Article

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Abstract

The search for PD-MCI biomarkers has employed an array of neuroimaging techniques, but still yields divergent findings. This may be due in part to MCI's broad definition, encompassing heterogeneous cognitive domains, only some of which are affected in Parkinson's disease. Most domains falling under the MCI umbrella include fronto-dependent executive functions, whereas others, notably learning, rely on the basal ganglia. Given the deterioration of the nigrostriatal dopaminergic system in Parkinson's disease, it has been the prime target of PD-MCI investigation. By testing well defined cognitive deficits in Parkinson's disease, distinct functions can be attributed to specific neural systems, overcoming conflicting results on PD-MCI. Apart from dopamine, other systems such as the neurovascular or noradrenergic systems are affected in Parkinson's disease. These factors may be at the basis of specific facets of PD-MCI for which dopaminergic involvement has not been conclusive. Finally, the impact of both dopaminergic and noradrenergic deficiency on motivational states in Parkinson's disease is examined in light of a plausible [...]

Reference

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Apathy and noradrenaline: silent partners to mild cognitive impairment in Parkinson's disease?

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Purpose of review
Mild cognitive impairment (MCI) is a comorbid factor in Parkinson's disease. The aim of this review is to examine the recent neuroimaging findings in the search for Parkinson's disease MCI (PD-MCI) biomarkers to gain insight on whether MCI and specific cognitive deficits in Parkinson's disease implicate striatal dopamine or another system.

Recent findings
The evidence implicates a diffuse pathophysiology in PD-MCI rather than acute dopaminergic involvement. On the one hand, performance in specific cognitive domains, notably in set-shifting and learning, appears to vary with dopaminergic status. On the other hand, motivational states in Parkinson's disease along with their behavioral and physiological indices suggest a noradrenergic contribution to cognitive deficits in Parkinson's disease. Finally, Parkinson's disease's pattern of neurodegeneration offers an avenue for continued research in nigrostriatal dopamine's role in distinct behaviors, as well as the specification of dorsal and ventral striatal functions.

Summary
The search for PD-MCI biomarkers has employed an array of neuroimaging techniques, but still yields divergent findings. This may be due in part to MCI's broad definition, encompassing heterogeneous cognitive domains, only some of which are affected in Parkinson's disease. Most domains falling under the MCI umbrella include fronto-dependent executive functions, whereas others, notably learning, rely on the basal ganglia. Given the deterioration of the nigrostriatal dopaminergic system in Parkinson's disease, it has been the prime target of PD-MCI investigation. By testing well defined cognitive deficits in Parkinson's disease, distinct functions can be attributed to specific neural systems, overcoming conflicting results on PD-MCI. Apart from dopamine, other systems such as the neurovascular or noradrenergic systems are affected in Parkinson's disease. These factors may be at the basis of specific facets of PD-MCI for which dopaminergic involvement has not been conclusive. Finally, the impact of both dopaminergic and noradrenergic deficiency on motivational states in Parkinson's disease is examined in light of a plausible link between apathy and cognitive deficits.

Keywords
apathy, learning, neuroimaging, noradrenaline, Parkinson's

INTRODUCTION

Mild cognitive impairment (MCI) refers to cognitive decline that does not meet the clinical criteria for dementia. MCI is a widely reported comorbid factor in Parkinson's disease [1]. Whereas MCI can predict dementia in Parkinson's disease [2], MCI assessment accuracy based on cognitive batteries is relatively poor [3,4]. As such, neuroimaging techniques are now being used to identify its neural signature. MCI is a profile that arises in many populations, including the aged and Alzheimer's patients. Since its cause is unknown, it is unclear whether the same mechanism prompts its emergence in different diseases [5]. Further, MCI incorporates deficits across heterogeneous cognitive domains [6], most related to fronto-dependent executive function [7], but at times inclusive of learning processes [8,9]. Studies

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KEY POINTS

- Neuroimaging research supports a diffuse neural marker for PD-MCI with a neurovascular basis emerging as a strong candidate in its cause.
- Though difficult to image, the locus coeruleus noradrenaline complex, given its widespread cortical projections, chemical link to dopamine, and marked deterioration in Parkinson's disease, should be investigated as a strong contributor to Parkinson's disease behavioral impairments.
- The widespread emergence of apathy in Parkinson's disease, supported by behavioral and EEG markers, should be investigated in relation to a dopaminergic or noradrenergic neural basis and known cognitive profiles in Parkinson's disease.

