; Shohamy, Myers & Kalanithi, 2008). Explicit rule-based category structures are learned using logical reasoning and hypothesis testing processes that demand working memory (WM) resources. Typically, the optimal classification rule is easily verbalized, although rules vary in complexity (Bruner, Goodnow & Austin, 1956). Often, categorization depends upon a single dimension that must be appropriately mapped onto each stimulus. One of the most commonly used measures of explicit rule-based category learning is the Wisconsin Card Sorting Task (WCST; Berg, 1948; Heaton, 1981), in which stimuli vary along several dimensions and participants must sort according to one while ignoring the others. Additionally, some tasks rely upon multi-dimensional rules that require the consideration of several stimulus dimensions.

Much of the current knowledge regarding the cognitive neuroscience of explicit rule-based category learning stems from research with individuals with damage to specific brain areas. In particular, considerable work has focused on patients with fronto-striatal dysfunction due to Parkinson's disease (PD). PD is associated with degeneration of dopamine (DA) neurons in the substantia nigra pars compacta (SN_{PC}), leading to a substantial drop in DA within the dorsal striatum (putamen and caudate) (Agid, Javoy-Agid, & Ruberg, 1987; Albin, Young & Penney, 1989; Robertson & Robertson, 1988). This results in excessive inhibition of thalamic projections to cortical regions, namely premotor and prefrontal structures (de Long, 1990; Scatton, Worms, Lloyd, & Bartholini, 1982). As PD progresses, DA neurons in the ventral tegmental area (VTA) are also lost, resulting in dysfunction of the ventral striatum and its cortical projections, including orbitofrontal cortex (OFC) and anterior cingulate (ACC) (Farley, Price & Hornykiewicz, 1977; Kish, Shannak & Hornykiewicz, 1988; Uhl, Hedreen & Price, 1985). Additionally, significant degeneration of the locus ceruleus results in dysfunction of the noradrenergic system, including the ceruleo-cortical projections to PFC (see Rommelfanger & Weinshenker, 2007 for a review).

The neurochemical changes associated with PD often lead to dysfunction of a number of cognitive processes (Brown & Marsden, 1990; Salmon, Lineweaver, & Heindel, 1998). This includes impairment in WM, selective attention and cognitive flexibility, each of which are fundamental to explicit, rule-based category learning. Patients with PD commonly exhibit rule-based category learning impairment but the nature of this impairment is highly variable. In the present review, we examine the particular conditions in which rule-based category learning deficits emerge in PD and consider how these deficits are explained by the neurobiological dysfunction associated with the disease. While dysfunction in a number of brain regions and neurotransmitter systems might contribute to rule-based category learning deficits in PD, in

the present review we primarily focus on the potential role of the caudate nucleus, nucleus accumbens, prefrontal cortex, and dopaminergic systems as these brain regions and neurotransmitter have been highly implicated in explicit rule-based category learning.

A better understanding of the mechanisms that underlie rule-based category learning impairments in PD holds several benefits. Although it is the case that deficits on other cognitive tasks predict future cognitive decline in PD, measures of rule based category learning, such as performance on the WCST, are highly predictive as well (Dujardin, Degreef, Rogelet, Defebvre & Destee 1999; Jacobs et al., 1995; Janvin, Aarsland, & Larsen, 2005; Levy et al., 2002; Maddox, Filoteo & Zeithamova, in press; Mahieux et al., 1998; Piccirilli, D'Alessandro, Finali, Piccinin, & Agostini, 1989; Woods & Troster, 2003). Thus from a clinical perspective, increased understanding of PD-related deficits may enhance knowledge regarding the predictors and causes of dementia. Such knowledge may also stimulate the development of additional neuropsychological tools to predict the onset of dementia.

Further, integration of findings across multiple paradigms enriches our understanding of the neurobiological mechanisms that support category learning and helps to clarify the sources of rule-based category learning impairment in PD. The evidence we review here indicates that particular components of explicit rule-based category learning are differently affected by PD. Variability in PD performance appears to reflect deficits attributable to the disease itself and its commonly used treatments. Accumulating evidence indicates that pharmacological therapies ameliorate certain cognitive deficits while creating other forms of cognitive impairment (Cools, 2006; Cools, Barker, Sahakian, & Robbins, 2001; 2003; Cools, Altamirano & D'Esposito, 2006; Cools, Lewis, Clark, Barker & Robbins, 2007; Gotham, Brown & Marsden, 1988; Owen, Roberts, Hodges, Summers, Polkey & Robbins, 1993). Increased knowledge regarding currently available PD treatments and their impact on cognitive function informs clinical decision making and improves understanding of the potential cognitive impact of emerging therapeutic interventions (e.g. stem cell therapy, novel drug therapies, gene therapy).

Rule-Based Category Learning

Several computational models of category learning have addressed the explicit, rule-based system, and each tends to invoke similar components, namely WM and hypothesis testing processes (Ashby et al., 1998; Ashby & Valentin, 2005; Erickson & Krushke, 1998; 2002). One of the most successful neurobiological models of rule-based category learning is the COmpetition between Verbal and Implicit Systems (COVIS) model proposed by Ashby and colleagues (Ashby et al., 1998; Ashby & Valentin, 2005; Maddox & Ashby, 2004)¹. FF According to the COVIS model, rule-based category learning depends upon hypothesis testing processes that place heavy demand on WM, including the selection, maintenance, and shifting of classification rules. Here, we elaborate on the COVIS model to better address patterns of variation in the performance of PD patients on these particular aspects of hypothesis testing. In addition, we extend the model to address the process of rule generation and further articulate the process of rule selection, each of which are often overlooked in empirical and theoretical examinations of category learning.

Although each hypothesis testing component represents a distinct phase within the category learning process, the components are interdependent. Figure 1 summarizes the manner in which these processes interact to support rule-based category learning. On the WCST, for example, participants must sort a deck of cards according to one of three dimensions (color, shape or number), but they are not told which dimension is relevant and must learn this information

¹The COVIS model also details implicit category learning but we focus only on the components devoted to explicit, rule-based learning.

through feedback. Before beginning to sort, most participants will readily generate several possible sorting rules (e.g. sort according to color). The process of rule generation, which refers to the initial activation of one or more rule representations in WM, demands inductive reasoning and spontaneous cognitive flexibility, but places little demand on WM. Although several rules may be maintained in WM, one must select a particular rule to guide classification. Initially, rule selection is likely to be fairly random but as the task progresses, the pattern of recent feedback will increase or decrease activation of a particular rule representation in WM. The most strongly activated rule is selected to guide responding. If the selected rule remains associated with a consistent history of positive reinforcement, that rule should be maintained in WM, protected from interference by irrelevant information/rules. If the selected rule is not associated with a recent history of positive reinforcement, then one should shift away from that rule. Once the incorrect rule is abandoned, one must either guess until a new rule can be generated or select a new rule based upon its relative activation in WM.

In the sections that follow, we examine the impact of PD on the component processes of rule-based category learning, namely rule generation, maintenance, shifting and selection. In doing so, we have worked to identify and, where possible, resolve discrepancies within the neuropsychological literature to clarify the manner in which PD affects each component process. Often, variability in performance may be attributable to whether patients are tested while on or off their usual medication and we have worked to specify the potential role of PD-related medication on patients' performance. For each component process of hypothesis testing, we integrate relevant neuropsychological evidence from patients with PD with neuroimaging and computational modeling evidence to clarify the neural architecture of rule-based category learning and the neurobiological impact of PD. The proposed neural architecture of rule based category learning is illustrated in Figure 2.

