



Dying-back of ascending noradrenergic projections in Parkinson's disease

This scientific commentary refers to 'Regional locus coeruleus degeneration is uncoupled from noradrenergic terminal loss in Parkinson's disease', by Doppler *et al.* (doi:10.1093/brain/awab236).

Parkinson's disease is a neurodegenerative disorder characterized by progressive loss of nigro-striatal dopamine neurons. The cardinal motor signs of the disease, particularly bradykinesia and rigidity—and to a lesser extent tremor—have been linked to dopaminergic dysfunction of the basal ganglia. In addition, it has long been known that Parkinson's disease patients also have profound noradrenergic, cholinergic and serotonergic cell loss. Clinically, noradrenergic deficits have been linked to cognitive dysfunction, to specific non-motor symptoms such as REM sleep behaviour disorder (RBD), and to axial symptoms such as freezing of gait.^{1,2}

A key outstanding question is how Parkinson's disease propagates through the brain, and what this pattern tells us about the underlying mechanisms of progressive cell death. The classical post-mortem studies by Braak and colleagues have suggested that there is a bottom-up progression of disease, which may initially start in the gut, before progressing towards caudal and later more rostral parts of the brainstem, and ultimately reaching the cortex.

Other studies point to the role of top-down pathophysiological mechanisms, where increased cortical demands may lead to energetic failure in the highly branched dopaminergic and noradrenergic neurons, causing them to dysfunction and ultimately perish.³ The clinical observation that motor symptoms in Parkinson's disease can start out very localized (e.g. resting tremor of one hand, or bradykinesia of one foot) supports this idea, since this detailed level of somatotopy is observed much more clearly at cortico-striatal than at nigro-striatal projections.³

In addition, several recent studies have shown important inter-individual differences in disease propagation patterns, which are linked to the expression of clinical symptoms such as the presence or absence of RBD.^{4,5} In this issue of *Brain*, Doppler and colleagues⁶ address some of these issues, by using neuroimaging techniques to decipher the anatomical pattern of noradrenergic dysfunction in Parkinson's disease.

In a comprehensive study, Doppler *et al.*⁶ used a combination of two imaging techniques to measure different compartments of the noradrenergic system: PET with ¹¹C-MeNER (Fig. 1B), a reboxetine analogue that binds specifically to noradrenaline transporters located at the terminal sites of noradrenergic cells, and neuromelanin-sensitive MRI (Fig. 1C), which is a turbo spin-echo (TSE) T₁-weighted sequence that is sensitive to the loss of pigmented neurons in the locus coeruleus.

The locus coeruleus is a small nucleus in the dorsal pons that is the primary source of noradrenergic projections in the brain (Fig. 1A). In 47 patients with Parkinson's disease and 26 healthy control subjects, Doppler *et al.*⁶ applied both techniques within a timespan of a few weeks. The authors hypothesized that more severe deficits would be seen at the level of the noradrenergic terminals (PET) than the cell bodies (MRI), in line with findings in the dopaminergic system, where a 'dying-back' mechanism of neurodegeneration has been found in Parkinson's disease. They also tested for regional differences in neurodegeneration within the locus coeruleus, by comparing rostral, intermediate, and caudal portions of the locus coeruleus.

There are three main findings. First, and most importantly, the authors found that pronounced axonal damage exceeded somatic damage of the noradrenergic system in patients, as has also been found for the dopaminergic system. This effect was quantified as a smaller ratio of ¹¹C-MeNER PET to neuromelanin-MRI contrast in Parkinson's disease patients, compared to healthy control subjects (Fig. 1D). The authors refer to this effect as 'uncoupling', which should be understood as disproportionately large noradrenergic deficits at the distal ends of the axonal tree. This effect may be related to the extremely large arborization of both dopaminergic and noradrenergic neurons.³ This anatomical configuration makes these ascending neurotransmitter systems particularly vulnerable to insults.

