may contribute to the diffuse neuronal damage detected in PPMS. In addition, IL-1β can also act on astrocytes, triggering pro-inflammatory and neurotoxic responses while interfering with the metabolic support of neurons to further amplify neurodegeneration (Chao *et al.*, 2019; Wheeler *et al.*, 2020). Surprisingly, IL1 receptor blockade did not ameliorate EAE, suggesting that NLRP3 activation contributes to disease pathogenesis through IL-1β-independent mechanisms and/or that anakinra levels in the CNS may not be high enough to block most IL-1β-driven pathogenesis. Future studies should determine the mechanisms through which NLRP3 inflammasome activation in peripheral and CNS-resident cells contributes to PPMS pathogenesis.

Finally, although the study by Malhotra *et al.* suggests a role for inflammation in PPMS pathogenesis, other mechanisms are also thought to contribute to PPMS pathology (Faissner *et al.*, 2019). Future studies should investigate the heterogeneity of pathogenic mechanisms in PPMS, and in particular the relative contribution of inflammatory and non-inflammatory processes. In combination with biomarkers such as those described by Malhotra and co-workers, these studies may guide the development of efficacious personalized therapies for patients with PPMS.

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# Shaking with fear: the role of noradrenaline in modulating resting tremor

**This scientific commentary refers to 'Cognitive load amplifies Parkinson's tremor through excitatory network influences onto the thalamus', by Dirkx *et al.* (doi: 10.1093/brain/awaa083).**

Parkinson's disease is a complex neurodegenerative disease that is characterized by motor impairments, such as bradykinesia, postural instability and tremor. These motor deficits are presumed to arise secondary to the depletion of a group of dopaminergic cells in the midbrain that project to the striatum and cerebral cortex. In addition, a proportion of patients also

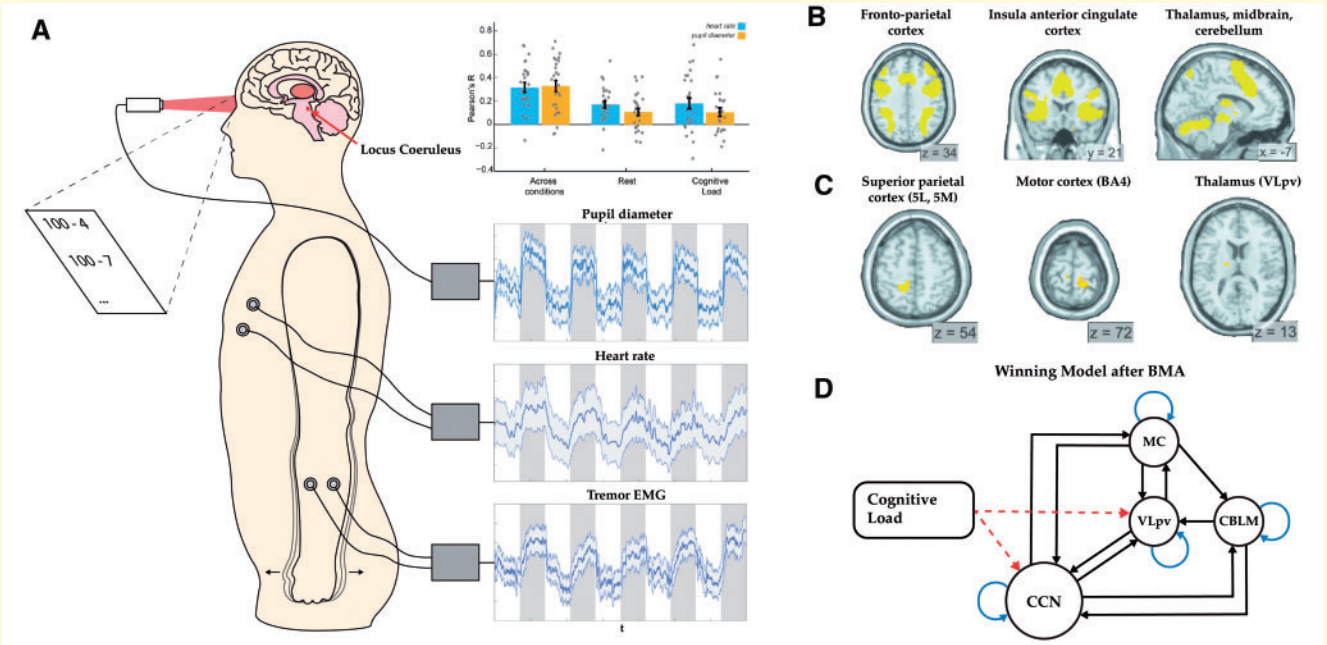


**Figure 1 Overview of the findings of Dirkx *et al.*** (**A**) Behavioural measures of ascending sympathetic arousal—pupil diameter and heart rate—increased during cognitive load (grey blocks), as did tremor amplitude. Tremor amplitude correlated with heart rate and pupil diameter. (**B**) Findings from functional MRI depicting the cognitive control network during cognitive load compared to rest. (**C**) The increase in tremor amplitude during cognitive load correlated with activity in the superior parietal cortex, motor cortex (MC), and thalamus; and (**D**) a model of the effects of cognitive load, in which cognitive load acts both indirectly by strengthening connectivity between cerebello-thalamo-cortical circuits and the cognitive control network (CCN), and directly by activating the contralateral ventrolateral thalamus. BMA = Bayesian Model Averaging; CBLM = cerebellum; VLpv = ventrolateral nucleus of thalamus.