1B Rule Generation

Examinations of rule generation in PD, which are summarized in Table 1, typically employ one of two techniques. The first requires participants to state the rule they are testing as they perform feedback-mediated category learning. On these tasks, patients with PD tend to verbalize fewer hypotheses, regardless of whether the task involves unidimensional (e.g. respond according to shape; Channon, 1997) or multi-dimensional rules (e.g. respond based upon the shape, color and number of stimuli showing; Price, 2006). Unfortunately, this measure of rule generation is confounded by the operation of rule shifting and selection processes. Further, it is not clear whether deficits reflect an impairment to rule generation or feedback-mediated learning, which some have argued is disrupted in PD (Charbonneau, Riopelle & Beninger, 1996; Frank, 2005; Frank, Seeberger, & O'Reilly, 2004; Shohamy et al., 2005; Vriezen & Moscovitch, 1990).

To more specifically target rule generation, the second type of measure presents participants with a set of stimuli that vary along multiple dimensions and participants must generate as many sorting rules as possible without receiving any form of feedback. Studies using this type of measure have produced evidence of normal (Beatty & Monson, 1990; Dimitrov, Grafman, Soares & Clark, 1999) and impaired rule generation performance (Farina, 1994; Swainson et al., 2006) in PD. One recent study suggests this discrepancy may reflect variations in disease severity and patients' medication status (Swainson et al., 2006). Specifically, medication worsened rule generation performance in patients with early PD but improved performance among patients with moderate or severe PD.

Detrimental effects of medication in PD have been observed with other tasks and it has been argued that medication may "overdose" particular neural processes (Cools, 2006; Cools et al., 2003; 2007; Gotham et al., 1988; Swainson et al., 2000). More specifically, the "overdose hypothesis" posits that the medication required to treat motor impairment, associated with

degradation of the dorsal striatum, results in excessive DA in ventral striatum, which is relatively unaffected in early PD (Kish et al., 1988; Farley et al., 1977). Consistent with this “overdose hypothesis”, medication in early PD has been shown to disrupt activity within the ventral striatum (Cools et al., 2007). As PD advances, DA neurons in the ventral striatum degenerate and the ventral cortico-striatal circuits become increasingly compromised (Kish et al., 1988; Farley et al., 1977). Among moderately affected PD patients, medication appears to sufficiently overcome this deficit and improve performance on tasks mediated by the ventral circuit (Cools et al., 2001; 2006; Swainson et al., 2006). However, once the ventral striatum is heavily compromised, as in severe PD, medication may be insufficient to support normal task performance, resulting in impaired performance both on and off medication.

The overdose hypothesis posits that for processes mediated by ventral cortico-striatal circuitry, the effect of medication in PD interacts with disease severity according to an “inverted U” function. Specifically, such processes are impaired in medicated, early PD patients, due to excessive DA, and medicated, late PD patients, due to insufficient DA; medicated patients with moderate PD perform normally (Cools et al., 2001; 2006; Swainson et al., 2006). This “inverted U” pattern has been observed with rule generation (Swainson et al., 2006) and may explain the variation in rule generation performance across studies. Those studies demonstrating normal rule generation involved medicated patients of moderate severity (Beatty & Monson, 1990; Dimitrov et al., 1999) whereas those studies reporting impairment involved medicated patients of mild severity (Farina, 1994; Price, 2006).

The possibility that rule generation depends upon ventral cortico-striatal circuitry is supported by converging neuroimaging and neuropsychological evidence from a variety of problem solving tasks indicating involvement of the OFC and ACC in hypothesis generation (Burgess, 2000; Dimitrov et al., 1999; Elliot & Dolan, 1998; Goel & Dolan, 2000; Goel & Grafman, 2000; Miller & Tippet, 1996; Reverberi, D’Agostini, & Skrap, 2002; Reverberi, Lavaroni, Gigli, Skrap & Shallice, 2005; Vartanian & Goel, 2005). Anti-Parkinsonian medications may “overdose” the ventral striatum, thereby creating dysfunction in its cortical targets, namely OFC and ACC. Taken together, the general pattern of evidence suggests that PD patients experience difficulty generating rules, a problem that may stem from PD-related treatments rather than the disease itself.

2B Rule Maintenance

Once a rule is generated, it must be maintained in WM to guide responding. Maintaining rule representations within WM demands selective attention, which consists of two general processes: a) active maintenance of relevant information and b) inhibition of irrelevant information. In this context, active maintenance refers to processes which sustain activation of a distinct pattern of neural activity associated with relevant information. This pattern of activation persists unless destabilized by a signal to update WM. On the other hand, inhibition in this context refers to those processes that are responsible for actively reducing the likelihood that irrelevant items will achieve a representation in WM and potentially disrupt the maintenance of relevant information. Together, active maintenance of relevant information and inhibition of irrelevant information support rule maintenance. Generally, PD has little impact on WM maintenance (Lewis, Cools et al., 2003; Lewis, Dove et al., 2003; Lewis, Salbosz, Robbins, Barker & Owen, 2005; Owen, Bekinska et al., 1993; Owen, Roberts et al., 1993), whereas inhibitory processes are less stable (Dujardin et al., 1999; Filoteo & Maddox, 1999; Maddox, Filoteo, Delis, & Salmon, 1996; McDowell & Harris, 1997; Sharpe, 1990). Thus, rule maintenance deficits in PD may emerge under conditions of high interference by irrelevant information.

In category learning tasks, rule maintenance is typically measured by the frequency of set-loss errors, which occur when one abandons a rule that has been consistently reinforced. Table 2

summarizes findings from examinations of rule maintenance in PD. Most commonly, rule maintenance has been examined using the WCST and a large scale analysis of set loss errors on the WCST, involving over 180 PD patients, revealed normal patterns of rule maintenance (Paolo, Troester, Axelrod, & Koller, 1995). A number of studies involving the WCST and other category learning tasks have reported similar findings in PD, although a few have reported impairment (see Table 2). In contrast to generally preserved rule maintenance on the WCST, PD patients exhibit deficits on the similarly structured Odd-Man-Out task (OMO; Flowers & Robertson, 1985; Richards, Cote & Stern, 1993). On the OMO, participants must indicate which of three stimuli is different from the others using a simple categorization rule (e.g. letter or shape) and this rule changes several times over the course of the task. PD patients show normal rule maintenance for the first few rules but set loss errors increase following several rule switches. Previously reinforced rules create considerable proactive interference and increased inhibition is necessary to prevent these rules from disrupting maintenance of the currently relevant rule. This may be especially problematic for PD patients, who tend to be more susceptible to proactive interference (Helkala, Laulumaa, Soininen, & Riekkinen, 1989; Rouleau, Imbault, Laframboise & Bedard, 2001), a deficit that likely stems from prefrontal dysfunction associated with PD (Feredoes, Tononi & Postle, 2006; Turner, Cipolotti, Yousry & Shallice, 2007).