The findings do not immediately demonstrate where such insults could come from: the 'dying-back' of noradrenergic cells may be the outcome of different pathophysiological processes that can be either bottom-up (e.g. α -synuclein affecting the cell bodies in the locus coeruleus), top-down (e.g. altered synaptic demands at projection sites, or cortico-fugal projections to the locus coeruleus), or a combination of both. Cellular mechanisms such as impaired protein clearance, altered mitochondrial function, inflammation, and management of reactive oxygen species have all been proposed to play a role in cell death in Parkinson's disease.⁸ Furthermore, recent development of a rodent model exhibiting an age-dependent production of human-like neuromelanin in the substantia nigra has led to the hypothesis that too much intracellular neuromelanin accumulation may compromise neuronal function and trigger a Parkinson's disease-like pathology.⁹

A second finding by Doppler and colleagues⁶ is that there was no correlation between MRI and PET findings, either in healthy control subjects or in patients with Parkinson's disease. This could be another instance of the 'uncoupling' between noradrenergic terminals and cell bodies. The fact that there was no correlation in

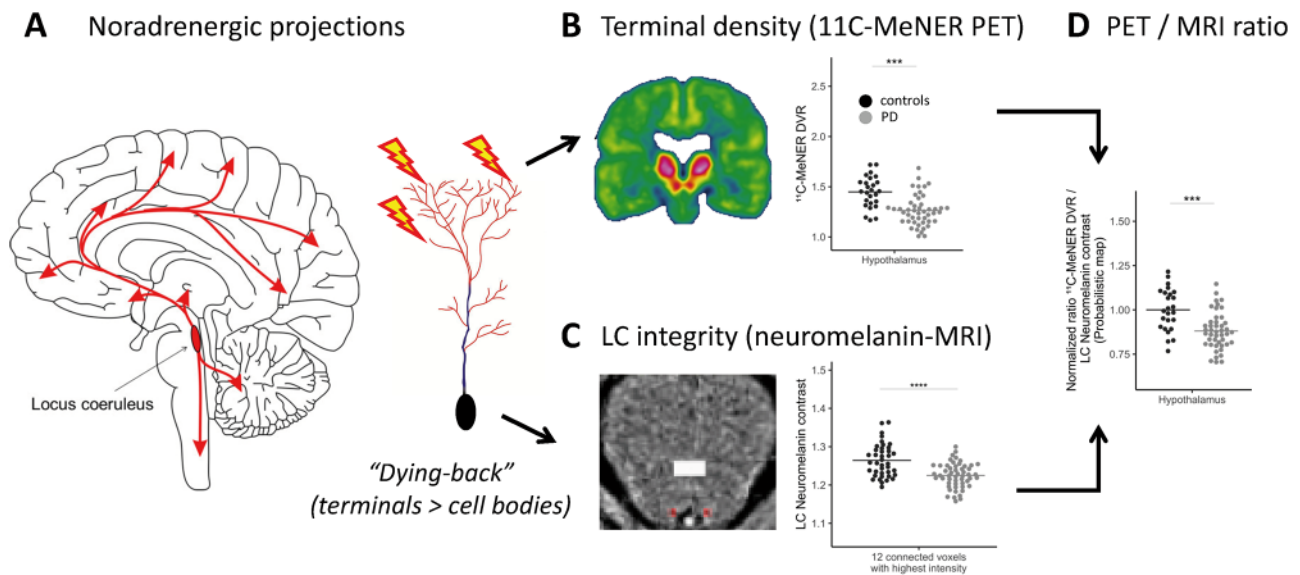


Figure 1 ‘Dying-back’ of noradrenergic projections in Parkinson’s disease. (A) Noradrenergic neurons in the locus coeruleus project to cortical and subcortical brain regions (modified from Augusto and Gambino⁷). (B) The density of noradrenergic terminals, shown with ^{11}C -MeNER PET (taken from Fig. 5 and Supplementary Fig. 1 in Doppler et al.⁶). (C) The structural integrity of the locus coeruleus (indicated in red), as compared to a control region (pons), using neuromelanin-sensitive MRI (from Fig. 1 in Doppler et al.⁶). (D) The ratio between PET and MRI signal shown for the hypothalamus (from Fig. 7 in Doppler et al.⁶). Data were normalized to the average in healthy control subjects. In patients, the significantly lower ratio means that noradrenergic dysfunction of the terminals (PET) exceeded that of the cell bodies (MRI). DVR = distribution volume ratio; LC = locus coeruleus; PD = Parkinson’s disease.

