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Introduction: The Importance of Cognition in Movement Disorders

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In the past decade, there has been an explosion in clinical attention and research on the cognitive aspects of all movement disorders. This is, in part, driven by the aging of the world's population in developed countries, which has increased attention on neurodegenerative diseases that differentially affect the elderly, including Alzheimer's disease (AD), Parkinson's disease (PD), and atypical parkinsonism (corticobasal syndrome [CBS], MSA, PSP, and SCA). Additionally, the increasing recognition of dementia with Lewy bodies (DLB) has highlighted the overlap between movement disorders and dementia. Another contributing factor is emerging data from prospective, long-term epidemiological studies that have led to a dramatic increase in estimates of cumulative dementia prevalence in PD. Finally, with the focus increasingly on those patients in the predementia stage, the scope of cognition-related clinical care and research has broadened significantly. Besides the aforementioned disorders, other movement disorders have either long been associated with frank cognitive impairment (i.e., Huntington' disease; HD) or are increasingly recognized to be associated with mild cognitive deficits (i.e., essential tremor).

Improvement in motor symptom control and increased longevity likely contribute to the higher cumulative frequency for dementia in PD than previously recognized. Dementia was previously considered to be an exclusion for the diagnosis of MSA, but recent studies indicate that significant cognitive impairment is not uncommon in this disorder. The clinical spectrum of four-repeat tauopathies continues to broaden, with a behavioral frontotemporal-like variant, primary progressive aphasia, and posterior cortical atrophy syndrome all now associated with corticobasal degeneration. Large, prospective, multicenter studies, such as TRACK-HD, have highlighted that cognitive measures in early HD are predictive of functional decline. Recent studies have also consistently shown that the frequency and severity of most neuropsychiatric symptoms increase with advancing cognitive impairment in neurodegenerative diseases, leading to excess disability and caregiver burden.

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A plethora of assessment tools exist for assessing cognitive and neuropsychiatric impairments in people with movement disorders, ranging from disease-specific to more generic instruments. Problems can arise with use of nonvalidated scales or making comparisons between studies that have used different instrument. Do we need new scales? Perhaps not, but we need to better evaluate and compare those that exist. Recent International Parkinson and Movement Disorder Society–supported task forces have done a sterling job in evaluating neuropsychiatric instruments for use in PD, whereas new criteria for mild cognitive impairment and dementia in PD should better harmonize recruitment and data pooling across studies.

In terms of management, there has been only incremental progress in recent years. Perhaps a "big bang" was always going to be unlikely, and this frustratingly slow progress mirrors the scene in other neurodegenerative dementias such as AD. Nevertheless, there is hope for optimism in the clinical trial landscape as we develop better distributed clinical recruitment networks, assessment protocols, and improved biomarkers.

Advances in the cognitive neuroscience of PD have certainly had to take account of the increasing evidence of its clinical heterogeneity, including so many (at least a dozen) newly discovered genetic influences and a rich characterization of its molecular pathology, including Lewy bodies (LBs), synucleinopathies, and tauopathies, in brain regions quite far removed from the striatum. One important example concerns the impact of the the catechol-O-methyl-transferase (COMT) polymorphism in PD, which has been paradoxically associated with greater frontoexecutive deficits in met/met rather than val/val carriers. Pioneering studies are now being done using a range of imaging modalities, including functional MRI, EEG, and ligand-based PET, to understand the neural basis of these effects. This has led to the hypothesis that overactivity of frontal dopamine systems may be responsible for such cognitive impairments, which, together with epidemiological evidence, suggests that the dopamine-dependent "frontostriatal" deficits can (1) fluctuate quite markedly during the course of the disease and (2) may be both mechanistically and therapeutically distinct from the cognitive symptoms of parkinsonian dementia. This conclusion raises the important issue of which cognitive symptoms respond to dopaminergic medication (either adversely or beneficially) and which nonmotor symptoms may be related to other neurotransmitter changes, such as cortical cholinergic loss. Increasingly important may be the use of ancillary clinical or neuroimaging signs as possible biomarkers for the likely progression of different aspects of the disease, potentially to guide early treatment strategies.