If set loss errors increase following multiple rule switches, it is possible that rule maintenance deficits may be underestimated by the WCST. Due to a number of issues, PD patients tend to achieve fewer WCST categories than controls, and therefore experience fewer rule switches. Patients who would have difficulty inhibiting previously successful rules may also fail to achieve many previous rules and therefore experience little proactive interference. It would be worthwhile to systematically examine whether set loss errors increase as a function of previously reinforced rules. On tasks like the WCST, where the rule frequently changes, set loss errors should increase as patients achieve more categories. In contrast, if the rule remains the same throughout the task, set loss errors should be fairly low. Several studies that examined category learning using a single-rule task found no evidence of increased set loss errors among PD patients (Channon, Jones & Stephenson, 1993; Filoteo, Maddox, Ing, Zizak & Song, 2005; Price, 2006), suggesting that rule maintenance is more challenging under conditions of high proactive interference.

Additionally, it appears that high levels of concurrent interference within a task create problems for PD patients. On single-rule tasks, set loss errors among PD patients are more common when irrelevant dimensions vary randomly (Filoteo, Maddox, Ing & Song, 2007), and this occurs even when participants are explicitly told which rule to use (Filoteo & Maddox, 1999; Maddox et al., 1996). In contrast, set loss errors are not as prevalent in PD patients when there is no irrelevant dimension variability, despite an increase in active maintenance demands within WM (Filoteo et al., 2007). These data suggest that PD has relatively little impact on rule maintenance unless conditions require a high level of selective attention.

Computational models of WM typically depict active maintenance as a function of recurrent excitation among frontal neurons (Braver & Cohen, 1999; 2000; Frank, Loughry & O'Reilly, 2001; Moody, Wise, & Pellegrino, 1998; O'Reilly & Frank, 2006; O'Reilly & Munakata, 2000) or recurrent connections between PFC and thalamus (Ashby et al., 1998; 2005; Dominey, Arbib & Joseph, 1995; Goldman-Rakic & Friedman, 1991; Houk & Wise, 1995; f, 2000; Taylor & Taylor, 2000; Zipser, 1991). If WM maintenance depends upon low levels of tonic DA stimulation in PFC, then among PD patients, available DA should be sufficient to support the maintenance of WM. Alternatively, the FRONTAL-Striatal-Thalamic model of WM (FROST; Ashby et al., 2005), proposes that WM maintenance depends upon excitatory projections from PFC to associated neurons within the head of the caudate. When WM load is high or complex, the caudate becomes necessary to inhibit the GP and support prolonged maintenance. Striatal

dysfunction, such as in PD, limits the caudate's ability to inhibit the GP from disrupting active thalamo-cortical loops. Thus, the FROST model predicts that PD impairs active maintenance only when the WM load is especially high.

Whereas active maintenance is generally preserved in PD, patients may have greater difficulty inhibiting irrelevant information from accessing WM. This type of inhibition is commonly attributed to some type of WM gating mechanism (Ashby et al., 2005; Braver & Cohen, 2000; Cohen, Braver & O'Reilly, 1996; Frank et al., 2001; Moody et al., 1998; O'Reilly, Braver & Cohen, 1999; O'Reilly & Munakata, 2000; Zipser, 1991). Rougier et al. (2005) recently demonstrated the necessity of a gating mechanism in rule-based category learning through a simulation of WCST performance. When WM was modeled to include a gating mechanism, relevant features were rapidly encoded, resulting in activation of the correct rule. Simpler models without a gating mechanism tended to activate new rule representations with each stimulus presentation and failed to settle on a particular rule.

A number of WM models emphasize the importance of some type of gating mechanism, which is thought to rely upon phasic changes in DA. Brief, phasic changes in DA are known to follow reinforcement prediction errors, which reflect differences between an expected and actual outcome (Bayer & Glimcher, 2005; Delgado, Locke, Stenger & Fiez, 2003; Frank, Woroch & Curran, 2005; Holroyd & Coles, 2002; Shultz, Dayan & Montague, 1997; Schultz, 2007). In addition, DA appears to enhance the contrast between the relevant and irrelevant dimensions of a stimulus by enhancing the firing rate of currently active cells and suppressing less active cells (Cohen, Braver, & Brown, 2002; Cohen & Servan-Schreiber, 1992; Foote & Morrison, 1987; Hernandez-Lopez et al., 1997; Nicola, Surmeier & Malenka, 2000; Rolls, Thorpe, Boytun, Szabo, & Perrett, 1984). Thus, gating supports selective attention via active suppression of the representation(s) associated with the irrelevant dimension(s) and maintenance of the representation of the relevant dimension(s).

Several WM models posit that gating is accomplished by DA input to PFC (Braver & Cohen, 1999; O'Reilly et al., 1999). Consistent with this, profound DA depletion within PFC leads to high distractibility and great difficulty maintaining mental set (Collins, Wilkinson, Everitt, Robbins & Roberts, 2000; Crofts et al., 2001). The impact of DA on WM performance appears to be largely dose-dependent, such that especially high or low levels of DA increase one's susceptibility to distraction (Kimberg, D'Esposito & Farah, 2007; Williams & Goldman-Rakic, 1995). In early PD, prefrontal DA availability is relatively normal (Brück et al., 2006; Sawamoto et al., 2008) and medication may yield excessive DA activation in PFC. Among healthy adults, WM under conditions of high distraction is impaired by D2 agonists that target receptors abundant in PFC and striatum, presumably because the excessive DA disrupts the gating mechanism, allowing both relevant and irrelevant information to access WM (Frank & O'Reilly, 2006). Pharmacological treatments for PD, which increase the tonic availability of DA within PFC and caudate, may similarly reduce the discriminatory power of phasic changes in DA (Frank et al., 2004). Excessive prefrontal DA may disrupt the WM gating mechanism by lowering the threshold for updating the contents of WM, resulting in rule maintenance deficits, especially under conditions of high interference.

Alternatively, difficulty filtering irrelevant information may reflect disturbances to a DA-mediated gating mechanism within the striatum (Frank et al., 2001; Hazy, Frank & O'Reilly, 2007; O'Reilly & Frank, 2006). According to the Prefrontal, Basal ganglia, Working Memory (PBWM) model, each viable cognitive response is separately maintained in the PFC as a distinct stripe, or "isolated group of interconnected neurons" (Hazy et al., 2007, p. 4). Each PFC stripe is interconnected with striatal neurons that govern WM updating based upon recent feedback. Receipt of unexpected positive feedback triggers a phasic burst of DA within the caudate. This excites the direct, or "Go" pathway of the basal ganglia and inhibits the indirect,

or “NoGo”, pathway, thereby preventing the GP_i from inhibiting relevant fronto-thalamic activity and increasing the likelihood that relevant information accesses WM. Irrelevant stimulus dimensions are not updated despite receiving intermittent reinforcement. This is because the frequent non-reinforcement of irrelevant dimensions results in inhibition of the direct, “Go” pathway and excitation of the indirect, or “NoGo” pathway, which indirectly allows GP_i to inhibit the thalamus and decreases the likelihood that the irrelevant dimension (s) will access WM. In this way, striatal DA selectively gates only the most relevant representations, namely those consistently associated with positive reinforcement. Consistent with this, McNab & Klingberg (2008) demonstrated that high levels of within-task distraction were associated with increased GP_i activation, presumably reflecting the gating mechanisms of the “Go” and “NoGo” pathways. Moreover, the extent of GP_i activation was associated with WM capacity across participants, suggesting that this gating mechanism within the basal ganglia has important implications for selective attention processes in WM.