experience symptoms of apathy, depression and anxiety. Despite the success of the classical 'dopaminergic model' of Parkinson's disease, neither class of symptoms can be fully explained by dopaminergic impairments. Crucially, there is substantial evidence to suggest that individuals with Parkinson's disease also display pathology within other non-dopaminergic neuromodulatory systems, such as the noradrenergic, serotonergic and cholinergic systems (Lim *et al.*, 2009). This hypothesis thus necessitates a more detailed characterization of the relationship between the symptoms of Parkinson's disease and disease-specific pathology within a broader set of neuromodulatory systems. In this issue of *Brain*, Dirkx and co-workers embark on precisely this line of enquiry by examining the relationship between sympathetic tone and resting tremor (Dirkx *et al.*, 2020).

A particularly salient example of non-dopaminergic pathology in Parkinson's disease can be found in the noradrenergic locus coeruleus. It has long been known that individuals with Parkinson's disease show both Lewy body pathology and cell loss within the locus coeruleus and that the removal of the locus coeruleus in animal models typically leads to worsening of motor symptoms (Rommelfanger and Weinshenker, 2007). In addition, pathology within the locus coeruleus may also contribute to the progression of disease by exacerbating damage to the nigrostriatal tracts (Gesi *et al.*, 2000). Together these results implicate the locus coeruleus as a key player in Parkinson's disease, and suggests that the limitations of the 'dopaminergic model' could be due in part to the impact of noradrenergic system pathology. So, what role does the locus coeruleus play in normal brain function?

The locus coeruleus is critically involved in cognitive function as the major source of noradrenaline in the CNS with widespread projections innervating large portions of the thalamus, cerebellum, and the entire cerebral cortex (Aston-Jones and Cohen, 2005). These noradrenergic projections can alter the responsivity of targeted neurons in a context-dependent manner by changing the neural response gain. This in turn changes the global functional architecture of the brain (Shine *et al.*, 2016), modulating not only attention-related processes (e.g. task performance and focused alertness) but also facilitating working memory, memory consolidation and retrieval (Vermeiren and De Deyn, 2017). In short, noradrenaline can facilitate cognition by repurposing the brain's resources in line with task-specific requirements.

The locus coeruleus exhibits tonic low firing rates during sleep, whereas high firing rates have been observed during anxiety and stress in association with activation of the sympathetic nervous system (Samuels and Szabadi, 2008). In addition, the locus

coeruleus modulates anxiety through its innervation of the amygdala (Wallace *et al.*, 1992). Locus coeruleus pathology in Parkinson's disease may thus underlie the emotional dysregulation prevalent in the disorder. Furthermore, the expression of some symptoms, such as resting tremor and freezing of gait, is amplified by cognition and anxiety (Ehgoetz Martens *et al.*, 2014). Despite these associations, the absence of a mechanistic framework tying the noradrenergic system to Parkinson's disease has resulted in few therapeutic options targeting this axis of pathology. Current theories postulate that the dysfunctional rhythms inherent to resting tremor emerge within loops interconnecting the basal ganglia, cerebellum, thalamus and cerebral cortex (Dirkx *et al.*, 2016). It has been further suggested that this circuit can be augmented by the ascending arousal system; however, direct evidence of this phenomenon has been lacking.

Dirkx *et al.* therefore asked whether cognitive load amplified tremor through augmentation of the noradrenergic system. They conducted a 3 T multi-echo functional MRI study, in which 33 participants with tremor-dominant Parkinson's disease OFF their regular medications performed an alternating cognitive task to investigate the impact of cognitive load on resting tremor. The cognitive task involved performing mental arithmetic as fast as possible (e.g. 'subtract 3 from 100'), with interspersed intervals of rest. Three behavioural measures were concurrently recorded: EMG to characterize tremor, and pupil diameter and heart rate as indirect measures of the ascending sympathetic arousal system (Fig. 1A). The authors hypothesized that sympathetic arousal and cognitive load should together act to increase the severity of resting tremor.

