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The Parkinson's You Can't See

We principally see the motor phenomena of Parkinson's disease, but is there an early stage without visible features? Might this provide a window for disease-modifying therapy? If so, how could we detect this stage?

It is no surprise that we often focus on the visual phenomena in medicine: they are readily available to a sensory system that has an insatiable hunger for visual cues. As Nobel prize winning psychologist Daniel Kahneman and his colleague Amos Tversky might explain, cognitive illusions such as the heuristic of availability fool our mind into focusing on what we see and neglecting alternative information. Moreover, observation is taught as the key to neurological examination and therefore the observable phenomena have taken centre-stage since James Parkinson's description of *The Shaking Palsy* in 1817. Today, features that we can see still dominate the Movement Disorder Society's diagnostic criteria for Parkinsonism; at least two, and arguably all three, of the classic triad of *bradykinesia plus rigidity or resting tremor* are observed visually by the examiner.

In *The Parkinson's You Can't See*, I will focus on early Parkinson's disease, so-called pre-motor Parkinson's disease, which we cannot yet see because the motor features have not yet emerged. But just because we cannot see the disease does not mean that it is not there, nor that it is undetectable. I will explore a modern understanding of pre-motor Parkinson's disease and argue that this stage could provide a window of opportunity for disease-modifying therapy. I will then explore how new diagnostic techniques might detect these early stages of the disease before it can be seen on clinical examination. By identifying this new patient group for novel therapies, the outlook for patients with pre-motor Parkinson's disease could be transformed from *the Parkinson's disease you can't see **yet*** to *the Parkinson's disease you **may never see***.

Parkinson's before you can see it: pre-motor Parkinson's disease

The neuropathological hallmark of Parkinson's disease is the presence of Lewy bodies, which are aggregates of misfolded alpha-synuclein protein. By the time patients have visible motor features, Lewy bodies have already formed in the dopaminergic neurones in the pars compacta of the substantia nigra. This disrupts the basal ganglia's crucial role in the initiation of movement and, as James Parkinson (1817) vividly described, there is 'not general weakness, but merely interruption of the flow of nervous influence to the affected parts'.

More recently, Braak and others (2003) have argued that there is a stepwise progression of Lewy body pathology in a stereotyped march through the nervous system. They described how the earliest Lewy bodies do not form in the basal ganglia but rather in the olfactory bulb and the enteric nervous system (figure 1). They even suggested that the disease may be initiated by sniffed or swallowed environmental substances and that the disease progresses through the vagus nerve into the brain (Visanji *et al.*, 2013).

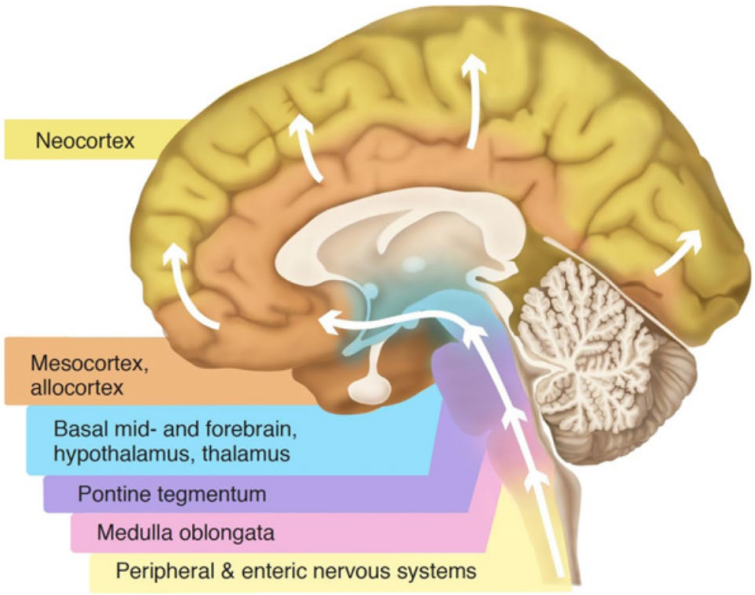

Figure 1. Braak staging of Parkinson's disease. From Visanji *et al.* (2013).