In PD, significant DA depletion results in too little inhibition of the “NoGo” pathway and excessive inhibition of the thalamus by the GP_i (Frank, 2005; Frank & O’Reilly, 2006). Animal research indicates that DA depletion in the caudate leads to decreased updating and enhanced resistance to distraction (Crofts et al., 2001; Collins et al., 2000). Thus, it is unlikely that the increased susceptibility to interference among PD patients stems from striatal DA depletion. Instead, patients’ increased distractibility could reflect elevated DA levels due to levodopa or DA agonist medication, which increase tonic DA stimulation within the caudate. Although a phasic increase in DA should selectively enhance only the most active synapses, excessive tonic DA stimulation, due to medication, may enhance all active synapses, thereby reducing the discriminatory power of phasic changes in DA and lowering the threshold for updating WM. Notably, prolonged levodopa ingestion may create a secondary problem by sensitizing striatal DA receptors, resulting in excessive response to DA stimulation (Calon et al., 2002; Deogaonkar, Piallat & Subramanian; Fillion, Tremblay & Bedard, 1991; Obeso, et al 2000; Papa, Desimone, Fiorani, & Oldfield, 1999). Once this occurs, medications that target DA receptors will inappropriately increase excitation along the “Go” pathway and decrease inhibition along the “NoGo” pathway. Consonant with this hypothesis, prolonged use of levodopa is associated with inappropriate motor activity, specifically uncontrollable, choreatic movements known as dyskinesias. The mechanism that causes drug-induced dyskinesias may also be reduce the ability to inhibit inappropriate cognitive responses. Future research is needed to clarify the possible relationship between WM impairment in PD and specific forms of PD treatment.

To summarize, neuropsychological evidence suggests that PD patients exhibit increased susceptibility to irrelevant stimulus dimensions during category learning, which disrupts rule maintenance under conditions of high concurrent or proactive interference. It appears this deficit may stem from excessive tonic DA stimulation in PFC and/or caudate. Additional work is necessary to clarify how pharmacological therapies impact rule maintenance performance in PD.

Rule Shifting

In contrast to rule maintenance, which occurs when one persists with a successful rule, rule shifting occurs when one ceases with an unsuccessful rule. Discussions of executive function in PD commonly assert that patients exhibit rule shifting deficits (e.g. Brown & Marsden, 1990; Lees & Smith, 1983; Salmon et al., 1998; Taylor, Saint-Cyr & Lang, 1986). However, as shown in Table 3, this generalization fails to capture the variability across studies.

Neuropsychological examinations of rule shifting have typically relied upon the WCST and the Intra-Extra Dimensional Set Shift task (ID/ED task; Downes et al., 1989). These tasks

require a participant to categorize simple stimuli according to some rule that is not specified. Following a certain number of correct sorts, the experimenter changes the rule without notice. [The exception to this is the modified WCST (Nelson 1976), in which participants are told that a switch has occurred.] Since the previously relevant rule no longer receives reinforcement, it should be abandoned. However, participants may occasionally persevere with that rule and a high frequency of preservative responses indicates rule shifting impairment.

As detailed in Table 3, patients with PD often exhibit increased perseverative responses during category learning. One meta-analysis of rule shifting on the WCST found an increase in perseverative responding among PD patients of moderate effect size, although considerable variability existed across studies (Zakzanis & Freedman, 1999, $N = 11$, $\text{mean}(d) = .46$, $\text{range}(d) = -.66 - +.92$). This variability may reflect differences in the patient samples across studies. In particular, increased disease severity may be associated with increased shifting impairment (Starkstein et al., 1989; but see Gotham et al., 1988). Medication, however, appears to have little effect as it neither improves (Gotham et al., 1988) nor worsens shifting performance on the WCST (Bowen, Kamienny, Burns & Yahr, 1975; Cooper et al., 1991; 1992; Kulisevsky et al., 1996).

Though variation across patient samples may explain some of the inconsistencies across studies, shifting deficits also appear to vary depending upon the WCST version in use. In the original 128 card version of the WCST (Berg, 1948; Heaton, 1981; Milner, 1963), a sort could be correct along several dimensions. In contrast, simplified versions (Hart, Kwentus, Wade & Taylor, 1988; Nelson, 1976) include only those cards that can only be matched along a single dimension. Although healthy older adults perform comparably on the two versions (Greve & Smith, 1991), it appears that PD patients have greater difficulty with the simplified version. Studies using the simpler version often indicate rule shifting deficits among PD patients, whereas the majority of studies using the original WCST report normal shifting performance (see Table 3). On the simplified versions of the WCST, rule shifting deficits emerge in patients of various stages of severity; on the original WCST, deficits primarily emerge among patients with more severe PD.

It can be difficult to interpret a group's performance on the WCST, however, because the task measures myriad processes. For this reason, researchers also rely on the ID/ED task (Downes et al., 1989). On this task, participants view two stimuli and must determine which is correct based upon trial-by-trial feedback. The task proceeds through a series of stages, each of which is designed to measure a particular type of shift. On the final, extra-dimensional shift (EDS), stage participants must begin to respond according to the previously irrelevant dimension and ignore the previously relevant dimension. Rule shifting is determined either through the number of errors made on this phase, the number of trials required before the participant reaches criterion, or the percentage of participants who reach criterion. Each of these methods indicate rule shifting impairment in PD (Downes et al., 1989; Gauntlett-Gilbert, Roberts & Brown, 1999; Lange et al., 1992; Slabosz et al, 2006; Tomer, Aharon-Peretz, & Tsitrinbaum, 2007).

The generally poor rule shifting performance of patients on the ED/ID task mirrors the poor performance of patients on the simplified versions of WCST and contrasts with the generally preserved performance on the traditional WCST (see Table 3). In contrast to the traditional WCST, positive feedback on the simpler WCST (Nelson, 1976; Hart et al., 1988) and the ID/ED (Downes et al., 1989) task reinforces only the appropriate dimension. By insuring that irrelevant dimensions do not receive any reinforcement, the modification was designed to simplify the WCST. Unfortunately, this change may create particular difficulty for patients with PD. Slabosz et al. (2006) demonstrated that PD patients experience shifting impairment, but only when the newly relevant dimension had previously been completely irrelevant, as with

the simplified WCST and ID/ED tasks. When the newly relevant dimension had previously received some reinforcement, as it does on the traditional WCST, patients shifted normally.

As discussed in the previous section, medicated PD patients are more susceptible to distraction by irrelevant dimensions that randomly vary with the relevant dimension. Although this may disrupt rule maintenance, it also enables patients to more readily shift toward the dimension once it becomes relevant. Consequently, medicated patients shift normally when the newly relevant dimension had previously received intermittent reinforcement (Kulisevsky et al., 1996; Slabosz et al., 2006). In contrast, when a newly relevant dimension has no history of reinforcement, or a history of complete non-reinforcement, patients have difficulty identifying the newly relevant rule (Channon et al., 1993; Price, 2006; van Spaendonck, Berger, Horstink, Brom & Cools, 1995). This possibility is discussed further in the Rule Selection section. These findings suggest that medicated PD patients may not necessarily have problems shifting away from an inappropriate rule. Instead they may have difficulty selecting the newly appropriate rule, especially if the new rule has no prior history of reinforcement.

