REM sleep behaviour disorder – an early window for preventing neurodegeneration?

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Abbreviations:
DLB, dementia with Lewy bodies; MSA, multiple system atrophy; RBD, REM sleep behaviour disorder; PD, Parkinson's disease

We are entering a new era in Parkinson's disease and the related alpha-synuclein deposition disorders, dementia with Lewy bodies (DLB) and multiple system atrophy (MSA). New treatments, directed towards abnormal alpha-synuclein, are emerging with the potential to change the disease course (Athauda *et al.* 2017). But by the time patients receive a diagnosis, they are typically far along in their disease progression. It has been estimated, for example, that over 70% of nigrostriatal neurons have already died by the time Parkinson's disease is diagnosed. Early diagnosis will be essential for maximizing the chances of effective disease-modifying treatment.

REM sleep behaviour disorder (RBD) is a parasomnia in which affected individuals enact their dreams due to loss of the muscle atonia that normally occurs during rapid eye movement sleep. However, RBD is usually part of a more widespread disorder. If people with RBD are followed-up for long enough, they almost always go on to develop Parkinson's disease or a related alpha-synuclein deposition disorder (Iranzo *et al.* 2013). RBD is more than an isolated clinical syndrome, but rather represents an important opportunity to intervene early, with the

potential to prevent neurodegenerative disease from taking hold. But even within RBD, there is wide variation in the timing and onset of a progressive neurodegenerative syndrome. In this issue of *Brain*, Postuma and colleagues add to our understanding of RBD by determining predictors of phenoconversion in a large multinational cohort comprising 1280 patients from 24 centres worldwide (Postuma *et al.* 2019).

The study is a *tour de force* of collaboration and of the combination of clinical instruments to produce a coherent clinical picture. The pragmatic approach of Postuma and colleagues to collecting different measures and harmonising metrics across centres enabled them to recruit very large numbers of patients from many different countries. They gathered information on variables including motor symptoms, olfaction, colour vision, autonomic symptoms, cognition and mood, and prospectively followed patients over a mean of 3.6 years. This enabled them to calculate predictive values for each variable individually and in combination. During the study follow-up period, 28% of RBD patients converted to Parkinson's disease, DLB or MSA, with 73.5% conversion in those followed for 12 years. The authors showed that several variables predicted outcome. The most striking of these were measures of motor dysfunction, cognitive performance, erectile dysfunction, and colour vision. The combination of a higher score on the Unified Parkinson's Disease Rating Scale (UPDRS) and mild cognitive impairment resulted in a particularly high hazard ratio for phenoconversion, approaching 5.

The strong predictive value of sensory testing, including both olfaction and colour vision, is notable as impairments in these domains are not primary defining features of Parkinson's disease, MSA or DLB. They highlight the multisystem nature of these diseases, and the role that sensory tests can play in early detection of at-risk individuals. Quantitative measures of sensory, cognitive and motor function could help stratify patients into at-risk groups. As Postuma and colleagues note, some of these measures may be refined by emerging new technologies including wearables, sensors and web-based sensory testing.

Colour vision was assessed by the Farnsworth-Munsell 100 hue test, which is frequently used in studies of Parkinson's disease progression. It involves arranging 100 coloured discs into colour order. One criticism of this test is that it is vulnerable to confounding effects of general cognition. People with deficits in cognitive domains such as executive or visuospatial function also make errors in this task that may be unrelated to colour vision (Regan *et al.*

1998). Another limitation of the study is the absence of quantitative visuo-perceptual measures. There is converging evidence that deficits in visual processing are a sensitive and early measure of cognitive change in Parkinson's disease and that subtle cognitive deficits occur in the prodromal stage (Darweesh *et al.* 2017). New quantitative measures of visuo-perceptual function may thus allow cognitive change to be detected at early disease stages (Weil *et al.* 2017). The importance of visuo-perceptual changes in RBD is also recognised, with dysfunction in visuospatial construction as well as colour vision. Individuals with RBD and impaired visuo-perceptual function are more likely to go on to develop Parkinson's disease (Postuma *et al.* 2011). Combining quantitative measures of visuo-perception with other variables identified in the current study could yield even more powerful predictions for disease conversion.

