Heterogeneity in Parkinson's disease cognitive impairment

University of Glasgow

The Neurosciences Foundation

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Cognitive decline in PD

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- Parkinson's disease (PD) is primarily a movement disorder.
- However, non-motor symptoms are common.
- Cognitive decline, including dementia, is especially common and debilitating.
- In many respects, cognitive impairment is highly variable in PD.

Variation in cognitive decline in PD

Clinical

Genetic

Neuropathological

Variation in cognitive decline in PD

Clinical

Genetic

Neuropathological

Systematic review (1)

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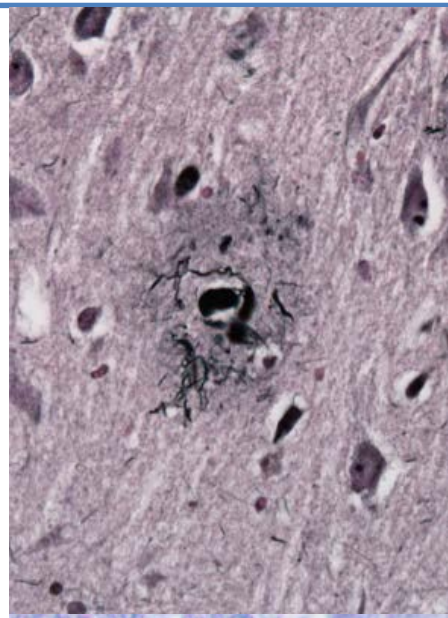
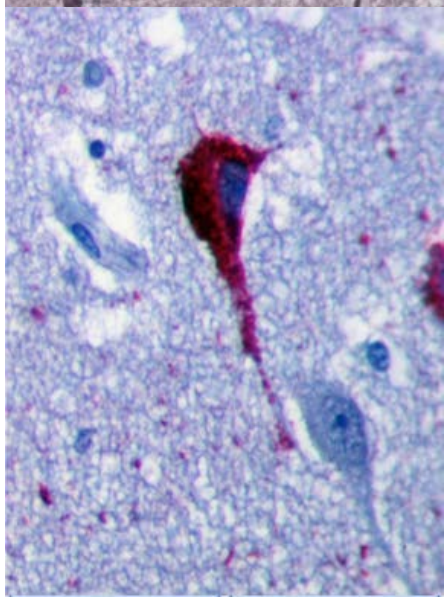
Major protein pathologies:

- Alpha-synuclein (Parkinson's)
- Amyloid-beta (Alzheimer's; *top image*)
- Tau (Alzheimer's; *bottom image*)
- TDP-43 (frontotemporal dementia, LATE)





Vascular pathology (e.g. stroke).

All of these pathologies are common autopsy findings in people with PD.

Systematic review (2)

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Objective: To describe the neuropathology of dementia in PD using a systematic review of autopsy studies.

- Five databases were systematically searched for relevant articles. 1566 potentially eligible articles were found.
- Of these, 44 reports met inclusion criteria.
- These involved 2002 PD cases, 57.2% with dementia.

Systematic review (3)

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TDP-43 and cerebrovascular pathologies were not significantly more common in PD cases with dementia compared to those without. However…

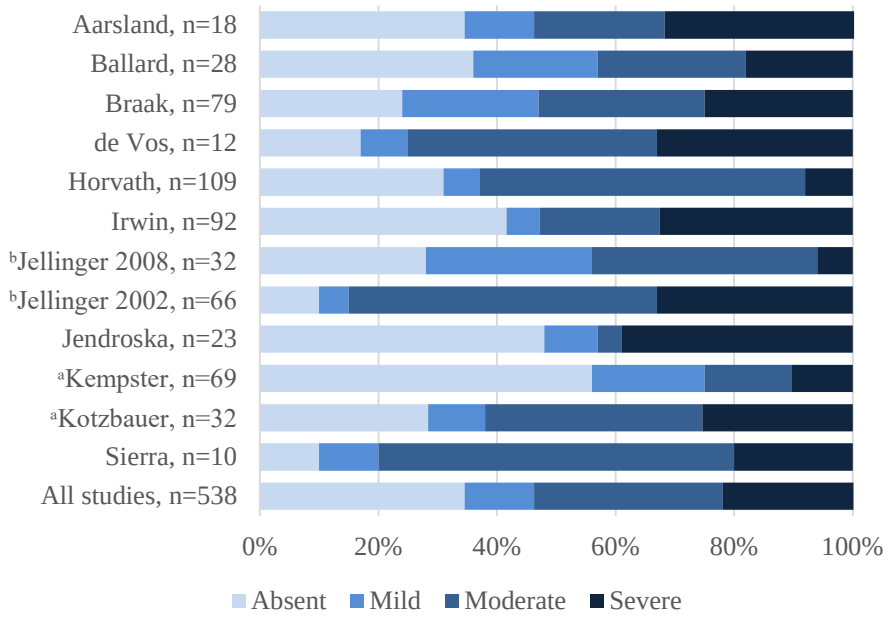

Figure 1. Severity of amyloid-beta pathology in PD cases with dementia.

