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Trends and Issues in Characterizing Early Cognitive Changes in Parkinson's Disease

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Abstract

In this review, we first discuss trends and issues in measuring cognitive changes in PD, including recent efforts to define the diagnostic classification of "PD Mild Cognitive Impairment" (PD-MCI). After reviewing some limitations associated with this diagnosis, we discuss how measures derived from the neurocognitive sciences offer better precision in detecting early cognitive changes in PD. To support this idea, we highlight 2 influential lines of current investigation that are unveiling novel insights about specific cognitive processes that are vulnerable early in PD and of critical importance to clinicians involved in treating PD: action control and reward learning and decision making. We conclude by highlighting some extant issues and unresolved questions for future investigations.

Keywords

Parkinson disease; Mild cognitive impairment; Action control; Reward

Introduction

Recognition of Early Cognitive Deficits in PD

Parkinson's disease (PD) is recognized increasingly as a multifaceted neurodegenerative disease that alters motor, cognitive, and motivational functions. In the last 20 years, this conceptual shift in our understanding of the most common of the classic movement disorders has ignited investigations of alterations to cognitive and motivational processes, and the impact of treatments on these functions. Individuals with PD are more likely to be diagnosed with dementia than their healthy peers, and recent longitudinal data suggest that dementia may be an inevitable fate of most cases of PD [1]. Yet, the patterns and course of cognitive changes in PD can be quite heterogeneous, and it is now clear that deficits emerge very early in the course of the disease. This underscores the need for effective measurement, tracking, and treatment of the earliest and most debilitating cognitive changes in PD.

Measuring Early Cognitive Changes in PD

The investigation of early cognitive changes in PD has been driven largely by 2 approaches. One approach uses standard clinical neuropsychological tests to detect patterns of impairments. These tests carry the advantages of standardized assessment and psychometric procedures, broad coverage of major cognitive domains, and normative data that permit

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inferences about individual performance. Alternatively, early cognitive changes in PD have also been studied using tasks developed in the cognitive sciences. These measures offer comparatively greater precision in isolating specific cognitive processes than most standard neuropsychological measures, are embedded within rich theoretical frameworks, and in most instances are linked with greater precision to underlying functional neural circuitries. Perhaps the greatest advantage of experimental cognitive measures in studies of PD lies in their capacity for measuring changes to cognitive processes that have been associated with basal ganglia function, particularly those mediated by prefrontal-basal ganglia circuits.

There are important clinical implications associated with these measurement approaches, particularly regarding inferences about the presence or absence of early cognitive changes in PD. For example, an influential trend surrounds the recent effort to conceptualize so-called Parkinson's Disease-Mild Cognitive Impairment, PD-MCI [2–6, 7•, 8–10]. The impetus behind this effort is of clear importance; this diagnostic classification might hold promise in capturing early cognitive changes in PD that might be treatable, offering predictive utility in identifying risk for dementia, and potentially delineating subgroups of patients with distinct neuropathologies. The concept and its diagnosis bear resemblance to the MCI term used to identify individuals with early memory problems at increased risk for developing Alzheimer's dementia [11]. Thus, individuals meeting criteria for PD-MCI may be in a transitional state between healthy cognitive aging and dementia. The diagnostic approach relies exclusively on standard neuropsychological test performance. While there is some debate regarding the specific criteria for PD-MCI, generally there must be a subjective complaint of cognitive difficulties, preserved independence in performing typical daily activities, and demonstration of impaired performance (eg, >1.5 standard deviations below expected levels) on 2 or more conventional neuropsychological tests that assess broad cognitive domains (eg, language, visuospatial, executive functions, memory, and attention) [8].

While a detailed critique of the concept of PD-MCI is beyond the scope of this article (see [7•]), it is important to note a few conceptual limitations regarding how well this construct captures specific, early cognitive changes in PD. First, the utility of the PD-MCI diagnosis is only as good as the measures used to diagnosis it. One shortcoming of nearly all attempts to establish criteria for PD-MCI on the basis of neuropsychological test performance is the absence of specificity regarding the underlying pattern of cognitive deficits. For example, consider patients A and B who express a subjective cognitive complaint and report independence in typical daily activities. Patient A might perform below expectation on a measure of object naming and on a measure of attention span, but Patient B might perform poorly on measures of memory retrieval and spatial judgment. Both patients would be diagnosed with PD-MCI, suggesting that PD-MCI represents a very heterogeneous, imprecise mixture of cognitive difficulties. Second, there is no formal specification of what measures should be used for diagnosing PD-MCI. Thus, the diagnosis of patients with PD-MCI, and that of patients classified as cognitively normal PD, is biased by what types of instruments were used to measure cognitive performance. Consider that a battery of cognitive tests that place greater emphasis on measuring executive cognitive control processes may be more sensitive at picking up early deficits in PD than a battery that administers only a couple of less demanding tests in this domain. The same criteria would still be applied to both test batteries. Adding to these complexities, there is recent evidence that variations in cutoff scores used to designate impairment across a single set of measures lead to drastically different numbers of patients classified as PD-MCI [12]. This problem is likely compounded by the use of different tests and cutoff scores across centers.

