SCIENTIFIC COMMENTARIES

Early nucleus basalis of Meynert degeneration predicts cognitive decline in Parkinson's disease

This scientific commentary refers to 'In vivo cholinergic basal forebrain atrophy predicts cognitive decline in de novo Parkinson's disease' by Ray *et al.,* (doi:XXXXXXXX).

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Dementia eventually affects up to 75% of patients with Parkinson's disease (PD), and is associated with significantly increased morbidity (Gratwicke et al., 2015). Mild cognitive impairments are detectable from early in the disease, and may predict conversion to Parkinson's disease dementia (PDD), although this is variable (Goldman et al., 2014). This heterogeneity gives rise to several problems; first it is difficult to provide accurate prognostic information to patients regarding their future risk of cognitive decline. Second, given that many medications used for motor symptom control in PD have detrimental cognitive side effects, this lack of accurate prognostication makes it difficult for the clinician to know in which patients they should be avoided. Third, it is difficult to stratify patients appropriately for inclusion in therapeutic trials to try to prevent progression to dementia. Recent efforts have shown that a model combining age, the presence of anosmia and REM sleep disorder, amyloid beta levels in cerebrospinal fluid and abnormal DAT imaging can predict the occurrence of cognitive impairment at two years in de novo PD patients with good accuracy (Schrag et al., 2017). However, a readily accessible non-invasive biomarker would be a welcome addition, while given the strong contribution of cholinergic dysfunction to the pathogenesis of cognitive decline in PD (Candy et al., 1983) it is apparent that a measure reflecting this is lacking in current predictive models. In this issue of Brain, Ray and colleagues address both these issues by combining detailed stereotactic mapping of cholinergic nuclei and MRI morphometry to show that early degeneration of the nucleus basalis of Meynert in de novo PD patients is associated with an increased risk of cognitive decline at up to five years (Ray et al., 2017).

The nucleus basalis of Meynert (NBM) is one of several predominantly cholinergic nuclei located in the basal forebrain, alongside the medial septum, and vertical and horizontal limbs of the diagonal band of Broca (Gratwicke et al., 2013). The NBM provides the major source of cholinergic innervation to cortex, and degeneration of this structure has long been implicated in the pathophysiology of PDD, as well as Alzheimer's disease (Candy et al., 1983; Gratwicke et al., 2013). Consequently, structural imaging of the basal forebrain region has previously been investigated as a biomarker of cognitive decline in PD (Choi et al., 2012), however difficulties in accurately delineating the anatomy of the NBM amongst the crowded nuclei within this region has hitherto hindered the utility of this approach.

The authors combined recent advances in stereotactic mapping with voxel-based morphometry to enable much more detailed analysis of basal forebrain structures than was previously possible. The process involved extracting grey matter volumes for these individual nuclei from MRI brain images according to a stereotactic map of the basal forebrain derived from a healthy reference subject. Volumetric calculations of individual cholinergic nuclei were then performed adjusting for the subject's head size.

The authors used data from the Parkinson's Progression Markers Initiative – a large cohort study of well characterised de novo PD patients and controls, incorporating longitudinal imaging, clinical and cognitive assessment data up to five years since enrolment. They first applied their novel methodology to MRI imaging from 76 control subjects to derive normative data, and then to baseline imaging data from 168 PD patients. They used the normative data from the controls to construct and validate linear regression models to predict volumes of individual cholinergic basal forebrain nuclei based on an individual subject's total intracranial volume and age. They then used these models to calculate expected cholinergic nuclei volumes for each individual PD patient, and compared these to the actual volumes measured; those patients in whom the volume of least one cholinergic basal forebrain nucleus was at least one standard deviation lower than expected were classified as having basal forebrain atrophy at baseline, while others were classified as intact.

The primary analysis used regression modelling to test for association between individual cholinergic nuclei volumes at baseline and change in score on the MoCA (Montreal Cognitive Assessment, a test of global cognitive ability) at two years, adjusting for disease duration, age, sex, and baseline MOCA score. They found that in the PD patients

NBM atrophy at baseline, in particular atrophy in its posterior subsector (labelled 'Ch4p'), was a significant predictor of decline on MoCA scores, but atrophy in other cholinergic basal forebrain nuclei was not. Furthermore, cox proportional hazards modelling showed those PD patients with NBM atrophy at baseline had a significant 3.5 fold greater risk of developing either mild cognitive impairment or dementia over up to five years of follow up compared to those without. These results are significant as they potentially identify the first in-vivo cholinergic biomarker of cognitive decline in PD, which is also readily measurable using widely-available 3T MRI. However, only some of the PD patients with NBM atrophy at baseline progressed to meet diagnostic criteria for PDD over five years, while others only met criteria for mild cognitive impairment. Given that the latter state is not necessarily a preclude to dementia in all patients (Goldman et al., 2014) further longitudinal follow up is needed to determine if baseline NBM atrophy can be regarded as a predictive biomarker for mild cognitive impairment alone, or also for future PDD. In light of this the authors stop short of calculating the sensitivity, specificity or positive predictive value of baseline NBM atrophy for future cognitive impairment or dementia in PD, and this will clearly be a focus for future work.