on Parkinson's disease MCI (PD-MCI) have been inconclusive with regards to the domains affected and dopaminergic involvement. PD-MCI is thought to be a consequence of cortical dopaminergic changes in Parkinson's disease arising from compromised fronto-striatal circuits, notably the mesocortical and nigrostriatal loops (see Fig. 1) [10]. However, evidence of changes in prefrontal dopamine is equivocal [8,11,12]. Since Parkinson's disease is marked by nigrostriatal dopaminergic loss, basal-ganglia-dependent learning processes have been studied extensively [13,14], with a particular focus on the striatum. It is generally thought that the ventral and dorsal striatum play distinct functional roles, which are only partially understood to date. The dopamine overdose hypothesis may explain observed selective impairment in Parkinson's disease patients on dopaminergic replacement therapy (PDON) relative to unmedicated patients (PDOFF) [15]. In early Parkinson's disease, the dorsal striatum displays extensive degeneration, whereas the ventral striatum remains preserved. Dopaminergic medication relieves dorso-related motor symptoms, but may overdose a functional ventral striatum, prompting selective behavioral impairments such as impulse control disorders (ICDs). PDOFF populations thus offer a window into dorsal striatum-dependent functions. Further questions regarding cognitive deficits converge on recent recognition that apathy is a common symptom in early Parkinson's disease [16]. Questions on apathy's behavioral impact and its neural basis remain open. Dopamine has long been the focus of Parkinson's disease research; however, disease characteristics extend beyond the dopaminergic system, suggesting other factors may drive observed deficits.

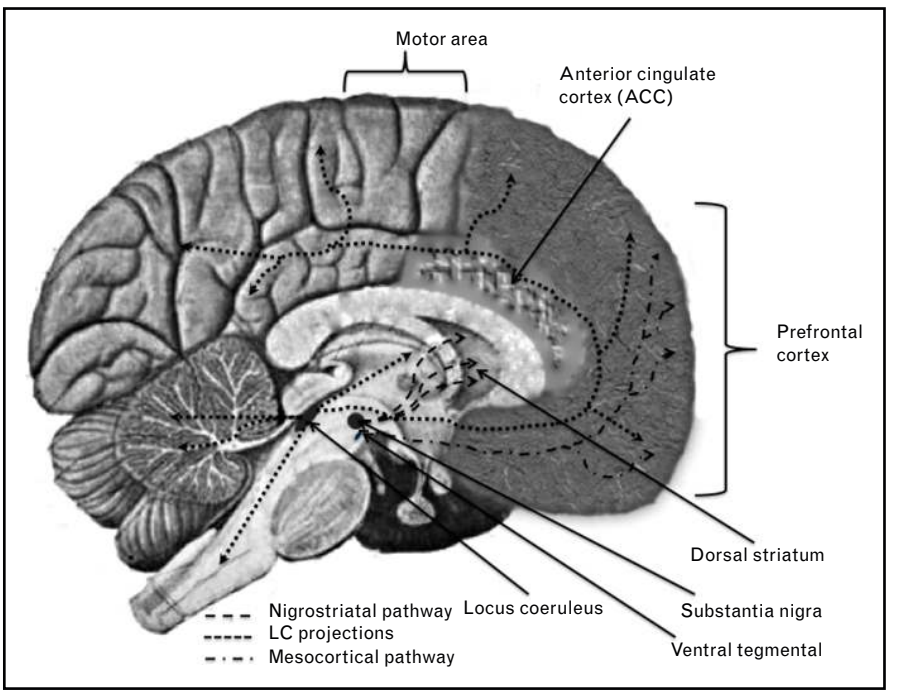

FIGURE 1. An overview of brain regions implicated in MCI, Parkinson's disease, and the locus coeruleus noradrenergic system. MCI test batteries primarily include executive function, which is traditionally linked to the prefrontal cortex (as well as the anterior cingulate cortex). PD is characterized by a damaged nigrostriatal pathway that starts in the substantia nigra and projects to the dorsal striatum (dashed lines). Noradrenergic projections start from the locus coeruleus and project out to the cortex and the cerebellum (dotted lines). LC, locus coeruleus; MCI, mild cognitive impairment; PD, Parkinson's disease.