Another critical limitation of currently conceptualized PD-MCI concerns the lack of consideration of the influence of dopamine medications [13]. An emerging literature shows

that dopamine medications can produce facilitating or degrading effects on certain cognitive processes that varies across stages of PD [14]. Even for a specific cognitive process, dopamine medications can produce contrasting effects depending on an individual's baseline cognitive performance [15]. For example, several studies now show that certain cognitive processes (eg, working memory, learning, and inhibitory control) benefit from dopamine medications in individuals who perform poorly on these measures Off of their medications, but are compromised by dopamine medications in individuals who show intact or high levels of performance Off of their medications [16–18]. Moreover, dopamine medications with distinct mechanisms (eg, dopamine agonists vs. levodopa, a dopamine precursor) can produce different as well as synergistic effects on cognitive processes [18, 19].

Perhaps the most important limitation concerns the reality that typically used neuropsychological measures are too insensitive or completely fail to capture many aspects of cognitive performance that are expected to be particularly vulnerable to dopamine depletions and resulting alterations in basal ganglia circuits. For example, few (if any) neuropsychological tests offer precise measurements of performance and error monitoring, reward and punishment learning, speeded decision-making, risk behavior, procedural learning and habit formation, and motor impulsivity. Extensive literature demonstrates close links between these aspects of cognitive performance and basal ganglia function. For these reasons, it is difficult to accept that patients not meeting current criteria for PD-MCI on the basis of standard neuropsychological test performance are “cognitively normal” despite severe dopamine depletions and altered basal ganglia circuitry.

Many of the criticisms noted above raise concerns about the precision of using standard neuropsychological measures and statistical decision rules to characterize early cognitive changes in PD. That is not to say that standard neuropsychological tests do not capture meaningful cognitive changes in PD or that the concept of PD-MCI does not have clinical utility. Indeed, neuropsychological assessments represent an essential, and often underutilized, component of clinical care for PD. However, we submit that a more precise characterization of early cognitive deficits will emerge from investigations that rely on specific, theory-guided measures. Over the last several years, improved understanding of the functional roles of prefrontal-basal ganglia circuits and the modulatory role of dopamine on these circuits has fueled hypothesis-driven investigations of specific cognitive deficits in PD. Investigations utilizing contemporary cognitive science tools to measure specific cognitive processes linked to these circuits reveal that PD produces very specific and early cognitive changes in complex cognitive control, decision-making, and learning processes. Here we provide recent examples from 2 lines of research that illustrate how studying specific prefrontal-basal ganglia circuit-mediated functions provides novel insights about vulnerable cognitive processes in PD and how treatments impact these cognitive processes.

The Study of Action Control and Reward Learning in PD

Example 1: Action Control in Times of Conflict

While most of the cardinal features of PD (tremor, rigidity, postural dysfunction) reflect involuntary motor processes, one of the most important areas of cognition impacted early in PD involves changes in voluntary control over actions. *Action control* refers to the set of dynamic cognitive operations that guide, coordinate, and monitor the selection, inhibition, and switching of competing actions afforded in any given situation [20]. Complex environments afford many potential reactions, some of which may be relevant to completing behavioral goals and others that are irrelevant and potentially disruptive to goal completion. Action control processes are engaged reactively to resolve response conflicts as well as proactively to adapt action selection and inhibition processes in anticipation of conflicts [21–23]. An extensive literature has linked these forms of action control to specific

prefrontal-basal ganglia circuits that are modulated by nigrostriatal dopamine [20, 24]. Recent studies of action control in PD have addressed questions such as: (1) How proficiently can PD patients stop (or inhibit) their actions or inhibit impulsive or habitual action tendencies when such actions conflict with immediate goals? (2) Does PD disrupt the ability to proactively adjust action control processes after making action errors or when response conflict is anticipated? (3) How do treatments for PD affect action control? Recent studies suggest that these action control processes are particularly vulnerable in early PD and provide new insight into the range of motor control deficits that patients encounter in everyday life.

