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Editorial comment for MDS-12-0410.R1 Pifl et al - Thalamic noradrenaline in Parkinson's disease: deficits suggest role in motor and non-motor symptoms

An evidence-base for noradrenergic deficits in Parkinson's disease

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The concept of very significant non-dopaminergic involvement in Parkinson's disease (PD) is no longer contentious. This is largely due to the landmark work of Heiko Braak and colleagues who highlighted the systematic deposition of widespread α-synuclein pathology in PD.[1] In particular, their very detailed anatomical molecular localization of the pathological changes provided a comprehensive evidence base that is being replicated in (and challenged by) other research centres. This pathologically-based concept has invigorated clinical research into focusing more on the assessment of early non-dopaminergic symptoms in PD, although the neuroanatomical and pathophysiological bases for many of these symptoms remain to be determined. Unfortunately, there has not been a similar stimulation of studies assessing the non-dopaminergic neurochemical changes that must parallel such widespread pathology. In fact, most biochemical measurements of non-dopaminergic

neurotransmitter changes in pathologically-confirmed cases of PD have been published more than 20 years ago. At this time there was no consideration of disease staging or phenotypes with overlapping dementia and variable regional pathologies. The importance of relooking at such studies in light of more modern concepts should not be underestimated, as at least symptomatic treatments for many neurotransmitter systems are already available and may have therapeutic benefit in targeted populations of patients or at certain disease stages.

A study in this issue of movement disorders by Pifl and colleagues[2] partially addresses this deficit. The authors detail the regional changes in a single neurotransmitter, noradrenaline, within the thalamus of patients with end-stage, well-documented PD.[2] The thalamus was selected as it occupies a pivotal position in the brain. All neocortical areas receive thalamic inputs and large ensembles of cortical and thalamic neurons discharge synchronously at stereotyped frequencies to effect different conscious states and perceive specific events, thoughts and actions.[3] By assessing some 14 different thalamic territories, neurons involved in processing both motor and non-motor information were evaluated without having to sample across diverse brain sites.[2] The thalamus is innervated by a single noradrenergic nucleus (the locus coeruleus)[4], and consistent with older biochemical studies, the authors found a noradrenergic deficiency in PD.[2] The surprise was that it occurred in most PD thalamic territories (except the sensory thalamus), and the scale of the deficit was as marked as that of dopamine in the putamen.[2] While these findings are consistent with the significant loss of noradrenergic locus coeruleus neurons observed by end-stage PD,[5] the comparison to the substantive dopaminergic deficit has been completely under-appreciated. As pointed out by the authors,[2] such a deficit would have a more direct impact on thalamic activity than the basal ganglia dopaminergic deficit, and may be a more significant contributor to treatment-resistant pathological thalamic oscillations observed in patients with PD. While this concept requires further evidence, the study overall adds significantly to the literature on non-dopaminergic deficits in PD and their potential impact. Of importance is the potential for direct therapeutic targeting of this major deficit.

More work now needs to be done to determine when in the disease such a deficit becomes manifest, whether the deficit actually initiates the multiple functional changes in the thalamus, as suggested,[2] or occurs subsequent to other contributing pathological changes, and also whether other ascending neuromodulators of thalamic activity are involved. There are several studies which suggest central dopamine and noradrenaline changes occur concurrently very early in PD, including cerebrospinal fluid measurements,[6] although imaging suggests an early upregulation of noradrenaline reuptake in the locus coeruleus consistent with enhanced noradrenaline release in response to degeneration of dopaminergic neurons.[7,8] There is also evidence for an increase in dopamine-beta-hydroxylase mRNA in surviving locus coeruleus neurons in PD compared with Alzheimer's disease.[5] Such compensation appears short-lived as there is a decline in noradrenergic reuptake in the first few years of PD suggesting an exhaustion of any noradrenergic compensation.[8] Peripheral blood levels of noradrenaline are not reduced in *de novo* patients with PD but decline as the disease progresses.[9-11] These studies suggest that the central noradrenergic deficit is not an early feature in PD, a finding consistent with the variability documented in the degree of neuronal loss in pathologically-confirmed cases.[12-16] Whether selective neuronal projections are targeted at different times and could initiate functional deficits in certain brain regions compared with others still needs to be determined.

Apart from the noradrenergic innervation of thalamus, the pedunculopontine and lateral dorsal tegmental nuclei send cholinergic afferents to the thalamus, while the dorsal raphe nucleus sends serotonergic afferents.[4] Both acetylcholine and noradrenaline reduce thalamic oscillatory and busting activity, while serotonin has a more variable affect depending on the region innervated.[4] The dorsal raphe nucleus is relatively unaffected in PD patients at postmortem,[12] while many postmortem studies have shown a profound loss of the pedunculopontine tegmental nucleus in PD.[17] However, the loss of the cholinergic innervation of the thalamus appears to occur later in PD, reducing in association with

impaired postural control and gait dysfunction.[18-20] It may be that the most troubling non-dopaminergic symptoms in PD require more than one system to be perturbed (eg. both the noradrenergic and cholinergic afferents to the thalamus), as this would negate any possible compensation of increased activity in one system for another. Data on the neurochemical deficits of the multiple neurotransmitter systems known to be involved in PD is sorely needed.

Regarding the functional impact of the loss of noradrenergic neurons in the locus coeruleus, there is evidence that such a loss contributes to tremor (resting and essential)[21,22], as well as to depression in PD.[15] PD patients with dementia also have more significant locus coeruleus cell loss than PD patients without dementia.[14,16,23] Whether additional pathology in other neurotransmitter systems and brain regions contribute to such differences also remains to be determined, but substantial locus coeruleus cell loss is a well known feature of patients with Alzheimer-type pathology[5,16] which often coexist in PD patients with dementia.

The study by Pifl and colleagues in this issue of Movement Disorders[2] did not answer these important questions on the clinical sequelae of noradrenaline loss in the thalamus in PD due to a lack of clinical information in the patients studied. Perhaps most disappointingly, was that lack of details on other potentially contributing pathological factors. While the dataset provided is an important new evidence base for determining the progressive changes that occur in the brains of patients with PD, it remains to be determined whether thalamic noradrenaline content alone contributes to and varies with any motor or non-motor symptoms in PD, whether noradrenaline in other brain regions may contribute as well (or more), or whether the impact of other neuropathologies and neurotransmitter deficits plays a significant role in the changes observed. Such questions will only be answered with more studies of this type.

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