

## Title

Neuropathological progression of clinical Parkinson disease subtypes

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There have been many attempts to identify clinical subtypes of Parkinson disease (PD) but little progress has been made in determining whether they are simply a reflection of the clinical heterogeneity of PD or are due to different diseases hiding under one rubric.

In a recent News & Views article (Clinical Parkinson disease subtyping does not predict pathology)(1) Espay and Marras discussed our recent clinicopathological study showing that PD subtyping at diagnosis can provide useful information on subsequent disease progression and survival. (2) They stated correctly that the severity of Lewy and Alzheimer pathologies did not differ between the clinical subtypes but, importantly, they failed to mention that these pathological changes were reached over a significantly shorter disease duration in the diffuse malignant subgroup. This was one of the key findings of our study.

All patients with PD, despite differences in the disease course in the early and middle stages, eventually enter an accelerated terminal phase of illness often associated with falls and cognitive impairment.(3, 4) By the time of death, PD patients have reached an equivalent terminal neuropathological stage but, in the same way as the clinical progression, the rate of neuropathological deterioration differs among different subgroups and it was this finding that allowed us to conclude that different neuropathologies were important determinants of clinical PD subtypes.(2) Despite different rates of clinical and neuropathological progression we could not establish pathological features that would allow a neuropathologist 'blinded' to the clinical details to accurately categorise the clinical subtype. Neuropathological studies have inherent limitations given the inability to serially examine brain tissue over time to evaluate the dynamic neurodegenerative processes, which prevents analysis of differences in pathological severity and distribution in subtypes at earlier stages of the disease. We agree that other important factors such as regional cell loss independent of Lewy and Alzheimer neuropathologies must be involved and we have previously demonstrated that age of the patient is an important determinant to prognosis and also to clinical subtype definition.(2, 3)

## References

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