By contrast, rule shifting is generally impaired among PD patients off medication, which suggests a role for striatal DA in rule shifting. This possibility is illustrated in the PBWM model (Frank et al., 2001; O'Reilly & Frank, 2006), outlined in the previous section. According to the model, the occurrence of unexpected negative feedback triggers a phasic dip of DA within the caudate that decreases excitation of the "GO" pathway and inhibition of the "NoGo" pathway. The net effect is inhibition and destabilization of the stripe of prefrontal cortex that is associated with the rule in use. Negative feedback decreases the likelihood that the rule will be updated into WM the next time it is presented, and increases the likelihood of a rule shift (Frank et al., 2001; Hazy et al., 2007; O'Reilly & Frank, 2006). Among PD patients off medication, the model further predicts that depletion of striatal DA reduces the efficacy of phasic changes in DA following reinforcement prediction errors (Frank, 2005; Frank & O'Reilly, 2006). In the context of category learning, this means PD patients off medication should exhibit reduced distractibility and increased perseverative behavior. However, DA depletion within the dorsal striatum of non-human animals has no impact on set shifting, although animals did exhibit reduced distractibility (Crofts et al., 2001; Collins et al., 2000). These data call into question the assertion that rule shifting processes are mediated by DA activity within the caudate.

Instead, shifting may depend upon DA activity throughout the dorsal fronto-striatal circuit. Though rule shifting is unaffected by selective DA depletion in PFC (Crofts et al., 2001; Roberts et al., 1994) or caudate (Crofts et al.; Collins et al., 2000), it is possible that DA in either region compensates for loss in the other. Depletion of prefrontal DA is associated with upregulation of DA activity in the caudate (Roberts et al., 1994), which may explain why selective DA lesions in the caudate had little impact on shifting performance. This possibility is supported by evidence that the D2/D3 antagonist sulpiride, which targets DA receptors in the PFC and NoGo pathway of the striatum, impairs set shifting performance in healthy volunteers (Mehta et al., 1999; 2004; 2005). Thus, rule shifting in PD may vary with the degree to which prefrontal dopaminergic activity and medication can compensate for striatal losses. This may explain why rule shifting impairment in PD patients may persist among optimally medicated patients (see Table 3).

In addition to the involvement of the dopaminergic system, accumulating evidence indicates a role for the noradrenergic (NA) system in supporting rule shifting performance. Noradrenergic projections from the locus ceruleus target diverse forebrain sites, including thalamus, PFC and ACC. Pharmacological manipulations of prefrontal NA have been shown to alter set shifting performance in rats (Lapiz & Morilak, 2006; Lapiz et al., 2007; Newman et al., 2008; Tait et al., 2007). Although the mechanism by which cortical NA supports set shifting is unclear, it is possible that repeated failure to achieve positive reinforcement results

in a switch towards explorative behaviors, which would include shifting away from the rule governing classification responses. This switch is postulated to depend upon changes in the ceruleo-cortical noradrenergic system (Aston-Jones, Rajkowski & Cohen, 1999). Patients with PD typically experience significant degeneration of locus ceruleus (Rommelfanger & Weinshenker, 2007 for), which would result in altered NA activity and may cause a failure to switch towards more explorative behaviors). Further, given that many of the pharmacological treatments for PD, including L-dopa, increase NA production in locus ceruleus (Fornai, di Poggio, Pellegrini, Ruggieri & Paparelli, 2007), medication may improve shifting performance to the extent that locus ceruleus integrity is preserved.

In summary, rule shifting performance may reflect activity of the dopaminergic and/or noradrenergic systems, both of which are compromised in PD. Among PD patients off medication, decreased DA and NA availability appears to disrupt rule shifting and this impairment may be ameliorated by pharmacological treatment.

Rule Selection

The preceding section addressed the neural architecture of rule shifting, which should occur following negative feedback. The receipt of negative feedback must not only trigger a shift away from the rule in use, but the selection of a new rule to guide responding. The possible impact of PD on rule selection was initially suggested by Downes et al. (1989), who argued that PD deficits on the ID/ED task reflect difficulty identifying the newly relevant dimension rather than an inability to abandon the previous rule. The specific process of rule selection has received relatively little attention in the category learning literature, although other lines of research offer evidence relevant to the present discussion. Table 4 summarizes evidence relevant to rule selection in PD.

Arguably, the first examination of rule selection processes was completed by Owen, Roberts, et al. (1993), who modified the traditional ID/ED task to include an additional shift stage, termed the learned irrelevance shift. In this shift, the relevant dimension was replaced with a novel dimension and participants had to sort according to the previously irrelevant dimension. PD patients have difficulty with this “learned irrelevance” shift, regardless of whether they were on medication (Owen, Roberts, et al., 1993; Gauntlett-Gilbert et al., 1999; Lewis et al., 2005; Slabosz et al., 2006). This deficit was interpreted as reflecting enhanced latent inhibition (LI) (Owen, Roberts, et al., 1993; Slabosz et al., 2006), which refers to slowed attention to previously ignored stimuli relative to novel stimuli (De La Casa, Ruiz & Lubow, 1993; Lubow, Dressler & Kaplan, 1999; Lubow & Gewirtz, 1995).

Enhanced LI is likely among PD patients off medication, given previously discussed evidence of reduced distractibility and set shifting ability. The inability to appropriately update the contents of WM may similarly impair the capacity to disinhibit previously irrelevant rules. This deficit may be especially pronounced if a rule had previously been fully irrelevant to classification and thus not represented in WM (Slabosz et al., 2006). Among medicated PD patients, however, enhanced LI is unlikely. As previously detailed, medication may reduce inhibitory processes and medicated PD patients exhibit diminished LI in other paradigms (Filoteo, Rilling & Strayer, 2002; Grande, et al., 2006, but see Wylie & Stout, 2002). Further, medicated PD patients have difficulty selecting the appropriate rule even when conditions are manipulated to favor enhanced LI (Gauntlett-Gilbert et al., 1999). Finally, if rule selection deficits in medicated PD primarily reflect enhanced LI, then selection should be unimpaired on category learning tasks that involve a single rule. However patients perform poorly on such tasks, even though the relevant stimulus dimension would not have been inhibited at any point in the task (Channon et al., 1993; Filoteo et al., 2005; 2007; Price, 2006). Taken together, these

data suggest that difficulty on the learned irrelevance shift among medicated PD patients is not due to enhanced LI.

Instead, medicated PD patients may have difficulty with the learned irrelevance shift because they have difficulty identifying which stimulus dimension is most relevant for categorization. Category learning performance is normal among medicated PD patients when all dimensions are equally relevant to classification, but impaired when tasks include stimulus dimensions of varying relevance to classification (Channon et al., 1993; Channon, 1997; Filoteo et al., 2005; 2007; Knowlton, Mangels, & Squire, 1996; Maddox & Filoteo, 2001; Maddox, Aparicio, Marchant & Ivry, 2005; Price, 2006; Swainson et al., 2006). Moreover, when medicated PD patients identify the relevant dimension, they have difficulty selecting an appropriate decisional criterion along that dimension (Filoteo et al., 2007; Maddox et al., 2005).