A fundamental component of action control is the ability to inhibit actions that may be impulsive, premature, or no longer appropriate. This form of inhibitory action control has been linked to circuitry connecting specific prefrontal regions (ventrolateral, pre-supplementary motor area) to neostriatal and subthalamic nuclei [25–30]. Inhibitory control over prepotent, impulsive action tendencies can be studied elegantly using measures of response conflict, such as the Flanker Congruence task [31], and Simon Correspondence task [32, 33]. These tasks provide measures of an individual's susceptibility to making fast, impulsive errors as well as the proficiency of suppressing the interference from prepotent, impulsive actions (see [34]). Several studies have demonstrated that PD patients are less proficient than their age controls at suppressing interference from conflicting responses [35–37], and this deficit is worse in PD patients with more advanced motor symptom severity [38]. Moreover, difficulty suppressing conflicting responses is even more pronounced when PD patients must choose responses under time pressure [39]. Conflict can also arise when an action is initiated, but must suddenly be stopped due to an immediate change in goals or the environment. This ability to inhibit ongoing actions can be studied using the stop-signal task [40]. Across several studies, inhibiting initiated actions is significantly slowed in PD compared with healthy controls, even after accounting for any speed differences in initiating actions [19, 41, 42].

Another critical aspect of action control is the ability to adapt to the context. In a landmark study, Gratton and colleagues [23] demonstrated that after successfully navigating a conflicting response situation, individuals are better able to resolve conflict that occurs soon after. This observation fueled the *conflict adaptation* hypothesis, which asserts that individuals adapt their response control proactively to minimize conflict and promote efficient response selection [22]. This form of proactive action control has been studied in PD. Several studies have concluded that PD patients can show less proficient conflict adaptation; that is, PD patients show minimal improvement in resolving conflict even after experiencing conflict, whereas healthy controls show a marked reduction or even elimination of conflict effects after experiencing conflict [43–45]. These adaptive processes have been linked reliably to anterior cingulate circuitry (ACC), suggesting that ACC-basal ganglia circuits impacted by dopamine deficiencies may underlie early changes in adaptive action control [22, 30]. Adaptive control processes are not only engaged following instances of conflict, but also after response errors are made. Adaptive processes following action errors can be studied using event-related brain potentials (ERP), which represent changes in EEG signal over particular electrode sites that are time-locked to specific cognitive task events (eg, stimulus onset, response onset). Specifically, an ERP component called the error-related negativity (or error negativity) is recorded above frontal electrodes shortly after individuals commit action errors [46, 47]. Similar to conflict adaptation effects, this negative frontal component originates from sources in medial frontal areas, particularly the anterior cingulate cortex (ACC) [48]. Consistent with the behavioral data, the error-related negativity is generally reduced in amplitude in PD patients compared with healthy controls, further supporting the notion that PD patients are less proficient in their ability to monitor and adapt to action errors [49, 50].

Changes in aspects of action control have important implications for functional activities. For example, a reduced ability to inhibit or effectively adapt one's actions can have serious consequences during driving. From a clinical perspective, the study of action control has produced several new insights. For example, there is recent evidence that dopamine agonists impair the ability to suppress impulsive actions, although agonists can produce opposing effects that depend on patients' baseline performance in the Off medication state [18]. Subthalamic nucleus deep brain stimulation produces dissociable effects on impulse control, increasing the tendency to make fast impulsive errors but improving the ability to suppress the interference from conflicting actions that are not acted on impulsively [42, 51]. Interestingly, dopamine medications do not generally seem to improve deficiencies in adaptive action control among PD patients [50], although there are examples of intact adaptive control in patients both On and Off of their medications [38, 48]. More studies of medication effects are clearly warranted. Studies of action control have also provided new insights about subgroups of PD patients. For example, patients with freezing of gait symptoms show exaggerated difficulties resolving response conflict [52], suggesting that mechanisms involved in coordinating the selection and inhibition of actions may hold clues to freezing symptoms. Patients with predominant postural instability and gait difficulties show greater susceptibility to acting on strong motor impulses compared with patients with predominant tremor symptoms, which might be important for fall risk [53]. These represent just a few recent investigations of how early deficits in specific action control mechanisms may provide valuable insight into clinically significant issues.