Because the Braak model describes early involvement of regions outside the substantia nigra, it provides insight into four key features of pre-motor Parkinson's disease:

(1) *Impaired olfaction*
Hyposmia occurs because of early alpha-synuclein pathology in the olfactory bulb. It occurs in over 90% of Parkinson's disease patients, but only 10% of patients with idiopathic hyposmia will develop Parkinson's disease (Reichmann, 2017).

(2) *REM sleep behaviour disorder*
Structures in the pons and medulla modulate atonia in REM sleep, and early pathology in these structures causes REM sleep behaviour disorder (RBD) in pre-motor Parkinson's disease. In an important study in Barcelona, 20 out of 44 patients with idiopathic RBD developed Parkinson's disease or related disorders within 11.5 years (Iranzo *et al.*, 2006).

(3) *Constipation*
Impaired bowel motility arises as a result of enteric nervous system disruption and is often progressive (Reichmann, 2017).

(4) *Depression*
Depression is one of the earliest non-motor symptoms and probably results from involvement of the raphe nuclei or locus coeruleus (Reichmann, 2017).

Importance of the Parkinson's you can't see: benefits of detecting pre-motor Parkinson's disease

Progression from pre-motor to motor Parkinson's disease is thought to depend on propagation of misfolded alpha-synuclein in a 'prion-like' fashion (Visanji *et al.*, 2013). As the pathology advances and the substantia nigra becomes involved, patients convert from pre-motor *Parkinson's you **can't** see* to motor *Parkinson's you **can** see*. Unsurprisingly therefore, researchers have tried to develop novel therapies that could block this propagation (Oertel, 2017).

To date, potential therapies have fallen into three broad categories:

(1) Active and passive immunotherapy
(2) Modulation of alpha-synuclein aggregation
(3) Enhancement of autophagy of alpha-synuclein

Phase one and two trials are underway for several novel therapies. However, accurate identification of pre-motor Parkinson's disease is a major challenge that must be overcome in order to design adequate trials for potential disease-modifying therapies (Oertel, 2017).

Finding the Parkinson's disease you can't see: novel early detection techniques

In recent years there has been a wealth of research into detection of early Parkinson's disease. Detailed literature reviews have been performed elsewhere (e.g. Reichmann, 2017), so instead I have selected two particularly interesting studies published within the last year to illustrate the recent successes and ongoing challenges in the field. The first study combined hyposmia detection with DAT SPECT imaging in a two-step screening protocol (figure 2); the second employed a series of simple tests carried out from home.

(1) Parkinson Associated Risk Study: neuroimaging visualises the Parkinson's you can't see

In 2017, the Parkinson Associated Risk Study used a two-step screening strategy to provide a major step forward in the identification of members of the general population at risk of conversion to Parkinson's disease (Jennings *et al.*, 2017). First, 280 participants over 50 years old in the USA with no motor features of Parkinson's disease were screened for hyposmia using clinical smell tests. Participants found to have hyposmia then underwent DAT SPECT scans and clinical evaluation over four years. The study found that DAT deficit in the hyposmic participants was highly predictive of development of clinical Parkinson's disease: among 21 participants with hyposmia and DAT deficit, 14 (67%) converted to Parkinson's disease, compared to 2 out of 22 (9%) with an intermediate range DAT, and 3 out of 109 (2.8%) with normal DAT levels (figure 3). The study's two-step screening process successfully identified patients with high risk of conversion to motor Parkinson's disease among pre-motor individuals.

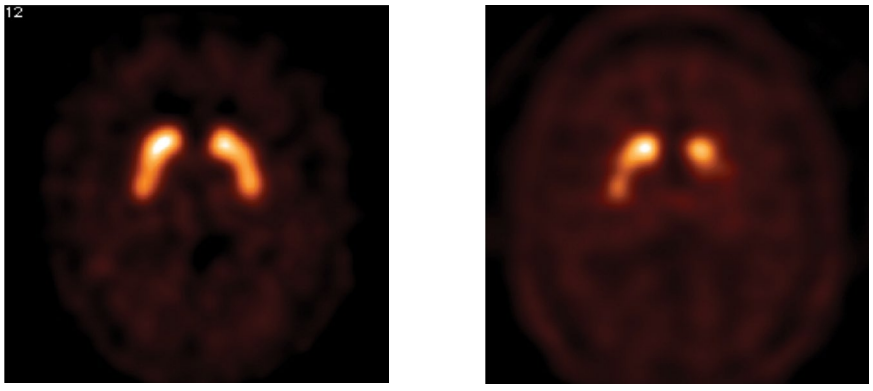

Figure 2. Dopamine transporter (DAT) single photon emission computed tomography (SPECT) uses a radiolabelled ligand to detect pre-synaptic dopamine transporters in the basal ganglia. Left: normal DAT SPECT. Right: reduced DAT signal in a Parkinson's disease patient. From Chaudhuri (2015).