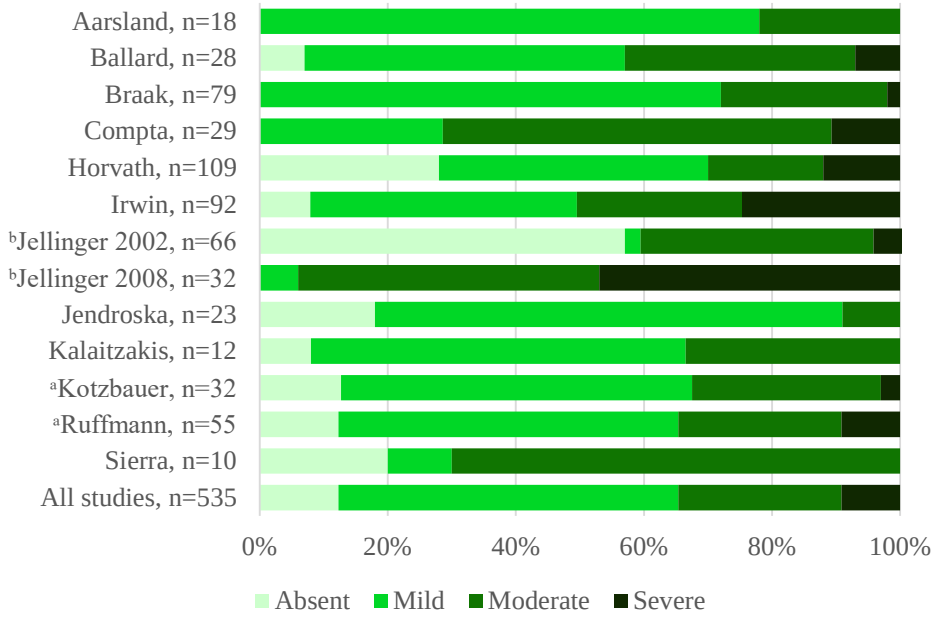

Figure 2. Severity of tau pathology in PD cases with dementia.

Variation in cognitive decline in PD

Clinical

Genetic

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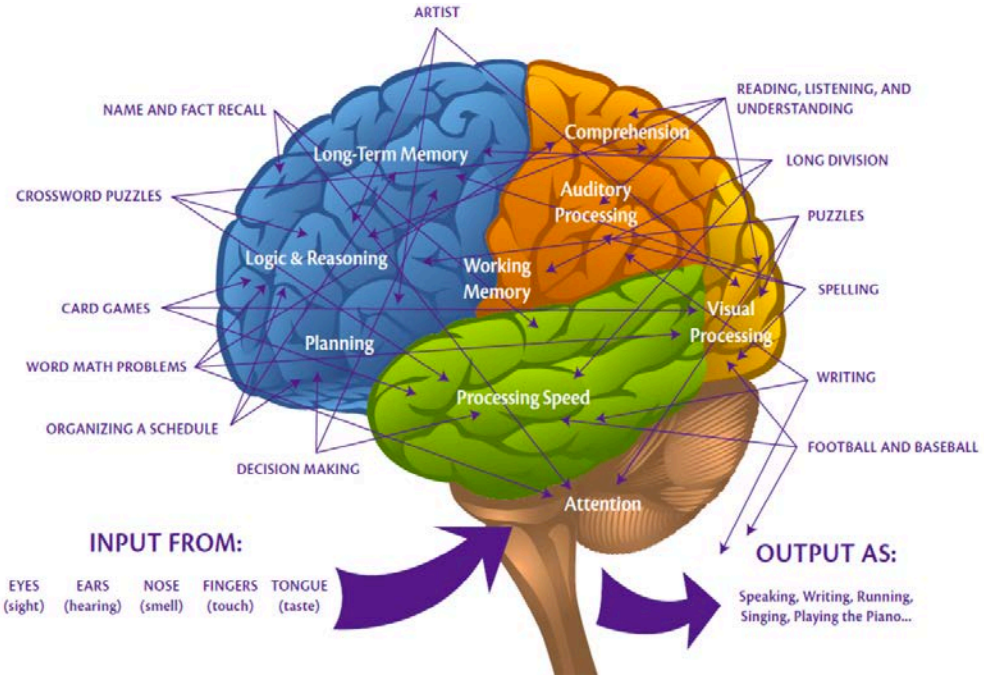
Clinical project (1)

Many PD patients have other disease pathologies (e.g. Alzheimer's) in the brain.

In life, different diseases are associated with different clinical profiles.

These profiles are summarised in diagnostic criteria for each disease.