Example 2: Reward Learning and Decision Making

Numerous studies have established that reward-based decision-making relies on dopamine (DA) neurotransmission [15, 54]. The mesocorticolimbic network describes the ventral midbrain projections to the ventral striatal, limbic, and ventromedial cortical regions. While DA neurons comprising the nigrostriatal pathways (caudate, putamen) are most vulnerable to degeneration early in PD, degeneration of neurons comprising the mesocorticolimbic pathway is generally thought to be more variable, often emerging later in the disease [55]. This neurodegenerative pattern provides important clues regarding the emergence of cognitive and motivational deficits at different stages of PD. Changes in action control processes mediated by nigrostriatal dopamine pathways manifest early in PD, whereas deficits in reward-based decision-making and learning attributable to mesocorticolimbic dopamine pathways can develop early or later across individuals [16]. Moreover, there is accruing evidence that intact mesocorticolimbic dopamine pathways in early stage PD can be overdosed by the administration of dopamine medications and disrupt cognitive performance [16]. Thus, degenerative processes as well as medication effects can produce cognitive deficits in reward-based learning and decision-making in the early stages of PD. Here we highlight some of the recent work using experimental cognitive measures that demonstrates the susceptibility of reward processing to dopamine depletions and medications in PD.

Reward-based decision-making and risk-taking are often investigated using simulated gambling tasks. For example, in the Iowa Gambling Task (IGT) [56], participants gamble to win money by making a series of selections from four decks of cards. Each card selection offers a money reward or a loss. Unbeknownst to the participant, 2 decks are advantageous (ie, long-term rewards exceed losses), while the other 2 decks are disadvantageous (ie, long-term losses exceed rewards). The disadvantageous decks are particularly tempting in that they provide larger immediate rewards than the advantageous decks. However, they are also the riskier choice because they contain cards with much higher and/or more frequent losses. While healthy adults gamble from each of the four decks of cards early on in the task, they eventually learn to avoid the riskier, disadvantageous card decks [57]. Recent studies of PD

suggest that performance on the IGT may detect early impairments in reward-based decision-making. In a recent study of early stage `*de novo*' drug naïve PD patients, one third of patients showed deficient learning of the optimal decks coupled with a stronger tendency to select the riskier, disadvantageous decks late in the task compared with healthy controls [58]. Similarly, Ibarretxe-Bilbao and colleagues [59] showed that 24 medicated patients with early stage PD made more risky, disadvantageous card selections late in the task compared with healthy controls. Perretta and colleagues [60] compared the IGT performance of early and late stage PD based on motor symptom severity and found that, irrespective of disease severity, all PD patients performed more poorly (ie, made significantly more disadvantageous card selections) compared with healthy controls. Notably, the early stage PD patients did not differ from the healthy controls on other standard neuropsychological measures, such as the Wisconsin Card Sorting Test, Stroop Interference Test, and the MMSE, showing the value of using more specific cognitive instruments. These studies suggest that even in early stages of PD, changes in rewarded decision-making and risk-taking can be detected.

The changes in reward-based decision-making may not be entirely related to risky behavior, but rather to dopamine related changes in reward-based learning. Recent investigations in PD using carefully designed measures of reward and punishment learning suggest that early stage PD and medications may cause subtle changes in these forms of learning. It is well documented that dopamine neurons show burst firing in response to unexpected rewards, but firing pauses to unexpected punishments [61]. These opposing firing patterns are thought important in establishing action-outcome associations that are essential to behavioral learning. It has been proposed in recent years that the severe dopamine depletions in PD reduce the capacity for burst firing, thus diminishing the ability to signal reward outcomes [62]. Because firing pauses would still be possible in PD, a bias toward punishment-based learning develops. Indeed, multiple studies have demonstrated that unmedicated or *de novo* PD patients show relatively intact punishment learning coupled with reduced reward learning [63]. Ironically, dopamine medications can produce the opposite effect. The increased dopaminergic release produced by dopamine medications reinstates dopamine burst activity, but the increased dopamine tone also diminishes the fidelity of the firing pause signal. Studies of medicated PD patients have supported these patterns by demonstrating improved reward learning coupled with diminished punishment learning [63]. Taking this idea a step further, Graef and colleagues [64] reasoned that if medicated PD patients form stronger associations from reward, then this might lead to reduced flexibility if outcomes suddenly changed. They tested 20 PD patients, both Off and On their dopamine medications, on a probabilistic reward task that introduced a reward reversal after the initial reward outcomes were learned. As expected, dopamine medications improved initial reward-based learning, but led to an impaired ability to avoid decisions that were no longer rewarding.