Recent evidence suggests that selection deficits among medicated PD patients may reflect an inability to make proper use of negative feedback to identify the relevant dimension for classification (Cools et al., 2006; Frank et al., 2004; Schott, Niehaus & Wittman, 2007). Feedback-mediated learning is driven by reinforcement prediction errors, which are known to rely upon midbrain DA signals (Hollerman & Schultz, 1998). Whereas unexpected positive feedback (positive prediction error) triggers a phasic DA burst, unexpected negative feedback (negative prediction error) triggers a phasic dip. These signals are thought to drive learning by biasing activity in a number of target regions (Schultz, 2007; Schultz & Dickinson, 2000), including the NAc (Aron et al., 2004; Rodriguez et al., 2006) and ACC (Holroyd & Coles, 2002; Holroyd & Coles, 2005; Ridderinkhof, Ullsperger, Crone & Nieuwenhuis, 2004). Functional neuroimaging examinations of category learning have indicated that unexpected negative feedback is associated with increased activation of NAc and ACC (Aron et al., 2004; Rodriguez, Aron & Poldrack, 2006). This activity is thought to integrate reinforcement values of consecutive events to bias changes in cognitive or overt responding (DePisapia, Slomski, & Braver, 2007; Mogenson, 1987).

At present, it is unclear whether ACC activation varies as a function of NAc activity or if the two regions respond in parallel to reinforcement prediction errors. It is possible that a negative prediction error triggers increased NAc activation, which would briefly inhibit the GPI, resulting in increased ACC activity. In this way, error-driven changes within NAc may govern the relative activation of ACC neurons associated with a given rule representation. Alternatively, since midbrain DA signals directly bias ACC activation, it is possible that reinforcement-mediated changes in the NAc and ACC occur independently. Regardless, ACC is commonly believed to support response selection, including cognitive responses (Barch, Braver & Noll, 2000; Botvinick, Braver, Carter, Barch & Cohen, 2001; Buckner, Raichle, Miezin & Petersen, 1996; Corbetta, et al., 1992; Elliot & Dolan, 1998; Petersen, Fox, Posner, Mintan & Raichle, 1988; Raichle et al., 1994).

The role of ACC in supporting rule selection is supported by several lines of evidence. First, functional neuroimaging with healthy controls performing the WCST found ACC activation following negative feedback, when rule selection must occur, but not following positive feedback, when the rule in use can simply be maintained (Monchi et al., 2001; 2004). Further, evidence from other decision making tasks indicates that ACC activation is highest on learning conditions where feedback must be integrated over a series of trials, pointing to the role of ACC in the temporal integration of feedback (Rushworth, Buckley, Behrens, Walton, & Bannerman, 2007; Yarkoni, Braver, Gray & Green, 2005). Finally, ACC activity occurs with category learning only when stimuli vary along multiple dimensions; uni-dimensional variation is not associated with ACC activation (Corbetta et al., 1992). These data led Ashby et al. (1998) to conclude that the ACC facilitates rule selection on multi-dimensional tasks by biasing the relative strength of rule representations within prefrontal cortex.

To summarize, rule selection appears to depend upon reinforcement-mediated activation of the ACC, which biases the relative activation of rule representations in PFC such that the most consistently reinforced rule is selected to guide responding. Recent evidence suggests that medication in early PD disrupts reinforcement-mediated activity within ACC (Holroyd, Praamstra, Plat & Coles, 2002; Stemmer et al., 2007; Willemsen et al., 2008), which may explain findings of impaired rule selection performance in this population (Channon et al., 1997; Price, 2006; Swainson et al., 2006). Medication in early PD likely results in an excessive level of tonic DA activity in the ventral cortico-striatal circuit, including NAc and ACC, an area that is typically spared until advanced PD (Cools, 2006; Farley et al., 1977; Kish et al., 1988). Increased tonic DA stimulation associated with PD medication may “fill in” the phasic dip in DA release that is triggered by a negative prediction error (Frank et al., 2004; Hollerman & Schultz, 1998). If this is the case, then negative feedback would fail to trigger the learning signal within ACC that should weaken the associated rule representation in PFC. Thus, insensitivity to negative feedback among medicated PD patients may stem from excessive DA activity in the ventral cortico-striatal circuit (Cools, 2006).

Alternatively, as detailed in the Rule Maintenance section, medication in early PD may disrupt dorsal striatal function in certain patients. According to the PBWM model (Frank et al., 2001; Frank & O'Reilly, 2006), feedback shapes the strength of individual rule representations through patterns of activity along the “Go” and “NoGo” striatal pathways. Medication in PD may lead to abnormally high levels of tonic DA stimulation such that the phasic dip triggered by negative feedback is insufficient to counteract tonic excitation of the “Go” pathway. Consonant with this prediction, a pharmacologically-induced increase in DA release in healthy volunteers was associated with greater inhibition of the “NoGo” pathway and impairments in learning from negative feedback (Frank & O'Reilly, 2006). Consequently, selection deficits among medicated PD patients may reflect decreased sensitivity to negative feedback due to excessive DA in the dorsal striatum. It is possible that decreased response to negative feedback may explain observed deficits in rule shifting among medicated PD patients. However, rule shifting and selection processes have been dissociated in several studies; although medicated patients have no difficulty shifting away from an inappropriate rule they tend to select a new rule that should have been ruled out by negative feedback (Channon, 1997; Price, 2006). This would suggest that although negative feedback triggers rule shifting and selection processes, the two depend upon distinct mechanisms.

In contrast to medicated PD patients, PD patients off medication have no difficulty making use of negative feedback to identify the relevant stimulus dimension (Cools et al., 2006; Frank et al., 2004; Holroyd et al., 2002; Swainson et al., 2006). Among PD patients off medication, DA levels within the NAc are relatively normal and the pattern of NAc and ACC activation during the period following feedback is normal (Cools et al., 2007; Monchi et al., 2004). Despite this, PD patients off medication have difficulty with tasks designed to assess rule selection, specifically the learned irrelevance phase of the ED/IDS task (Owen, Roberts et al., 1993). Such deficits may stem from an insensitivity to positive feedback (Frank et al., 2004; Schott et al., 2007; but see Cools et al., 2006; Frank et al., 2007). Normally, positive feedback is associated with phasic increases in DA within the dorsal striatum but DA depletion minimizes the size and efficacy of such bursts (Schott et al., 2007; Pizzigalli et al., 2008), thereby reducing sensitivity to positive feedback among PD patients off medication.

Although limited research exists on the impact of PD on rule selection, the evidence we have reviewed here suggests impairment among patients on and off medication. It appears that PD patients off medication may be less sensitive to positive feedback, whereas medicated PD patients are less sensitive to negative feedback. In either case, rule selection fails to proceed normally.

Summary and Conclusions

In this review, we explored PD patient performance on rule based category learning with specific focus on the component processes of rule generation, maintenance, shifting and selection. This neuropsychological evidence was then integrated with neuroimaging and computational modeling research to clarify the neural architecture of explicit rule-based category learning (see Figure 2).

Successful rule-based category learning demands the generation of one or more viable rules to guide responding. The data reviewed here suggests that rule generation relies upon activity within the ventral cortico-striatal circuit, namely ACC and OFC. This circuit also appears to support rule selection through feedback-mediated changes in the relative activation of rule representations within WM. Specifically, reinforcement prediction errors trigger midbrain DA signals that govern activity within the ACC. The pattern of ACC activation biases activity within PFC towards those rules that have not received recent negative feedback. Whereas rule generation and selection appear to rely on ventral cortico-striatal circuitry, rule maintenance and shifting rely primarily on dorsal circuitry, namely head of the caudate and dorsolateral PFC. Individual rule representations are maintained in WM via distinct loops of recurrent excitation between PFC and thalamus. Rule maintenance is most likely governed by a DA-mediated gating mechanism that insures WM access only to those cognitive responses that are consistently reinforced by positive feedback; irrelevant responses are reinforced only intermittently and are therefore not maintained. Receipt of unexpected negative feedback triggers a phasic dip in DA release, which destabilizes the rule representation in WM and increases the likelihood of a shift away from that rule. Normally, coordinated activity of these cortico-striatal systems supports successful learning of rule-based category structures.

