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Ruitenberg, M.F.L.

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Marit F.L. Ruitenberg*

People with neurodegenerative disorders often experience problems across a variety of functional domains, including cognition, movement, and psychosocial functioning. The classification of these disorders is based on the phenotypical manifestations that represent the most prominent clinical features. For example, Parkinson's and Huntington's disease are typically regarded as movement disorders, whereas Alzheimer's disease (AD) and other dementias are regarded as cognitive disorders. A problem with this classification is that it seems to disregard the fact that cognition and movement are actually strongly linked – successful motor performance does not only require the direct, physical control of muscles by the musculoskeletal system to generate movement and stability, but also involves cognitive control processes that allow us to engage in goal-directed behavior in the face of uncertain and/or changing environments (Abrahamse et al., 2013; McDougle et al., 2016). As a result, it seems difficult (if not impossible) to separate between "pure" motor or cognitive conditions. In this perspective article, I therefore propose that we should consider abandoning the classical movement versus cognitive disorder dichotomy when it comes to classifying neurodegenerative diseases.

Parkinson's disease (PD) is characterized primarily by cardinal motor problems such as resting tremor, bradykinesia, and rigidity, and thus traditionally classified as a motor disorder. In addition to these motor symptoms, however, many patients experience additional non-motor symptoms that can include (but are not limited to) problems with emotion, sleep, smell, and cognition. This list clearly shows that Parkinson's is not just a movement disorder and that labeling it as such could give people – whether it be patients, carers, or society in general – an incomplete understanding of the type of symptoms that individuals with this disease may experience. The importance of acknowledging that PD can affect both motor and cognitive processes is further illustrated by findings that these processes can be differently affected by dopaminergic medication. The majority of individuals with PD take dopaminergic medication to alleviate their motor symptoms. Paradoxically, however, such medication can actually negatively affect cognitive functions, including selective cognitive processes that are involved in movement control (Ruitenberg et al., 2021). According to the dopamine overdose hypothesis, this in particular can occur in the early to moderate stages of the disease – in those stages, dopamine levels in the dorsal striatum are depleted (and medication will improve functions relying on networks involving this structure), while dopamine levels in the ventral striatum are still relatively preserved (such that medication overdoses intact levels and thus impairs associated functions). When prescribing or adjusting medication regimens, it therefore is important that clinicians consider individual patient needs based on disease stage and specific symptoms.

A subset of individuals with PD experience problems with impulse control, which can lead to behaviors such as gambling, binge eating, or compulsive shopping. Such problems are collectively referred to as impulse control disorders (ICDs). Our team used a variety of brain imaging techniques to study the neural bases of ICDs (Ruitenberg et al., 2018, 2023). Results of our structural magnetic resonance imaging (MRI) scans showed that the gray matter volume of a set of subcortical brain areas called the basal ganglia was linked to impulsivity: greater volume of the putamen (i.e., the sensorimotor striatum) and smaller volume of the external portion of the globus pallidus were associated with more impulsivity. We also used resting-state functional connectivity MRI to evaluate potential differences in functionally connected networks of brain areas. We found that patients with ICDs showed stronger striatal-cerebellar connectivity compared to patients without ICDs, implicating the involvement of the sensorimotor network. Furthermore, patients with ICDs showed reduced connectivity between various basal ganglia areas (caudate, internal and external portions of the globus pallidus, subthalamic nucleus) and frontal cortical areas, thus implicating the involvement of cognitive and affective cortico-striatal networks as well. Finally, we used functional MRI to study differences in recruitment of brain areas during risk-related decision making and processing of outcomes. We observed that patients with ICDs showed more activation in a frontal area overlapping with the dorsal premotor cortex and less activation in several cerebellar areas during decision-making, suggesting alterations in sensorimotor processing. In addition, more impulsivity was associated with stronger activation in a variety of cortical and cerebellar motor areas during the processing of positive outcomes of risky decisions. This may suggest that individuals who are more sensitive to reward are also more likely to act in an impulsive manner. Overall, our work thus shows that alterations in both cognitive pathways and sensorimotor pathways contribute to problems with impulse control in PD. This suggests that patients with ICDs do not only seem to have a preference for more risky/rewarding decisions, but they are also more likely to act upon their impulses – thus highlighting the need for recognizing changes in both cognitive and motor processing and functioning in PD.