These results serve to reinforce the long-held view that degeneration specific to the NBM is a key pathophysiological event in the pathogenesis of cognitive decline in PD. In particular, it is interesting that atrophy in Ch4p, the posterior subsector of NBM, significantly predicts global cognitive decline over two years, but that at five years it is degeneration of the nucleus as a whole which is associated with cognitive deterioration rather than Ch4p alone. This suggests that Ch4p may be the site at which the degenerative process begins, before spreading forward to the rest of the nucleus. Through application of the same methodology the authors have previously found a similar relationship between Ch4p atrophy and cognitive deterioration in patients with early Alzheimer's disease (Grothe et al., 2010), adding weight to the argument that NBM degeneration is a common pathophysiological substrate between the two diseases (Gratwicke et al., 2013).

Lastly, the authors performed further regression modelling to investigate the relationship between baseline NBM atrophy and decline on specific cognitive tests across the five years of follow up, adjusting for global grey matter volume, age, sex and disease duration. They found that while all PD patients declined homogenously on the digit symbol task (a test of attention and executive function) over the follow up period, those patients

with NBM atrophy at baseline declined significantly faster on the Hopkins Verbal Learning Test (a test of immediate and delayed verbal recall and recognition) and semantic fluency (a test of previously learnt factual information, as well as language) than those without. We have previously argued in this journal that degeneration of the NBM in PD plays a greater role in memory/semantic processing deficits than in executive dysfunction (Gratwicke et al., 2015), and these results support this theory. Furthermore, semantic fluency deficits in early PD are a significant predictor of later dementia (Williams-Gray et al., 2009), strengthening the evidence for a mechanistic link between NBM atrophy and progression to PDD.

The key strength of this study is that the authors defined cholinergic structures of the basal forebrain according to a well-defined stereotactic map which accurately delineated all its individual nuclei, allowing for volumetric analysis of unprecedented detail. However, beyond imaging parameters it would be useful to consider whether additional phenotypic information (e.g. tremor predominance) or genotyping (e.g. glucocerebrosidase mutation status) might refine their predictive model. Previous work has also shown strong links between cholinergic neurodegeneration in PD, cognitive decline, worsening gait and balance difficulties and neuropsychiatric symptoms such as visual hallucinations (Fling et al., 2013; Gratwicke et al., 2015), and it would be interesting to investigate the relationships between NBM atrophy in this cohort and their longitudinal assessments of these clinical symptoms.

So how might the results of this study help with the issues identified at the start of this article? We are in an era of personalised medicine and clinical management should take as much account of prognostic data as possible: detection of normal NBM volumes on a baseline MRI scan may be useful to reassure a PD patient that they have lower risk of future cognitive decline. On the other hand, detection of early NBM atrophy should be handled sensitively to avoid exacerbating depression, but delivered in a proactive way such that additional actions become warranted; for example, avoidance of medications with cognitive side effects, early use of acetylcholinesterase inhibitors and perhaps an alternative view of risk when considering trials relevant to disease modification. Finally, from the research point of view detection of early NBM atrophy in PD patients will help with appropriate stratification into clinical trials aimed at preventing progression to PDD.

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Glossary

REM sleep disorder: a parasomnia manifested by recurrent dream enactment behaviour, including movements mimicking dream content. It is associated with lack of normal relaxation of limb muscles during rapid eye movement ('REM') stages of sleep. It is particularly likely if dreams involve a chasing/attacking theme and the patient or bed partner has sustained injuries from limb movements during sleep.

Stereotactic mapping: histological sections from a post-mortem healthy human brain are silver stained and cholinergic nuclei are manually traced on high resolution digital images. These are transferred onto corresponding MRI images of the same post-mortem brain. These MRI images are then co-registered to a standard digital atlas of the healthy brain, thereby creating digital representations of the detailed anatomy of the cholinergic nuclei.

MRI morphometry: here referring to voxel-based morphometry, an MRI analysis technique that allows investigation of focal differences in brain anatomy on a very small scale between subjects.

Executive dysfunction: an umbrella term encompassing impairments across several cognitive abilities, including problem-solving, planning/sequencing, rule-shifting/maintenance, task-switching, manipulation in working memory and response inhibition. Such impairments are mainly caused by damage to the frontal cortices.

Legend for the Figure:

Figure 1. Schematic of anatomy of the NBM and risk factors for cognitive decline and dementia in Parkinson's disease. (A) 3D representation of the anatomy of the NBM. *Left:* the medial surface of the left hemisphere of the human brain is closest to the viewer. The NBM is the green structure located in the basal forebrain inferior to the globus pallidus internus (GPi). The green arrows emanating from the NBM represent its corticopetal projections passing in the medial and lateral cholinergic pathways to all cortical areas. A = amygdala; C = caudate; P = putamen; T = thalamus. *Right:* the inset shows a 3D representation of the NBM itself. It is an elongated flat structure spanning 13-14 mm in the saggital plane. The posterior subsector of the nucleus termed 'Ch4p' is highlighted. The brown nucleus below represents an atrophic NBM, reduced in size compared to its previous intact form (represented in translucent green). (B) Model showing all the clinical features and biomarkers which have been shown to be predictive of cognitive decline and future dementia in PD. Those in green boxes all have a putative cholinergic basis, while those in yellow boxes represent non-cholinergic factors. The green arrows highlight the fact that degeneration of the NBM plays a major role in development of the linked predictive clinical features. $A\beta_{42}$ = amyloid β_{42}; CSF = cerebrospinal fluid; DAT = dopamine active transporter scan; REM = rapid eye movement.