Among patients with PD, however these systems become dysfunctional due to disruption of the dopaminergic and, possibly, the noradrenergic systems. When not on medication, early PD patients largely suffer rule-based category learning deficits that stem from a lack of dorsal striatal DA availability and cortical norepinephrine activity. Because of these changes, patients off medication have difficulty updating WM, failing to readily shift away from unsuccessful rules. Although the tendency to perseverate with an unsuccessful rule limits the necessity of selecting new rules, early PD patients off medication may have little difficulty generating potential rules and making use of feedback to identify the most relevant among them. As PD advances and the ventral striatum begins to suffer a significant loss of DA availability, advanced PD patients off medication may begin to experience difficulty with those processes mediated by the ventral striatum and its cortical targets, specifically rule generation and rule selection.

The nature of rule-based category learning deficits in medicated PD patients, specifically those in the earlier stages of disease, is quite different from those observed in patients off medication. Medication should improve patients' ability to update WM, thereby remediating rule shifting deficits. However, it appears that medication may also disrupt the gating mechanism that supports WM updating, causing increased distractibility among medicated PD patients. Presently, it is unclear if increased distractibility occurs in all medicated PD patients or if it stems from particular courses of treatment. Pharmacological therapies tend to also impact the ventral cortico-striatal circuits, which are relatively spared until advanced PD. Among earlier PD patients, medication may create a mild "DA overdose" within the ventral striatum and its cortical targets (e.g. OFC; ACC). Consistent with this overdose hypothesis, rule generation and selection processes, which we argue depend upon ventral cortico-striatal circuitry, are often impaired in PD patients when they are on, but not off, medication.

In summary, the available data indicate that rule-based category learning depends upon a network of striatal structures and frontal cortical regions. Learning to classify novel stimuli depends upon multiple processes, including the generation, maintenance, shifting and selection of classification rules. Dysfunction in any of these components, due to PD or its common treatments, will disrupt category learning, albeit in slightly different ways.

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Figure 1.

Summary of the component processes supporting rule based category learning, specifically rule generation, maintenance, shifting and selection.

Figure 2.

Neural architecture of explicit, rule-based category learning. Solid lines indicate excitatory input; dashed lines indicate inhibitory input. Generation of rules depends upon dopamine (DA) activity within the ventral cortico-striatal circuit, including nucleus accumbens (NAc), orbitofrontal cortex (OFC), and anterior cingulate cortex (ACC). Active maintenance of the rule in use depends upon recurrent excitation of the fronto-thalamic loop that represents that rule. Positive feedback supports rule maintenance through a phasic DA bursts to caudate, which increases excitation of the “Go” pathway and inhibition of the “NoGo” pathway and enables disinhibition of the relevant fronto-thalamic loop. Negative feedback triggers a phasic dip in DA availability in caudate, resulting in enhanced inhibitory output from GPi. This destabilizes the relevant rule representation in WM and increases the likelihood of a shift. Release of norepinephrine from the locus ceruleus may also govern shifting activity. Selection of the new rule depends upon the relative pattern of activation within ACC, which biases the relative patterns of activation of rule representations in prefrontal cortex (PFC). Unexpected negative or positive feedback triggers a phasic dip or burst, respectively, in DA release from the ventral tegmental area. These phasic changes alter activation in NA and ACC and these error-driven changes in ACC activation regulate activation of relevant rule representations in PFC.

Table 1

Source	Task	Patient sample	Result
Beatty & Monson, 1990	California Card Sort Task (Delis et al., 1989)	16 PD; Stages 1–4; M = 2.6	PD = NC ($d = .57$)
Channon, 1997	Unidimensional classification learning	20 PD	PD < NC ($d = .41$)
Dimitrov, Grafman, Soares & Clark, 1999	California Card Sort Task	8 PD; Stages 1–4; M = 3.0	PD = NC ($d = .93$)
Farina et al., 1994	Picture sorting task (Incisa della Rocchetta, 1986)	22 PD Stages 1–2	PD < NC
Hanes, Andrewes & Pantelis, 1995	Verbal solutions task (Reitan, 1972)	25 PD Stages 1–4; M = 2.76	PD < NC ($d = .41$)
Price, 2006	Multi-dimension classification learning	16 PD; Stages 1–3; M = 2.2	PD < NC ($d = 1.0$)
Swainson et al., 2006	Five Dimension Task (Swainson & Robbins, 2001)	11 mild PD _{OFF} 27 mild PD _{ON} 14 severe PD _{ON}	mild PD _{OFF} = NC; mild PD _{ON} < NC severe PD _{ON} = NC

Summary of studies examining rule generation in PD

Note. Stages refers to Hoehn & Yahr (1967) ratings of PD severity; M = mean level of PD severity; d = Cohen's d measure of effect size

Table 2

Summary of studies examining rule maintenance in PD

Source	Task	Patient sample	Result
Beatty & Monson, 1990	WCST (Heaton, 1993)	27 PD Stages 1–4 M=3.3	PD = NC ($d = .07$)
Beatty, Staton, Weir & Monson & Whitaker, 1989	WCST (Heaton, 1993)	25 PD Stages 2–3	PD < NC ($d = .86$)
Channon, Jones & Stephenson, 1993	Unidimensional classification learning task (single rule; no switching)	12 PD Stages 2–3	PD = NC ($d = .13$)
Cooper, Sagar, Jordan, Harvey, Sullivan, 1992	WCST (Heaton, 1993)	61 PD; newly diagnosed; unmedicated	PD = NC ($d = .06$)
Filoteo, Maddox, Ing, Zizak & Sang, 2005	Unidimensional classification learning task (single rule; no switching)	19 PD Stages 1–3	PD < NC
Filoteo, Maddox, Ing, Zizak & Sang, 2005	WCST (Heaton, 1993)	19 PD Stages 1–3	PD = NC
Flowers & Robertson 1985	Odd-Man-Out task	49 PD	PD < NC
Gauntlett-Gilbert, Roberts & Brown, 1999	ID/ED shift task; (Owen, et al., 1993)	10 PD Stages 1–3 M = 2.26	PD < NC
Green et al., 2002	WCST (Heaton, 1993)	61 PD; Stage 3–5	PD < NC ($d = 1.5$)
Monchi et al., 2004	WCST (Heaton, 1993)	8 PD Stages 1–2 off meds	PD < NC
Paolo, Troester, Axelrod & Kaller, 1995	WCST (Heaton, 1993)	181 PD Stages 1–4	PD = NC ($d = .12$)
Price, 2006	Multidimensional classification learning task	16 PD Stage 1–2	PD = NC
Price, 2006	WCST (Hart et al., 1998)	16 PD Stages 1–2	PD = NC
Richards, Cote, Stern, 1993	Odd-Man-Out task (Flowers & Robertson, 1985)	45 PD Stage M = 2.6	PD < NC
Tomer, Fisher, Giladi & Ahron-Peretz, 2002	ID/ED task of CANTAB (Robbins et al., 1998)	24 PD; Stage M = 1.6	PD = NC

Note. Stages refers to Hoehn & Yahr (1967) ratings of PD severity; M = mean level of PD severity; d = Cohen's d measure of effect size