Another strong trend in understanding the impact of PD on motivation, as well as cognition, has been its links with the dopaminergic coding of reward and punishment, which underlie reinforcement learning and may also contribute to the development of impulse control disorders (e.g., compulsive gambling) in PD. Neurocomputational and psychopharmacological approaches have led to the suggestion that patients with PD encode memories by reference to aversive, rather than appetitive, associations, and an important issue to resolve in future studies will be the extent to which PD involves dopamine-dependent motivational, as distinct from learning, mechanisms.

Regarding biomarkers, diffuse LB disease appears to be the major contributing pathology to cognitive decline in PD, but a significant percentage of PD patients also have AD-related neuropathological changes. Multiple imaging ligands exist for quantifying striatal synaptic dopamine system functioning, and they have been used to examine the effect of dopamine dysfunction on cognition. Ligands for detecting beta-amyloid have also been applied to PD patients and those for detecting alpha-synuclein and tauopathies are in development. Diffuse (primarily medial temporal lobe, parietal lobe, and prefrontal cortex) gray matter neurodegeneration on structural imaging and metabolic deficits on PET imaging are associated with cognitive decline. Besides dopamine, other neurotransmitter deficits associated with cognitive impairment include acetylcholine and norepinephrine. Functional imaging studies suggest that "system" impairments in the corticostriatal neural circuitry likely contribute to cognitive impairment. In addition to the COMT val^{158}met polymorphism, other genes have been associated with cognitive decline (e.g., brain-derived neurotropic factor) val^{66}met, microtubule-associated protein tau, and beta-glucosidase acid).

To improve the clinical management of patients with movement disorders, additional research is needed to address the incomplete understanding of the presentation, epidemiology, risk factors, neural substrate, and optimal management strategies for all of the aforementioned diseases or disorders. Examples of high priority areas (with examples of ongoing projects) for future research are: (1) conducting long-term, longitudinal epidemiological research focused on the development, course, and predictors of cognitive impairment in specific populations (e.g., Enroll-HD, the IPMDS MSA Study Group); (2) using statistical techniques to reconceptualize the presentation and classification of cognitive deficits by accounting for the significant heterogeneity in performance that occur both cross-sectionally and longitudinally; (3) improving recognition and diagnosis through continued development and validation of diagnostic criteria and assessment tools for use in clinical care and research (e.g., the IPMDS PD-MCI International Consortium); (4) improving our understanding of the neural substrate of cognition in PD, through well-conducted clinical-pathological studies, and development of disease-specific and cognition-related biomarkers; (5) coming to a consensus on whether DLB and PD dementia should continue to exist as separate diagnostic entities; and (6) conducting large-scale clinical trials to determine the efficacy of different cognitive-enhancing treatments, including pharmacologic, nonpharmacologic, and, ultimately, disease-modifying agents, which entails both acute (symptomatic) and long-term (disease-modifying) trial designs.

In view of the rapidly expanding interest in all aspects of cognitive function and impairment in people with movement disorders, it is timely to devote a themed issue to this topic. When the editors sat down to draft the contents for this special issue, we quickly realized that even a dedicated issue would not afford us space to cover all important topics. We felt that an overview of how best to assess cognition (addressed here by Marras et al.[1]), as well as a review of the cognitive neuroscience of movement disorders[2] and the neurobiological basis of cognitive impairment in PD,[3] was essential. Mollenhauer et al. tackle biomarkers for cognitive impairment and dementia in PD.[4] The issue also addresses the spectrum of cognitive and neuropsychiatric symptoms in LB disease (covered by Gold-man et al.[5] and Aarsland et al.,[6] respectively), because these problems are so commonly encountered and significant. Emre et al. give an up-to-date review of the management of cognitive

impairment associated with PD, including practical issues such as driving and capacity.[7] Although a main focus of this special themed issue is PD, cognitive issues in atypical parkin-sonism,[8] HD,[9] SCA, and non-HD choreas[10] are also featured. The issue concludes with a "blue skies" look to where we might be in 10 years, with particular reference to PD dementia.[11]

We apologize in advance if the reader is disappointed by any omission, but believe that overall this special issue is an up-to-date review on a topic that has a major impact upon our patients and their families, and one that represents an area major unmet therapeutic need. We thank all of our colleagues for their excellent and timely contributions.

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