Imaging in Parkinson’s disease: time to look below the neck

This scientific commentary refers to ‘Imaging acetylcholinesterase density in peripheral organs in Parkinson’s disease with $^{11}$C-donepezil PET’ by Gjerløff et al. (10.1093/brain/awu369).

The possibility of assessing disease progression in Parkinson’s disease was revolutionized by the ability to image dopamine synthesis in vivo, first described by Garnett and colleagues more than 30 years ago (Garnett et al., 1983). Since that landmark paper, there have been hundreds of publications presenting the results of molecular imaging using either SPECT or PET tracers for the synthesis, synaptic packaging and/or reuptake of dopamine. While the relationship between changes in dopamine function assessed by these techniques and clinical deterioration is imperfect and may be confounded by compensatory changes and the effects of medications, it is nonetheless possible to obtain an independent measure of disease progression and indeed to detect pre-motor dopaminergic dysfunction in subjects at high risk of future Parkinson’s disease (Nandhagopal et al., 2008; Iranzo et al., 2011). However, in recent years it has been proposed that changes in the dopamine system (and motor impairment) may not become manifest until relatively late in the disease course. By contrast, the autonomic nervous system shows early involvement; indeed it has been suggested that the deposits of aberrantly folded α-synuclein associated with Parkinson’s disease may originate in autonomic nerve endings of the gastrointestinal tract and be retrogradely transmitted to the caudal brainstem via the vagus nerve (Braak et al., 2003) (Fig. 1). Several studies have used imaging to demonstrate cardiac sympathetic denervation in early Parkinson’s disease and even in subjects with REM sleep behaviour disorder (Kashihara et al., 2010), but until now, the imaging community has paid little attention to the parasympathetic nervous system. In this issue of Brain, Gjerløff et al. describe the application of $^{11}$C-methoxy-donepezil PET to study the distribution of acetylcholinesterase activity in a semi-quantitative fashion in the periphery, and by implication in the parasympathetic nervous system (Gjerløff et al., 2014).

Gjerløff et al. report reductions of $^{11}$C-donepezil binding of 35% in the small intestine and 22% in the pancreas of patients with early to moderate Parkinson’s disease compared to age- and gender-matched healthy controls. There was no correlation between reductions in $^{11}$C-donepezil binding and disease duration. This may not be surprising if Parkinson’s disease starts in the peripheral nervous system and spreads in a caudal to rostral fashion. However, the authors also failed to find a correlation between $^{11}$C-donepezil binding and measures of vagal function such as gastric emptying and severity of constipation, raising questions regarding the relationship between $^{11}$C-donepezil binding and parasympathetic function. It must be noted that contrary to expectations, there was no evidence of delayed gastric emptying in this cohort of patients (indeed the opposite was observed, possibly reflecting the use of levodopa medication). A smaller but significant reduction was seen in myocardial uptake of the tracer, but the basis for this reduction is more difficult to determine, and it did not correlate with measures of heart rate variability.

The protocol described by Gjerløff et al. is technically challenging. Spillover from adjacent structures and peristaltic movement make it difficult to obtain robust measures from the regions of interest, and uptake in the small intestine is patchy. The estimation of distribution volumes requires accounting for the presence of radioactive metabolites. Such measures in arterial plasma are often noisy and subject to considerable error. Furthermore, radiolabelled metabolites may not necessarily be identical in the organs of interest and in arterial plasma. There seems to be no easy way to account for non-specific uptake of the radioligand. The authors have attempted to address these potential pitfalls as best they can and have used standardized uptake values (SUVs) for their comparisons and correlations. The SUV is more easily determined although not quite as readily interpreted from a biological perspective, but SUV measurements correlated reasonably well with distribution volume estimates. There is considerable interindividual variability in the SUV’s, particularly in pancreas, and an associated high degree of overlap between the Parkinson’s disease and healthy control groups. The kinetic analysis suggested that group differences were related to tracer washout rather than differences in blood flow to the organs of interest, although it should be noted (Table 3 of the article) that the difference in intestinal k2 was not significant (reflecting tracer washout) and there was in fact a modest but non-significant reduction in k1 (reflecting tracer delivery), so this must be regarded as not fully resolved. Whereas Gjerløff et al. have found that $^{11}$C-donepezil binding data are best fit using a single compartment model, other investigators favour a two-compartment model, at least in brain (Hiraoka et al., 2009), which would fit better with a specific binding/substrate compartment within the tissue of interest.

Donepezil binds to sigma1 receptors in the brain (Ishikawa et al., 2009) and as these receptors are also found in the gut (Harada et al., 1994), it is possible that the binding described here may not be entirely reflective of acetylcholinesterase activity. Furthermore, as the authors point out, cholinesterase...
activity is widely accepted as a reasonable but imperfect measure of cholinergic nerve terminal function. The authors have been extremely circumspect in their interpretation of the findings, and recognize the possibility of downregulated cholinesterase activity in preserved but dysfunctional cholinergic parasympathetic nerve terminals. Independent verification of cholinergic nerve terminal loss using a radioisotope marker for the vesicular acetylcholine transporter would be welcome.