NEUROIMAGING MILD COGNITIVE IMPAIRMENT

The search for biomarkers of PD-MCI has employed various neuroimaging measures including functional, structural, and diffusion measures. Although this endeavor has yielded a number of potential biomarkers, the evidence has simultaneously generated a less ordered view of PD-MCI signatures and causes. Cognitive scores in Parkinson's disease patients correlate with dorso-fronto parietal connectivity; inhibited subcortical primary sensory activation; and preserved nigrostriatal pathways in resting-state functional magnetic resonance imaging (fMRI), but not with presynaptic dopaminergic uptake [17]. Atrophy in various cortical regions is associated with neuropsychiatric symptoms [18▪], as well as MCI in some studies [19,20,21▪,22▪,23], though others found no such differences in PD-MCI compared to Parkinson's disease without MCI [24,25]. The expected effect of MCI on the subcortical regions is even less clear, though hippocampal atrophy was found to predict conversion to PD-MCI and to dementia from PD-MCI in a longitudinal study [26]. Research has also investigated white matter differences, which can indicate neurovascular abnormalities [27]. White matter hyperintensities were found to predict cognitive decline [24], and several recent studies reported white matter abnormalities in PD-MCI [26,28,29]. Early Parkinson's disease patients specifically show evidence of atherosclerosis alongside white matter hyperintensities – factors that lead to microvascular injury and possible cognitive decline [30▪▪]. Interestingly, both orthostatic and prandial hypotension is a sign of noradrenergic disturbance [13,31], a neurotransmitter which is affected early in Parkinson's disease [32]. The evidence suggests PD-MCI's neural footprint remains difficult to delineate even with various imaging measures, though neurovascular abnormalities emerge as strong causal candidates. Neurovascular differences indeed correlate with MCI in other patient populations [33–36]. The studies above do not show a distinct link between dopamine and PD-MCI, but they do yield an array of diffuse neural correlates, which may reflect the fuzzy nature of MCI's behavioral characterization.

COGNITIVE FLEXIBILITY IN PARKINSON'S DISEASE

Parkinson's disease patients display executive dysfunction, but evidence on specific domains affected remains murky [37,38]. One persistent finding is set-shifting impairment in Parkinson's disease patients [1,39]. Cognitive flexibility appears to rely on the dorsal striatum [40▪▪] and medication response correlates with improved task switching in Parkinson's disease, further supporting the dorsal striatum's role in cognitive flexibility [41]. One fMRI study in PDOFF patients found no impairment in set-shifting, but did reveal atypical task-related activation in the cortex, suggesting compensatory anomalous cortical activity inhibits behavioral impairment [42]. Previous studies produced conflicting results on medication's remedial effects on set-shifting impairment, but the studies above support striatal dopamine's role in cognitive flexibility, as well as a cortical up-regulation in early stages of the disease, perhaps masking striatal deficiencies.

LEARNING DEFICITS IN PARKINSON'S DISEASE

Reinforcement learning has been extensively studied in Parkinson's disease [43–45] to support models cast within a basal ganglia dopaminergic framework. When controlling for medication effects, studies reveal deficits in learning from trial-by-trial feedback [46], a hallmark of implicit learning [47]. Indeed, a meta-analysis found Parkinson's disease patients to be significantly impaired in implicit learning across 27 studies using the serial reaction time task [48]. While implicit learning is thought to depend on the basal ganglia, explicit, declarative learning relies on the hippocampus and medial temporal lobe [49]. The interplay between the two systems has yet to be defined [50], but a selective impairment in Parkinson's disease would suggest implicit learning occurs in the dorsal striatum. Most tasks measuring one type of learning versus another rely on both mechanisms [51], but recent evidence suggests explicit and implicit learning can be dissociated by manipulating a task's feedback structure (delayed versus discrete) [52]. An [^{11}C] raclopride PET study showed striatal (accumbens) D2 release accompanied learning from discrete feedback in a probabilistic classification task [53▪▪]. Further, learning from delayed feedback activates the hippocampus, whereas learning from immediate feedback engages the striatum [48]. A study investigated competing learning mechanisms in Parkinson's disease, with two initial tasks that tested novel tool features (explicit) and novel tool skill (implicit), and a follow-up task that assessed both learning acquisitions 3 weeks later. Patients did not differ from controls in either the initial learning session or on knowledge of novel tool attributes in the follow-up session; however, the Parkinson's disease group did not retain skilled tool use [54▪▪]. Two more recent studies highlight differences in retention for Parkinson's disease patients. An initial test