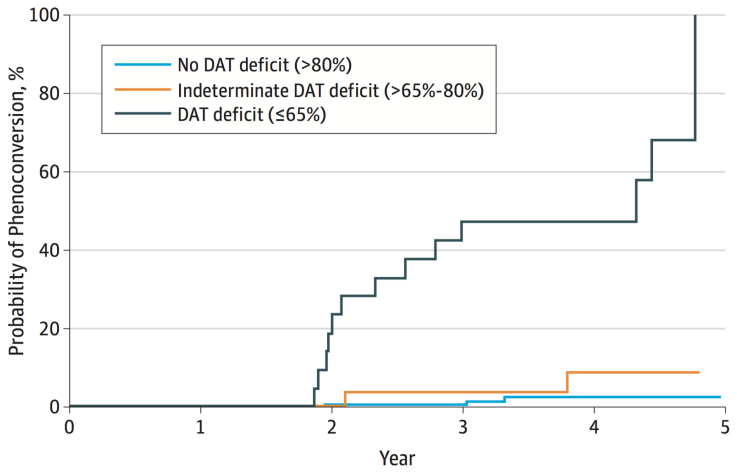

Figure 3. Kaplan-Meier curves from the Parkinson Associated Risk Study. In hyposmic individuals, DAT deficit was a strong predictor of phenoconversion from no diagnosis to diagnosis of Parkinson's disease. From Jennings *et al.* (2017).

(2) PREDICT-PD: detecting abnormalities from home

An important limitation of the Parkinson Associated Risk Study's two-step approach is cost: it would require an estimated $24 million to identify enough patients for an appropriately-powered study of future disease-modifying therapy (Noyce & Lees, 2017). Therefore, a contrasting approach has been put forward in the innovative PREDICT-PD study in the UK (Noyce *et al.*, 2017). PREDICT-PD aimed to risk-stratify 1,323 participants from the general population based on four features assessed from the patient's own home (an online survey, home smell testing, genotyping of two high-risk genes, and subtle motor differences in a computerised keyboard-tapping task). Preliminary results showed good correlation between predicted risk and intermediate markers of Parkinson's disease at three years follow-up. There was also a significant correlation between predicted risk and incidence of Parkinson's disease diagnosis: five out of the seven patients who developed Parkinson's disease were 'high risk' at diagnosis. Advantages of the PREDICT-PD approach include ease of use, potential for high uptake rates, and cost-efficient scalability. However, only 1.2% of 'high risk' patients actually developed Parkinson's disease, suggesting that this technique would ultimately need to be combined with other more specific tests.

(3) Ongoing challenges

Whilst these studies represent substantial advances, they also highlight ongoing challenges of early detection:

- Failure to detect pre-motor Parkinson's disease in patients who have minimal prodromal features.
- Inability to differentiate idiopathic Parkinson's disease from other Parkinsonian syndromes.
- Uncertainty over whether these techniques could identify pre-motor Parkinson's disease early enough for effective intervention.

Seeing the path forward: conclusions

By the time a doctor can see Parkinson's disease, the patient is at a late stage of a progressive alpha-synucleinopathy. For many years before, the pathology has been invisibly progressing through the patient's nervous system. This early Parkinson's disease, or *Parkinson's you can't see*, might provide a crucial window of opportunity to therapeutically modify disease progression, but two developments would be needed: (1) techniques to reliably detect pre-motor Parkinson's disease and (2) novel alpha-synuclein modifying therapy that can limit alpha-synuclein spread. Whilst these goals have proved challenging, the rewards would be great - the ability to halt the progression of pre-motor Parkinson's disease so that it remains *the Parkinson's you can't see.*

Word Count: 1,496

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