Postuma and co-workers included among their measures DAT-SPECT imaging, which captures striatal dopamine transport and is an objective measure of nigrostriatal cell loss or dysfunction. However, DAT-SPECT positivity was no more predictive than bedside clinical measures of motor performance, showing the power of careful clinical examination to predict clinical outcomes. Other neuroimaging modalities were not examined. Neuroimaging, especially MRI, has not previously had a key role in diagnosing or monitoring progression in Parkinson's disease. But novel neuroimaging technologies, such as quantitative susceptibility mapping which provides measures of brain iron content, show potential for improved early detection and stratification.

The addition of genetic analysis could also enhance risk prediction. A recent study showed that in common diseases, a polygenic risk score based on multiple common risk alleles can approach the predictive accuracy of carrying a single gene mutation in Mendelian disease (Khera *et al.* 2018). We have previously shown the ability of genetic risk profiles, including rare risk variants in genes such as *GBA* and *LRRK2*, to distinguish patients with Parkinson's disease from healthy controls (Nalls *et al.* 2015). Incorporating genetic biomarkers such as these could further enhance the predictive accuracy of clinical risk profiling.

An interesting aspect of the Postuma *et al*. study is that there does not seem to be a clinical prodromal signature that is specific to Parkinson's disease, DLB or MSA. One might hypothesise that MSA would involve predominant autonomic features, Parkinson's disease

motor features and DLB cognitive features, but in this multicentre cohort this does not seem to be the case. In fact, motor symptoms were more predictive of the development of DLB.

A useful analysis performed by Postuma and colleagues was that they used their follow-up information to estimate the sample size requirements for future disease-modifying trials (Postuma, Iranzo, Hu *et al*. 2018), taking into consideration the stratification that could be achieved using their identified risk factors. For example, they were able to show that by stratifying using olfaction, the sample size of a clinical trial powered to detect a 50% reduction in phenoconversion could potentially be reduced by over 28%.

However, there are several key challenges to consider before embarking on an RBD-neurodegeneration prevention trial. Firstly, RBD is a prodromal marker for three separate diseases: Parkinson's disease, DLB and MSA. Although these share a common mechanism in terms of the aggregation of abnormal fibrillary alpha-synuclein, they have fundamental differences in their accumulation of neuronal and glial pathology and its distribution throughout brainstem and cortex. A clinical trial in this cohort would need to include a therapy that could plausibly have an effect on these separate conditions with different clinical endpoints and markedly different clinical courses. Secondly, emerging therapeutic approaches include antibody and antisense oligonucleotide therapies. These gene/protein-based therapies are likely to involve intensive treatment with a high possibility of side effects. Exposing people with RBD to such therapies, when they currently have the fewest symptoms, may be difficult from a regulatory and ethical standpoint. Postuma and colleagues' study is vital in quantifying the exact phenoconversion risks. Finally, and perhaps most challenging, is that such trials would mean informing members of the general population of their high risk of neurodegenerative disease, in effect carrying out predictive testing and counselling in patients without familial disease. The general population is not necessarily interested in advance knowledge of neurodegenerative disease risk. For example, in families with Huntington's disease only 10–20% of at-risk individuals choose to undergo predictive testing (Morrison *et al.* 2011). The situation has clear analogies with incidental/additional findings in genome-wide genetic analysis – if there is a clear preventative strategy e.g. for individuals with *BRCA1* mutations, then disclosure and medical follow-up is recommended where possible. For individuals in the general population with no family history and perhaps no personal experience of Parkinson's disease/DLB/MSA, effective communication and counselling will be crucial. However, the appetite for medical information is increasing, as

evidenced through the wide uptake of direct to consumer genetic and imaging investigations, and physicians should be prepared to engage with the challenges of population-based early stage preventative treatment.

The neurological community will need to grasp the nettle of large scale identification of high risk individuals in the population. We will need to build on the expertise of investigators working with RBD cohorts, both in terms of counselling and population stratification to realise the promise of our rapidly expanding understanding of the biology of synucleinopathies. Ultimately, this will pave the way towards new treatments to prevent neurodegenerative disease.

Competing interests statement:

RSW reports no competing interests of relevance to this article.

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Glossary

DAT-SPECT imaging: A neuroimaging technique that probes dopaminergic integrity. It uses single-photon emission computed tomography and injection of radiolabelled tracers that target the dopamine transporter at the presynaptic terminal of dopaminergic cells in the striatum.

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