of sequence learning was not affected in Parkinson's disease, though patient retention a week later was [55]. Patients tested on an implicit learning sequence task performed as well as healthy controls in a first block, but not in a second block [56]. Further, no differences were found in an implicit learning task of semantic categorization between healthy controls and Parkinson's disease patients [57,58]. These divergent findings call into question the impairment of implicit learning in Parkinson's disease, as well as its dependence on the dorsal striatum. It has been posited that dorsal striatal dopaminergic signals are necessary for performance, or action-selection, rather than learning *per se* [14,43,59,60]. These two roles may be specific to distinct striatal regions, but action-selection is often used to determine learning. Thus, recent studies have examined the functional dissociation of the dorsal and ventral striatum in relation to learning acquisition (or memory encoding) and action-selection (or memory retrieval). An fMRI study in the healthy controls investigated stimulus-response learning with feedback, followed by a session that assessed how well associations were learned. Activation in the ventral striatum was confined to the learning session, whereas activation in the dorsal striatum emerged in the second session, where associations had already been learned and the task demand was appropriate response selection [61]. A novel fMRI study dissociated dopamine's roles in anticipation and reward to determine whether placebo would be as effective as dopaminergic replacement therapy in Parkinson's disease reward learning. Both placebo and medication groups exhibited learning signals in the ventral striatum [62]. Vo *et al.* [63], in 2014, found PDOFF patients learned stimulus–response associations as well as controls, whereas PDON patients were impaired. Further, PDOFF patients outperformed controls and PDON patients, supporting the hypothesis that cortical D1 is up-regulated in Parkinson's disease [64,65]. The studies listed above support the dorsal striatum's role in action-selection, but a recent case study of a patient suffering bilateral damage to the dorsal striatum showed specific impairment in learning stimulus values and not action values [66]. The evidence suggests a different frame within which to study functions specific to the ventral and dorsal striatum. Notably, learning's dependence on the ventral striatum and action-selection's reliance on the dorsal striatum merit closer scrutiny in future studies.

APATHY

Apathy is a common, early symptom in Parkinson's disease that predicts MCI and dementia [67]. Apathy may significantly impact processes requiring motivation, such as action-selection and cognitive task performance, if not cognition itself. While apathy's neural correlates remain unknown, the search for a neural mechanism of Parkinson's disease apathy focuses on the dopaminergic system. Compared to healthy and Parkinson's disease controls, apathetic patients showed a reduction in left limbic striatal and frontal connectivities in resting-state fMRI, though apathy scores showed no correlation with structural differences [68▪▪]. An fMRI study [69] examined dopaminergic medication effects during an emotional Stroop task in PDON and PDOFF patients, and found that when presented with negative Stroop stimuli, PDOFF patients had higher apathy scores, decreased fear recognition, and reduced anterior cingulate cortex (ACC) activation. While ACC activation was recovered with medication, it is interesting to note that the cingulate receives projections from the locus coeruleus noradrenaline (LC-NE) system [70]. Though Parkinson's disease-related apathy is an early symptom, it can also emerge following deep brain stimulation (DBS) implantation as a suspected consequence of dopaminergic medication washout. Increased apathy after DBS correlated with reduced right ventral striatal activity in a PET study [71]. Further, dopamine-resistant apathy correlated with nucleus accumbens atrophy [72▪]. Like MCI, apathy in Parkinson's disease is primarily assessed via psychometric scale [73], but electroencephalogram (EEG) studies have yielded compelling behavioral and physiological consequences of Parkinson's disease apathy. An event related potential (ERP) study measured feedback-related negativity (FRN) in response to gains and losses. Apathetic patients showed a reduced difference between FRN for losses and FRN for gains when compared to Parkinson's disease patients and healthy controls [74]. In a similar vein, an EEG study examined differences in ERPs between Parkinson's disease patients and healthy controls during the Iowa Gambling Task – a task of decision-making under ambiguity [75]. ERP for gains differed from ERP for losses in the healthy controls, as expected, but no differences emerged in Parkinson's disease patients. Another study reported a blunted P3 signal in apathetic PDOFF patients [76] (a P3 signal arises upon encounter of a salient stimulus). Furthermore, Parkinson's disease patients did not display the Von Restorff effect, where novelty enhances stimulus recall [77▪]. In the same study, the P3 signal was larger for novel stimuli in healthy controls relative to patients, irrespective of medication status, implicating a nondopaminergic system. A potential candidate is the noradrenergic system whose activation has been linked to the P3 signal via pupillometry