Clinical project (2)

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Objective: To see how many cognitively impaired PD patients meet diagnostic criteria for other cognitive disorders.

- 45 patients kindly took part. Each nominated one relative.
- Each completed a detailed neuropsychological assessment and various questionnaires. Medical notes were accessed.
- This data was transferred to an expert panel for a consensus diagnosis, referencing current diagnostic criteria.

Clinical project (3)

Preliminary results show that many PD patients meet criteria for other cognitive disorders.

Most patients show a typical PD profile.

Alzheimer's is the most common coexistent disease, occurring in about a third.

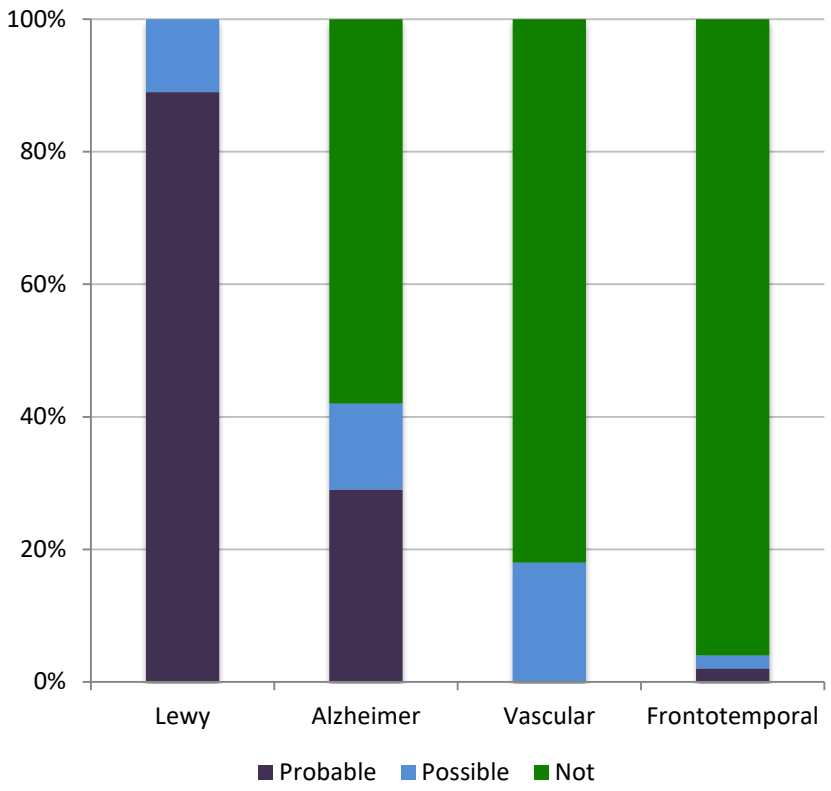
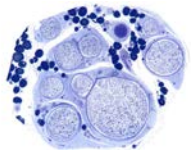


Figure 3. Percentage of cognitively impaired PD patients meeting criteria for each disease.

Variation in cognitive decline in PD

Genetic

Clinical



Neuropathological

Genetics project (1)

Many genetic variants affect the risk of dementia.

Two of the most widely studied are *APOE* e4, the strongest risk factor for Alzheimer's, and *MAPT* H1, which is implicated in several diseases.

Both have been associated with cognitive decline in PD, but results are inconclusive.

Need for large samples.

Genetics project (2)

Objective: To evaluate the association of variants of *APOE* and *MAPT* to cognitive decline in PD.

- 1016 recent-onset Tracking Parkinson's participants were analysed.
- *APOE* and *MAPT* variants were linked to MoCA score at baseline, 18 months, and 36 months.
- These genes were also linked to the magnitude of change in MoCA score between each of these visits (i.e. rate of decline).

Genetics project (3)

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APOE e4 was associated with poorer cognitive function at 36 months.

APOE e4 was strongly related to the rate of cognitive decline in early PD.

The deleterious effects of *APOE* e4 on cognition only appeared in men.

MAPT was not associated with any outcome.

Conclusions

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1. In PD, the pathology, clinical presentation, and genetics of cognitive decline vary.

1. Coexistent Alzheimer's pathology has a substantial contribution to dementia in PD.

1. Various coexistent pathologies cause different cognitive profiles to emerge in life.

2. Genetic factors associated with Alzheimer's also contribute to cognitive decline in PD.

Implications for treatment

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1. Clinicians should not assume that cognitive decline in PD is purely the result of PD itself.

1. Trials of new treatments targeted directly against abnormal proteins must take into account the variability within PD.

1. The optimal treatment strategy for cognitive symptoms must be tailored to the individual.

Thanks for listening!

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And thanks for your continuing work on Tracking Parkinson's!

The Neurosciences Foundation

Thanks to all patients, relatives, supervisors, and funders.

TRACKING PARKINSON'S CENTRES

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If you have any questions, please ask.