control subjects may suggest that the two compartments of the noradrenergic system are independent of each other in the physiological situation. This would be surprising, since the noradrenergic terminals are ultimately connected to the cell bodies in the locus coeruleus. Alternatively, the lack of correlation could be driven by methodological factors, such as different sensitivity of PET and MRI to the underlying biology, large variability of signal and volume measurements in the locus coeruleus using MRI, and lack of statistical power owing to a moderate number of patients. In addition, the subjects’ RBD status, which was not considered, may also contribute: disease propagation patterns have been found to differ between parkinsonian patients with and without RBD.⁵

A third novel finding reported by Doppler and colleagues⁶ is that there were regional differences in the spatial pattern of locus coeruleus damage in Parkinson’s disease, such that the middle and caudal portions of the locus coeruleus were more affected than the rostral portion. These data are roughly in line with recent post-mortem investigations in Parkinson’s disease, although the differences between locus coeruleus subregions are relatively small. It would be interesting to study this pattern in relation to the presence of RBD, which is probably linked to the involvement of the locus subcoeruleus located in the caudal part of the locus coeruleus.² Interestingly, these effects were asymmetric in nature, being more pronounced in the hemisphere contralateral to the clinically most affected side.

The authors did not report correlations between noradrenergic deficits and clinical symptoms. This is partly due to the fact that different cohorts were combined, and unfortunately there was no homogeneous evaluation of non-motor symptoms across all individuals. Surprisingly, there was no correlation between noradrenergic dysfunction and progression markers of Parkinson’s disease, such as disease duration, Hoehn and Yahr stage, and total Unified Parkinson’s Disease Rating Scale (UPDRS) score. On the other hand, these findings are in line with another recent

neuromelanin-sensitive MRI study in Parkinson’s disease, which showed that motor severity correlated only with neuromelanin in the substantia nigra, while cognitive measures only correlated with neuromelanin signal in the locus coeruleus.¹

Doppler and colleagues⁶ measured performance on the Montreal Cognitive Assessment (MoCA), which was included as a covariate of no interest in the analyses. While the MoCA is a useful screening tool, it is not sensitive enough to detect subtle cognitive deficits in Parkinson’s disease, and it is not specific enough to localize these deficits to anatomical circuits.¹ It would be interesting to test if the dying-back of the noradrenergic system is associated with specific patterns of cognitive deficits in Parkinson’s disease. Within the motor domain, there may be a relationship between noradrenergic deficits and tremor severity. ^{11}C -MeNER PET studies have shown that the noradrenergic system is relatively spared in tremor-dominant Parkinson’s disease patients, who also have relatively spared cognitive function. Furthermore, noradrenergic excitation of the thalamus has recently been linked to the increase of Parkinson’s tremor during cognitive stress, which is a well known clinical observation.¹⁰ More specifically, while tremor is likely generated by dopamine-dependent changes in the basal ganglia and the cerebello-thalamo-cortical loop, relatively preserved noradrenergic projections to the thalamus modulate tremor amplitude during arousal.¹⁰ Hence, both a spared and a degenerated noradrenergic system may contribute to clinical symptoms in Parkinson’s disease.

This shows that the pathophysiology of Parkinson’s disease involves a complex cocktail of neurotransmitter changes, where the whole is greater than the sum of the parts. The absence of correlations between clinical measures of Parkinson’s disease duration and the effects reported here is perhaps not so surprising, given emerging evidence that different subgroups of patients have different disease propagation routes. The question of how Parkinson’s disease travels through the brain can then only be

answered in large datasets, where detailed clinical and cognitive phenotyping along multiple axes is available. The current study provides an excellent point of departure to begin unravelling these issues.

Rick C. Helmich¹ and Stéphane Lehéricy²

1 Radboud University Medical Centre, Donders Institute for Brain, Cognition and Behaviour, Centre for Cognitive Neuroimaging and Centre of Expertise for Parkinson and Movement Disorders, Nijmegen, The Netherlands

2 Institut du Cerveau—Paris Brain Institute (ICM), Centre de NeuroImagerie de Recherche (CENIR), Team ‘Movement Investigations and Therapeutics’ (MOV’IT), Sorbonne Université INSERM U1127, CNRS 7225, Paris, France

Correspondence to: Rick Helmich

E-mail: rick.helmich@radboudumc.nl

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Competing interests

The authors report no competing interests.

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