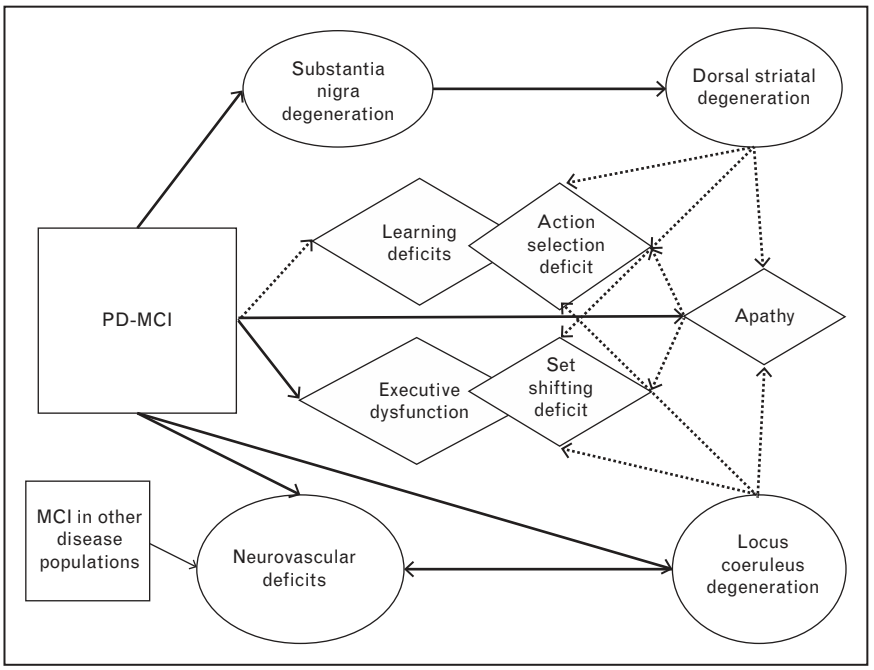

FIGURE 2. An overview of recent findings related to PD-MCI. Circles represent known neural correlates; diamonds represent putative behavioral symptoms. Solid lines indicate known relationships while dashed lines represent possible links between factors. MCI, mild cognitive impairment; PD, Parkinson's disease.

studies [78,79]. And while the neural correlates to apathy above implicate the ventral striatum, it should be noted that the region receives projections from the LC in addition to its dopaminergic projections. The dearth in research on apathy's link to observed cognitive deficits provides an avenue of investigation into the motivational factors of cognitive performance.

THE NORADRENERGIC SYSTEM

Parkinson's disease research has centered on the dopaminergic system; however, many of the observed cognitive deficits may also be linked to a pathological noradrenergic system in Parkinson's disease patients. Post mortem analysis of Parkinsonian brains reveals Lewy body accumulation in the LC [80], as well as a reduction in frontal norepinephrine and serotonin, but not dopamine [81,82]. LC degeneration precedes nigrostriatal neural loss [32]. Dopamine and noradrenaline are both tyrosine-derived catecholamines; their interaction may be of particular interest [83], given that the LC-NE system has widespread cortical projections (Fig. 2) [84]; noradrenaline may protect against dopaminergic deficiency [85]; and noradrenaline modulates dopaminergic activation [86]. Indeed, recent research in learning and decision-making has already moved beyond the bounds of the basal ganglia to scrutinize LC-NE's contribution to these functions [87,88]. As such, there is now compelling evidence that LC-NE degeneration in Parkinson's disease may contribute to PD-MCI [89]. Specifically, cognitive inflexibility in early Parkinson's disease could reflect early dysfunction of the LC-NE system [90]. Adaptive gain theory [91] describes LC neurons' dual firing modes: a phasic mode that signals exploitation, and a tonic mode that prompts exploration. A compromised LC-NE system could lead to decreased tonic noradrenergic transmission, inhibiting flexibility and enhancing perseveration [90]. A dysfunctional LC-NE system could further prevent patients from registering salient signals demanding action, which may explain action-selection deficits and contribute to Parkinson's disease-related apathy. Neuroimaging evidence of LC-NE involvement in Parkinson's disease has been sparse to date, due to the difficulty inherent in imaging a small, brainstem region [92], but among the many neurotransmitter systems affected in Parkinson's disease [93,94], noradrenaline's characteristics stand out as markedly relevant to the study of cognitive function.

CONCLUSION

Mild cognitive impairment in Parkinson's disease is not confined to dopaminergic deficits *per se*, behooving us to consider nondopaminergic mechanisms for its emergence. Two lines of investigation merit closer future inspection: the role apathy plays in observed behavioral deficits and the LC-NE's

influence on learning, apathy, and distinct measures of MCI in a Parkinson's disease model.

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Conflicts of interest

There are no conflicts of interest.

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