Another neurodegenerative disorder that is typically classified as a movement disorder is Huntington's disease, which is characterized by a triad of motor, cognitive, and psychiatric problems. Even though changes in each of these domains are well-established as being part of the Huntington's disease phenotype, the order in which they present can differ and remains difficult to predict. Studies have shown evidence for the onset of cognitive symptoms occurring as much as 15 years before the motor diagnosis of Huntington's disease (Paulsen, 2011). In addition, individuals with Huntington's and their families indicate that cognitive symptoms are considered to be among the most debilitating aspects of the disorder, more so than the motor symptoms. This further supports the notion that movement and cognition should not be considered independently in neurodegenerative disorders. In line with this notion, a task force from the Movement Disorder Society has argued that the clinical diagnostic criteria for Huntington's disease should be adapted to include both motor symptoms and cognitive symptoms (Ross et al., 2019).

In contrast to the aforementioned disorders, AD is typically viewed as a cognitive disorder. However, studies have shown that this clinical condition is also associated with problems in the motor domain – there are even indications that these latter classes of problems can be present before the onset of the more characteristic cognitive problems (Buracchio et al., 2010). Common motor deficits in AD include slower walking speed, poorer balance, poorer manual dexterity, larger cognitive-motor dual-tasking cost, and weaker muscle strength (for a review, see Koppelmans et al., 2022). In a recent study (Koppelmans et al., 2023), we used a finger tapping task to evaluate whether AD and amnestic mild cognitive impairment (often regarded a precursor for AD) were associated with problems in fine motor skills. We observed that individuals with AD performed poorer than healthy controls in dominant, non-dominant, and dual tapping conditions, whereas this was restricted to non-dominant hand tapping conditions in the group of individuals with amnestic mild cognitive impairment. Results further showed that finger tapping speed and variability were related to the volume of the hippocampus, a brain structure that is involved in memory and is known to be affected in AD. Specifically, we found that individuals with smaller hippocampal volumes showed slower and more variable finger tapping performance during the task. Finally, we applied machine learning to test whether we could use finger tapping performance to predict group classification. Results showed that our model could discriminate healthy individuals and those with Alzheimer's based on performance with an accuracy of 70%. Taken together, these results suggest that tests of fine motor functioning could be a promising tool to augment existing Alzheimer's biomarkers. When combined with cognitive and biomarker measures, finger tapping offers a cost-efficient, accessible, and non-invasive method for early screening and could become an integral part of a multi-modal diagnostic approach for AD.

Instead of relying on the classical motor versus cognitive distinction of neurodegenerative disorders, I propose a shift towards a more comprehensive and multi-dimensional approach that encompasses different aspects of these conditions (**Figure 1**). This approach should consider various dimensions of symptomatology,

such as cognitive impairment, motor and other physical dysfunctions, and psychological or behavioral disturbances. In addition, (neuro) pathological changes and disease biomarkers should be considered as these may allow for the development of interventions that address the underlying causes rather than just management of the symptoms. Overall, the proposed multi-dimensional approach thus acknowledges that neurodegenerative disorders often involve a combination of symptoms across different functional domains as well as various pathological changes. Moreover, I believe that this approach would allow for a more nuanced understanding and characterization of these conditions, more accurately capture their complexity and heterogeneity, and better reflect the experiences of individuals affected by them.

In summary, there is a strong fundamental link between cognition and movement. This is reflected in the fact that individuals living with what we currently classify as movement disorders can also experience cognitive problems, and vice versa. In this article, I therefore propose that we should consider moving away from the classification of neurodegenerative disorders into movement versus cognitive disorders towards a multi-dimensional approach. This better aligns with the occurrence of symptoms in multiple functional domains observed across the different disorders discussed here, as well as with evidence that there is an overlap in neuropathology between PD and AD (Compta and Revesz, 2021). Importantly, recognizing that neurodegenerative disorders are not purely cognitive or motoric in nature will also benefit patients, their family members, and society in general. By enriching their understanding of the type of symptoms people with these clinical conditions may be experiencing, symptoms that may have otherwise gone unnoticed or would not have been attributed to the disorder can be identified earlier. This subsequently means that clinicians can also intervene while symptoms have not become too severe and physical or cognitive rehabilitation is still likely to be successful, which in turn may reduce healthcare costs in the long run and allow for maintaining quality of life.

