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LETTER TO THE EDITOR

Reply: LATE to the PART-y

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Sir,

We are pleased that there is agreement from investigators beyond the consensus group of authors of the LATE paper that more research is required on ageing-related TDP-43 proteinopathy.

Nomenclature for emerging neuropathological disorders that evolve by research discoveries, such as the discovery of TDP-43 in frontotemporal degenerations and motor neuron disease (Neumann *et al.*, 2006), can be difficult. The recommendation of the term LATE for the clinical correlates of the TDP-43 proteinopathy in ageing (Nelson *et al.*, 2019) is intended to provide a common nomenclature and framework to better characterize this very common but poorly recognized disorder associated more often with deficits in episodic memory rather than the prominent language or behavioural disturbances typical of frontotemporal lobar degenerations. There is no current agreement on criteria to define the boundaries between LATE

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neuropathological changes (NC) and frontotemporal lobar degeneration with TDP-43 (FTLD-TDP) pathology that occurs in the elderly. We hope (and anticipate) that future work will help delineate the areas of overlap, and difference, between FTLD-TDP and LATE-NC.

In the neuropathological staging of LATE-NC, our recommendations were guided partly by recent experience with National Institute on Aging-Alzheimer Association (NIA-AA) consensus guidelines for Alzheimer disease (Montine *et al.*, 2012), where the term 'Alzheimer disease neuropathologic change' (ADNC) was used to document any amount of disease-defining histopathology, without regard to clinical correlates. The NIA-AA guidelines also included recommendations for methods to assess Alzheimer disease-related dementias, including Lewy body disease, hippocampal sclerosis and vascular brain injury. Even this proposal met with criticism by community and academic neuropathologists because the recommended immunostains were thought to be too numerous, and the particular choice of stains had not been independently validated. For LATE-NC staging, we proposed TDP-43 immunohistochemistry in three brain structures (amygdala, hippocampus, and middle frontal gyrus) that are most easily sampled by community pathologists and are likely to have already been sampled by most dementia research neuropathologists. We provided evidence that the proportion of individuals with cognitive impairment increases with each stage. The proposal is a minimum requirement for broad use, in no way precludes more detailed or refined approaches to staging TDP-43 proteinopathies associated with ageing, and does not discourage efforts to determine whether there might be added value in doing so.

Josephs *et al.* (2019) take issue with nomenclature of 'LATE'. Here, the consensus working group relied on precedents in consensus-based efforts by experts. For example, the term 'limbic-predominant' is used in Lewy body disease classification (McKeith *et al.*, 1996); the term 'age-related' is included in ageing-related tau astrogliopathy (Kovacs *et al.*, 2016) and primary age-related tauopathy (Crary *et al.*, 2014); while the term 'encephalopathy' is used in consensus recommendations for chronic traumatic encephalopathy (McKee *et al.*, 2016). Further, the term 'encephalopathy' literally means 'disease of the brain' and can apply to specific pathological changes proven to underlie disease conditions even if symptomology is unknown, including neuropil microvacuolation in spongiform encephalopathy (Brown, 2008) and swollen astrocytes in hepatic encephalopathy (Norenberg *et al.*, 2007). We acknowledge that the term 'encephalopathy' as used in current neurological practice may imply a clinically active process. This is why we recommend that LATE should be used to describe the clinical disease, which remains to be better defined by further studies, and LATE-NC should be the pathological description (similar to Alzheimer's disease and ADNC). As the term LATE indicates, this particular disease affects people in later life and can clinically mimic other late-life amnestic dementias, including limbic predominant Alzheimer's disease (Murray *et al.*, 2014). Our objective was to find a term that could concisely convey pertinent information about the underlying disease process, which the term LATE does quite well.

Defining LATE and LATE-NC may help address the uncertainty that surrounds the TDP-43 inclusions seen in other neurodegenerative disorders, such as Lewy body diseases, Huntington's disease and the tauopathies shown in Figure 1 of Josephs *et al.* It remains unclear in many cases whether the TDP-43 inclusion pathology observed in these patients represents a byproduct of the primary disease (yet may manifest in only a minority of patients) or represents comorbid LATE-NC. We hope that future biomarker discovery and neuropathological research stimulated by the LATE consensus process will enable disambiguation of these competing possibilities.

Finally, we would like to address the conclusion of the Letter that 'researchers ... (should) ... defer broad usage of LATE until (and only if) the science is mature'. We disagree strongly because this would take us back to a point with no common terminology for the TDP-43 proteinopathy predominantly in limbic brain regions of older individuals. The term LATE is intended to provide a means to describe a process that could be easily understood by patients, clinicians, and researchers. It provides a cross-disciplinary means to communicate and perform research on an entity that underlies one of the most common causes of late life memory impairment. This new terminology also augments efforts to better understand dementias in the oldest old, the most rapidly expanding age group in Western countries with highest prevalence of dementia, in whom traditional neuropathologies do not explain the dementia syndrome well enough. The primary goals of this new nomenclature were to mobilize research toward better recognition, diagnostic criteria, and therapeutic strategies. Achieving these goals will require carefully designed studies that incorporate (and integrate) the work of multiple researchers speaking a common language about prevalent and often co-occurring diseases. We look forward to rapidly increasing knowledge and advances in fighting all dementias in ageing, including LATE.

Data availability

Data sharing is not applicable to this article as no new data were created or analysed in this study.

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Competing interests

The authors report no competing interests.

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