These studies illustrate early and specific changes in reward-based processing that arise from dopamine depletions and efforts to restore dopamine activity. It is also quite clear that standard neuropsychological measures are generally unable to capture these specific aspects of reward learning and decision-making, although it is notable that a normed version of the Iowa Gambling Task is now available for clinical use. These reward-based processes have tremendous clinical utility, which is perhaps best illustrated by the recent surge of studies investigating PD patients who develop so-called Impulsive-Compulsive Behaviors (ICB) while taking dopamine (primarily dopamine agonist) medications. Clinically, ICBs involve unrestrained participation in activities related to sex, eating, shopping, gambling, and hobbies, and patients at all stages of the disease can develop ICBs [65]. Using specific cognitive measures of risk decision-making, recent behavioral studies emphasize that patients with ICB prefer smaller immediate rewards to larger delayed rewards, tolerate

greater risk for the opportunity of a reward despite the potential for negative consequences, and respond `more impulsively' to rewarding options during decision-making [66, 68]. Notably, these cognitive changes have been attributed to dopaminergic effects on mesocorticolimbic circuits [66]. The use of specific measures of risk decision-making and reward learning may also be important in studying mechanisms underlying apathy in PD.

Extant Issues and Unresolved Questions About Early Cognitive Deficits in PD

1. Can Standard Neuropsychological and Experimental Cognitive Measures Be Used Conjointly to Study Early Cognitive Changes In PD?

If, as recent longitudinal studies suggest, dementia is an inevitable consequence for most PD patients, then it stands to reason that specific cognitive and standard neuropsychological measures may be detecting changes at different points along the trajectory. For example, the PD-MCI criteria may help identify patients whose pathology is extending beyond frontal-basal ganglia circuits and progressing closer to dementia [67]. Thus, it is likely that for most patients meeting current criteria for PD-MCI, this diagnosis represents a clinically meaningful and predictive state, but not necessarily the state symbolizing the earliest cognitive changes (ie, “mild” impairment is not synonymous with “early” impairment). Ideally, longitudinal studies that combine both types of measures would be helpful for identifying the best combination of measures to optimize detection and tracking of the earliest cognitive changes to the early cognitive changes that are predictive of dementia. We would like to highlight a recent approach by Zgaljardic and colleagues [69, 70] who offer an important step in conceptualizing standard neuropsychological measures in a more theory-driven approach. These investigators proposed a battery of typical and less frequently used neuropsychological measures, inspired by functions linked to prefrontal-basal ganglia circuits. Thus, measures were proposed that putatively tapped into functions associated with orbitofrontal, dorsolateral, and medial/anterior cingulate circuits. Consistent with the results presented above, deficits in early stage PD were primarily related to functions associated with dorsolateral and anterior cingulate corticostriatal circuits [70]. Adding some experimental cognitive measures to this framework would likely yield even greater specificity in detecting the earliest cognitive changes in PD.

2. What Factors Account For Individual Differences In The Onset, Pattern, and Course of Cognitive Deficits?

Patients with PD not only want to know about their chances of developing dementia, but increasingly ask about the nature and potential impact of cognitive deficits. We still have much to learn about biological, genetic, or psychological factors that determine the onset, course, and pattern of cognitive and motivational deficits [7•]. Very few studies have embarked on longitudinal use of specific cognitive measures to track early changes in PD. Additional studies are clearly needed to determine the role of dopamine degeneration patterns, initial symptom patterns, and health factors in accounting for progression of cognitive deficits.

3. What Impact Do Treatments Have on Early Cognitive Deficits in PD?

As clinicians, we are still quite naïve about the impact of dopamine medications and interventions like subthalamic nucleus deep brain stimulation on specific cognitive vulnerabilities in PD. Given recent evidence that distinct medications may produce dissociable changes on cognition, and that medication effects often depend on baseline performance Off medications, additional studies on these issues are clearly warranted. Knowing the cognitive effects, beneficial or detrimental, of these treatments are critical as

treatments are started very early in the disease. One of the main challenges in clinical research is assessing precise cognitive outcomes for which to evaluate efficacy of a therapeutic intervention. For instance, using disease specific cognitive measures may aid in evaluating the use of subthalamic nucleus DBS to treat symptoms in early stage PD patients [71]. In order to properly understand treatment effects on cognition requires developing cognitive measures specific to PD, and using these in clinical research.

Conclusions

The study of cognitive changes in early PD is rapidly evolving. In order to advance the field towards improved disease characterization, treatment, and prognostic implications, an improved understanding of the nature of cognitive deficits in PD (both early and longitudinal) is needed. It is difficult to imagine a `one size fits all' approach to this issue, and we believe important steps must be made to ensure that the discussion of cognition and PD remains disease- specific, and the study theory-driven. Contemporary cognitive science tools may indeed prove an invaluable resource in this approach.

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