Table 3
Summary of studies examining rule shifting in PD

Source	Task	Patient sample	Result
Beatty & Monson, 1990	WCST (Heaton et al., 1993)	27 PD Stages 1–4; M=2.6	PD = NC ($d=.34$)
Beatty, 1989	WCST (Heaton et al., 1993)	43 PD; Stages 1–4	PD = NC ($d=.56$)
Beatty, Staton, Weir & Monson, 1989	WCST (Heaton et al., 1993)	25 PD; Stages 2–3	PD = NC ($d=.43$)
Bowen, Kamienny, Burns & Yahr, 1975	WCST (Berg, 1948)	18 PD _{OFF} 53 PD _{ON}	PD _{OFF} = NC PD _{ON} = NC
Canavan et al., 1989	WCST (Nelson, 1976)	19 PD; M = 1.5	PD < NC
Channon, Jones, & Stephenson, 1993	Unidimensional classification learning	12 PD Stages 2–3, M = 2.75	PD < NC ($d=.50$)
Cools, van den Bercken, Horstink, van Spaendonck, & Berger, 1984	Block sorting task	18 PD Stages 1–4; M = 2.3	PD < NC
Cools, Barker, Sahakian & Robbins, 2001	ID/ED task (Downes et al., 1989)	14 PD _{ON} ; M = 1.75 15 PD _{OFF} ; M = 1.80	PD _{OFF} = PD _{ON} < NC
Cooper, Sagar, Jordan, Harvey, & Sullivan, 1991	WCST (Milner, 1963)	60 PD; newly diagnosed; unmedicated	PD = NC ($d=.43$)
Cooper, Sagar, Jordan, Harvey, Sullivan, 1992	WCST (Heaton et al., 1981)	82 newly diagnosed PD; randomly assigned on or off meds	PD = NC in each case
Dalrymple-Alford, Kalders, Jones, & Watson, 1994	WCST (Heaton et al., 1993)	8 PD	PD = NC ($d = 0$)
Downes et al., 1989	ED/ID task	16 PD _{OFF} M = 1.1 6 PD _{ON} M = 2.4	PD _{OFF} < NC PD _{ON} < NC
Fimm, Barti, Zimmerman & Wallesch, 1994.	modified ID/ED task	19 PD _{ON} Stages 2–3 M=2; 8 PD _{OFF} Stages 1–3; M= 2.	PD _{ON} = NC; PD _{OFF} < NC
Gauntlett-Gilbert, Roberts & Brown, 1999	modified ID/ED task	10 PD Stages 1–3; M=2.2	PD < NC
Gotham, Brown & Marsden, 1988	WCST (Nelson, 1976)	16 PD Compared ON and OFF	PD _{ON} < NC ($d = .90$) PD _{OFF} < NC ($d = 1.1$)
Green, 2002	WCST (Heaton et al., 1993)	61 PD _{OFF} ; Stage 3–4	PD _{OFF} < NC
Kulisevsky et al., 1996.	WCST (Heaton et al., 1993)	20 PD Compared ON and OFF	PD _{ON} = NC PD _{OFF} = NC
Lange, Robbins, Marsden, Owen & Paul, 1992	ID/ED task (Downes et al., 1989)	10 PD Stages 3–5, M = 3.5; Compared ON and OFF	PD _{OFF} = PD _{ON} < NC
Lees & Smith, 1983	WCST (Neslon, 1976)	12 PD	PD = NC
Lewis et al., 2005	Modified ID/ED task	20 PD; M = 1.9 Compared ON and OFF	PD _{OFF} = PD _{ON} < NC
Monchi et al., 2004	WCST	8 PD _{OFF}	PD _{OFF} < NC
Owen et al., 1993	ID/ED task (Downes et al., 1989)	26 PD _{OFF} (stages 1–3) 23 PD _{ON} (stages 1–4)	PD _{OFF} < NC ($d=2.4$) PD _{ON} = NC
Paolo, Troester, Axelrod & Kaller, 1995	WCST (Heaton et al., 1993)	181 PD Stage 1–4	PD < NC ($d=1.03$)
Price, 2006	WCST (Hart et al., 1998)	17 PD Stages 1–4, M = 2.3	PD = NC
Slabosz et al., 2006	Modified ID/ED task	20 PD Stage M = 1.9 Compared ON and OFF	PD _{OFF} = PD _{ON} < NC

Source	Task	Patient sample	Result
Starkstein et al., 1989	WCST (Heaton et al., 1993)	48 mild PD; 20 moderate PD 26 severe PD	severe < moderate < mild PD; mild PD = NC
Tomer, Aharon-Peretz, & Tsitrinbaum, 2007	ID/ED task of CANTAB (Robbins et al., 1998)	35 PD	PD < NC ($d = 1.08$)
van Spaendonck, Berger, Horstink, Brom, & Cools, 1995	WCST and 2 variants (following Nelson, 1976)	45 PD	PD = NC
Witt et al., 2006	WCST (version not given)	20 PD Stages 1–3	PD = NC
Zakzanis & Freedman	WCST (Heaton et al. et al., 1993)	Meta-analysis (N= 11)	mean(d) = .46 Range(d) = -.66 – +.92

Note. Stages refers to Hoehn & Yahr (1967) ratings of PD severity; M = mean level of PD severity; d = Cohen's d measure of effect size

Table 4
Summary of studies examining rule selection in PD

Source	Task	Patient sample	Result
Channon, 1997	Unidimensional classification learning	21 PD	PD < NC $d=.62$
Channon, Jones, & Stephenson, 1993	Unidimensional classification learning	12 PD; Stages 2–3, $M=2.75$	PD < NC; ($d=.64$) PD tested fewer correct hypotheses
Filoteo, Maddox, Ing, & Song, 2007	Classification learning (uni-dimensional, conjunctive or disjunctive rules)	12 PD; $M=1.8$	unidimensional rule: PD < NC other rules: PD = NC
Filoteo, Maddox, Salmon, Song, 2005	Unidimensional classification learning tasks	19 PD; $M=1.7$	<2 irrelevant dimensions: PD = NC >2 irrelevant dimensions: PD < NC
Gauntlett-Gilbert, Roberts & Brown, 1999	Learned irrelevance shift on ID/ED task	10 PD Stages 1–3; $M=2.25$	PD < NC
Lewis, Slabosz, Robbins, Barker, & Owen, 2004	Learned irrelevance shift on ID/ED task	20 PD; $M = 1.9$ Compared ON and OFF	$PD_{ON} < NC$ $PD_{OFF} < NC$
Owen et al., 1993	Learned irrelevance shift on ID/ED task	26 PD_{OFF} (stages 1–3) 23 PD_{ON} (stages 1–4)	$PD_{ON} < NC$ $PD_{OFF} < NC$
Price, 2006	Multidimensional classification learning	17 PD Stages 1–4, $M = 2.3$	PD < NC
Slabosz et al., 2006	Learned irrelevance shift on ID/ED task	20 PD $M = 1.9$ compared ON and OFF	$PD_{ON} < NC$ $PD_{OFF} < NC$
Swainson, et al., 2006	Five Dimension Task (Swainson & Robbins, 2001)	11 mild PD_{OFF} 27 mild PD_{ON} 14 severe PD_{ON}	Mild $PD_{OFF} = NC$ Mild $PD_{ON} < NC$ Severe $PD_{ON} < NC$