As a first step, the authors confirmed that cognitive load was significantly associated with increased tremor, enlarged pupil diameter and increased heart rate (Fig. 1A), along with an overall increase in blood oxygen level-dependent (BOLD) signal within the cognitive control network (i.e. the bilateral anterior cingulate cortex, insula, thalamus, posterior parietal cortex, frontal eye fields and dorsolateral prefrontal cortex; Fig. 1B). Cognitive load subsequently increased the tremor amplitude-related activity within the secondary somatosensory cortex, contralateral superior parietal cortex and ipsilateral motor cortex (Fig. 1C). The amplitude of resting tremor was observed to increase rapidly upon initiation of cognitive load and correlated with activity within the thalamus. Notably, the study identified two pathways by which cognitive load can modulate tremor activity: directly through innervation of the contralateral ventrolateral thalamus, and indirectly through strengthening connectivity between the cerebello-thalamo-cortical circuits and the cognitive control network (Fig. 1D).

The authors extended their results using a dynamic causal modelling approach, which is a Bayesian method of inference where data are iteratively compared to various potential models of the underlying circuitry (e.g. connections between nodes and/or subsequent modulation of these nodes/connections) in an effort to determine the best 'fit' for the data. Within the eight model groups studied, the data were best explained by a class of models that had bidirectional connections between the cognitive control network and all the nodes of the cerebello-thalamo-cortical circuits (Fig. 1D). Bayesian model averaging determined that cognitive load drove network activity through stimulation of the cognitive control network and contralateral ventrolateral thalamus. Overall, there were significant increases in functional connectivity between the cognitive control network and thalamus during cognitive load. Importantly, cognitive load induced increases in pupil diameter, and fluctuations in pupil diameter were associated with dynamic changes in the cognitive control network. Together, these results confirmed the authors' initial hypothesis, and indicate that the ascending arousal system is active during cognitive load and further augments the expression of resting tremor.

While dynamic causal modelling is a useful method for obtaining insights into neurobiological mechanisms, it poses some inherent challenges, such as requiring a limited number of nodes for effective computation and its reliance upon fitting models to the BOLD signal, which reflects some, but not all, elements within the neural circuitry. In addition, it is often challenging to avoid scenarios in which the most complex model best fits the data, as was the case in the current study. The very fact that the more complex model is defined by more variables means that there are more degrees of freedom available for fitting prior distributions within the Bayesian models. One solution is to augment these approaches with computational models that integrate circuit principles and other biological mechanisms of neural activity that more accurately represent the behaviour of the entire neural circuit, whilst maintaining the complexity of the model. Together, these two complementary approaches can provide a more complete picture of the underlying neurobiology than either on their own.

The results of Dirkx *et al.* suggest that resting tremor expression in Parkinson's disease and its amplification under cognitive load may lie at the intersection of two distinct mechanisms: noradrenergic ascending modulation of the thalamus, and modulation from the cognitive control network onto the thalamus, cerebellum and motor cortices. Whether these impairments are due to Lewy body pathology, cell death within the locus coeruleus, or compensatory processes that occur secondary to damage within other arousal structures remains an open question and will require both multimodal and longitudinal imaging approaches to tease apart. More generally, this study supports a multidimensional view of Parkinson's disease pathology, in which simultaneous dysfunction within multiple neuromodulatory systems can mediate the expression of symptoms. Using an inventive combination of methods and

approaches, Dirkx *et al.* highlight an important association between cognitive load and noradrenergic neuromodulation, with results that pose tantalizing questions about the role of neuromodulators in shaping large scale brain dynamics relevant to cognitive function.

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## Competing interests

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# Neither white nor black: embracing clinical variability in dementia diagnosis

**This scientific commentary refers to 'Redefining the multidimensional clinical phenotypes of frontotemporal lobar degeneration syndromes', by Murley *et al.* (doi:10.1093/brain/awaa097).**

Making sense of the world's complexity and multidimensionality has been an ongoing intellectual endeavour for centuries. Within the field of dementia and related neurodegenerative progressive brain disorders, too, clinicians face the challenge of phenotypic complexity and multiple underlying pathologies. Accuracy of dementia diagnosis is of paramount importance, as it has repercussions for prognosis, disease management and potential interventions. Humans, however, are poorly equipped to deal with this complexity, with our default approach being to reduce it to manageable sets, ideally within clearly defined boundaries. Extreme case teaching, as used in clinical psychology and medical training, is an example of this reductionist approach. While it is an effective approach that provides frameworks and heuristics for hypothesis testing and solution generating, it often results in artificial categories, ignoring the variability within and across dimensions and fuzzy boundaries (Tversky and Kahneman, 1974). In this issue of *Brain*, Murley and co-workers reappraise this approach by examining how the multidimensionality of clinical features can be embraced to help understand the complexity of presentations, clinically and in neuroimaging, across frontotemporal lobar degeneration syndromes (Murley *et al.*, 2020).

In the dementia field, as in many others, the issue of complexity has been tackled by developing sets of diagnostic criteria, criteria that carve the dementia landscape into specific disease categories. Over the years, these criteria have been refined, reflecting the increasing knowledge about these brain disorders (Gorno-Tempini *et al.*, 2011, McKhann *et al.*, 2011; Rascovsky *et al.*, 2011), and enabling clinicians and researchers