Marit F.L. Ruitenberg*
Department of Health, Medical and Neuropsychology, Leiden University, Leiden, the Netherlands
Leiden Institute for Brain and Cognition, Leiden, the Netherlands
***Correspondence to:** Marit F.L. Ruitenberg, PhD, m.f.l.ruitenberg@fsw.leidenuniv.nl.
https://orcid.org/0000-0001-7435-3229 (Marit F.L. Ruitenberg)
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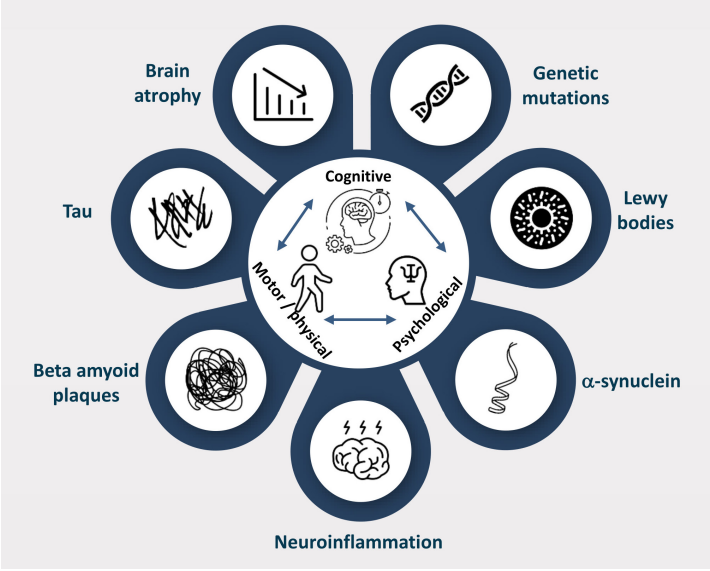

Figure 1 | **Illustration of the proposed multi-dimensional approach that encompasses the variation in dimensions of both symptomology (also illustrating their interrelations) and pathology.**
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References

Abrahamse EL, Ruitenberg MFL, De Kleine E, Verwey WB (2013) Control of automated behavior: insights from the discrete sequence production task. Front Hum Neurosci 7:82.

Buracchio T, Dodge HH, Howieson D, Wasserman D, Kaye J (2010) The trajectory of gait speed preceding mild cognitive impairment. Arch Neurol 67:980-986.

Compta Y, Revesz T (2021) Neuropathological and biomarker findings in Parkinson's disease and Alzheimer's disease: From protein aggregates to synaptic dysfunction. J Parkinson Dis 11:107-121.

Koppelmans V, Silvester B, Duff K (2022) Neural mechanisms of motor dysfunction in mild cognitive impairment and Alzheimer's disease: a systematic review. J Alzheimers Dis Rep 6:307-344.

Koppelmans V, Ruitenberg MFL, Schaefer SY, King JB, Hoffman JM, Mejia AF, Tasdizen T, Duff K (2023) Delayed and more variable unimanual and bimanual finger tapping in Alzheimer's disease: associations with biomarkers and applications for classification. J Alzheimer's Dis 95:1233-1252.

McDougle SD, Ivry RB, Taylor JA (2016) Taking aim at the cognitive side of learning in sensorimotor adaptation tasks. Trends Cogn Sci 20:535-544.

Paulsen JS (2011) Cognitive impairment in Huntington disease: diagnosis and treatment. Current Neurol Neurosci 11:474-483.

Ross CA, Reilmann R, Cardoso F, McCusker EA, Testa CM, Stout JC, Leavitt BR, Pei Z, Landwehrmeyer B, Martinez A, Levey J, Srajer T, Bang J, Tabrizi SJ (2019) Movement disorder society task force viewpoint: Huntington's disease diagnostic categories. Mov Disord Clin Pract 6:541-546.

Ruitenberg MFL, Wu T, Averbeck BB, Chou KL, Koppelmans V, Seidler RD (2018) Impulsivity in Parkinson's disease is associated with alterations in affective and sensorimotor striatal networks. Front Neurol 9:279.

Ruitenberg MFL, van Wouwe NC, Wylie SA, Abrahamse EL (2021) The role of dopamine in action control: Insights from medication effects in Parkinson's disease. Neurosci Biobehav Rev 127:158-170.

Ruitenberg MFL, Koppelmans V, Wu T, Averbeck BB, Chou KL, Seidler RD (2022) Neural correlates of risky decision making in Parkinson's disease patients with impulse control disorders. Exp Brain Res 240:2241-2253.

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