The demonstration by Gjerløff and colleagues of reduced parasympathetic innervation of the intestine and pancreas is interesting but not surprising, given what is already known about Parkinson’s disease from studies at autopsy. Alpha-synuclein pathology can also be assessed in vivo by colonic biopsy, although this might be considered more invasive (but also more widely available) than PET imaging. What might be the potential utility of demonstrating peripheral cholinergic denervation in patients with established parkinsonism? Could this approach help differentiate Parkinson’s disease (vagal denervation) from atypical parkinsonism such as multiple system atrophy and progressive supranuclear palsy, as has been suggested for cardiac scintigraphy to assess the presence or absence of post-ganglionic sympathetic denervation? Given that the vagus is affected in multiple system atrophy, this seems unlikely, and even the specificity of cardiac scintigraphy has been questioned (Raffel et al., 2006). Would assessment of gastrointestinal parasympathetic denervation provide an independent biomarker for disease progression? This also seems unlikely, given that the disease may start in the gut, such that the damage is done by the time motor symptoms appear, and given the failure to demonstrate a correlation between disease duration and cholinesterase activity. Is there any use in studying gut cholinergic activity in asymptomatic individuals at high risk of Parkinson’s disease, such as those with known pathogenic mutations, hyposmia, or REM behaviour disorder? This may be of limited practical value until neuroprotective therapies are identified, but the demonstration of gastrointestinal vagal denervation prior to imaging evidence of dopamine dysfunction would provide validation of Braak’s (Braak et al., 2003) provocative hypothesis.

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Figure 1 Proposed origins of Parkinson’s disease in the gut. A pathogen might cross the intestinal mucosa and be retrogradely transported to the CNS via efferent branches of the vagus nerve (upper panel). Within the CNS, the dorsal motor (dm) nucleus of the vagus is one of the first sites affected, with progressive rostral involvement (lower panel). ACh = acetylcholine; VIP = vasoactive intestinal polypeptide. From Braak et al., 2003 (reproduced with permission).
What does it mean to be ‘amyloid-positive’?

This scientific commentary refers to ‘Independent information from cerebrospinal fluid amyloid-β and florbetapir imaging in Alzheimer’s disease’ by Mattsson et al. (10.1093/brain/awu367).

Studies of fluid and imaging biomarkers of Alzheimer’s disease have contributed greatly to our understanding of disease pathobiology, and in so doing have fuelled a paradigm shift in the conceptualization of Alzheimer’s disease as a chronic condition characterized by a long (~10–20 year) preclinical phase during which hallmark pathologies develop, before the appearance of cognitive symptoms (dementia) clinically defined as Alzheimer’s disease. Revisions in diagnostic criteria to incorporate biomarker results have recently been proposed (Dubois et al., 2010; Albert et al., 2011; McKhann et al., 2011; Sperling et al., 2011) in order to increase confidence in identifying Alzheimer’s disease as the underlying aetiology of a clinical impairment and to permit a diagnosis across the disease continuum, eventually perhaps in the asymptomatic period. Biomarkers are currently being used in clinical trials for participant enrolment, evaluation of target engagement and as outcome measures (Hampel et al., 2011). Thus, validation of Alzheimer’s disease biomarkers is of critical importance. In this issue of Brain, Mattsson and colleagues (2015) evaluate and compare two amyloid-related biomarkers—CSF levels of amyloid-β42 (the primary component of amyloid plaques) versus amyloid imaging via PET with florbetapir (AMvidTM), a radiolabelled tracer approved by the US Federal Drug Administration in 2012 for the detection of brain amyloid—in their ability to predict clinical diagnosis and other measures and features of Alzheimer’s disease (Mattsson et al., 2015). Importantly, while the study confirms the previously reported diagnostic and prognostic utility of these two markers, the data expand upon previous results by exploring the discordance of these two measures in a large research cohort that spans the range of Alzheimer’s disease stages, from asymptomatic to mildly symptomatic to dementia. In addition to providing insight into processes associated with amyloid metabolism and aggregation into plaques, the results of Mattsson and colleagues will likely have an impact on the use of these two markers in ongoing and future clinical trials.

Low levels of CSF amyloid-β42 have long been associated with symptomatic Alzheimer’s disease (Morr et al., 1995), and are hypothesized to reflect the sequestration of soluble brain amyloid-β into insoluble plaques with a resultant reduction in the amount of amyloid-β42 that is cleared into the CSF. However, it was not until the advent of amyloid PET imaging with Pittsburgh Compound B (Pib) (Klunk et al., 2004) that this relationship between brain amyloid deposition and CSF amyloid-β42 could be demonstrated in living individuals (Fagan et al., 2006). This finding has subsequently been confirmed by many groups in many cohorts, leading to the use of CSF amyloid-β42 and amyloid-PET as often interchangeable metrics in defining ‘amyloid-positivity’. However, as is invariably the case with human biology, the story is not that simple. Whereas amyloid-positivity by PET is almost always associated with low CSF amyloid-β42 in individuals with symptomatic Alzheimer’s disease,