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SCIENTIFIC COMMENTARY

Progression in Parkinson's disease: a potpourri of plots and probabilities

This scientific commentary refers to 'Sequence of clinical and neurodegeneration events in Parkinson's disease progression' by Oxtoby et al. (doi: 10.1093/brain/awaa461).

An almost ubiquitous question raised by patients newly diagnosed with Parkinson's disease is what the future may hold for them. Whilst much is now understood about the spectrum of changes that can occur over time, for the most part applying group level descriptions to the individual in front of us remains beyond clinical reach. Although this difficulty in predicting disease trajectory is evident in most branches of medicine, Parkinson's disease presents particular challenges. It is widely heterogeneous, with clinically relevant manifestations varying significantly between patients, and extending far beyond a simple disorder of movement. Furthermore, progression in Parkinson's disease cannot be viewed as a singular construct, but instead must be considered along multiple, dissociable axes including motor, autonomic, behavioural and cognitive. That is, meaningful progression for one patient may be the development of disabling motor symptoms with fluctuations, whilst for another it may be insidious cognitive impairment across multiple domains. Despite these challenges, understanding the trajectories of Parkinson's disease progression remains a vitally important research question, with the potential to advance therapeutic approaches and patient management and identify pathways amenable to modification. In this issue of *Brain*, Oxtoby and colleagues apply a modern modelling approach to a cross-sectional dataset to delineate the likely order of changes—across a wide range of variables—that occur as Parkinson's disease progresses.[1]

Like many neurodegenerative diseases, Parkinson's disease is characterized by slowly progressive changes in brain structure and function that predate clinical symptoms by variable, but often extended, periods of time. The prominent Braak hypothesis postulates that this progression involves spreading Lewy body and neurite pathology from the gut and/or olfactory nerves, with relatively early changes in brainstem structures such as the locus coeruleus, followed by degeneration of the substantia nigra pars compacta leading to the classic movement issues, and increasing cortical involvement with associated cognitive deficits.[2] Although this hypothesis has been questioned, not least because of the wide heterogeneity seen in clinical syndromes of Parkinson's disease, studies spanning neuropathology, imaging modalities and neuropsychological tests have provided broad support to this conceptual trajectory.[3–6] Nevertheless, most work has focused on specific components or modalities, and an overarching view of Parkinson's disease progression, encompassing pathological, physiological and clinical measures is lacking.

The increasing availability of large-scale fine-grained datasets that span multiple features (e.g. clinical status, cognitive performance, neuroimaging measures such as atrophy, connectivity or brain iron accumulation, and other physiological markers) provides the opportunity to probe this issue. However, analysing such datasets in a meaningful way is not a trivial task. Normal background neural function, the consequences of progressing neuropathology, and the interactions between these together make up a complex, non-linear state. As an example, the importance of feature A for progressive cognitive decline may only be relevant in the setting of feature B, or a shift in state of feature C. Overly simplified modelling approaches risk missing these nuances that allow deeper understanding of the underlying 'truth', whereas increasing model complexity can make it harder to imbue parameter outputs with true biological meaning that translates to the clinic.

Oxtoby et al.[1] used an event-based model, previously used in other degenerative brain conditions[7] to estimate the order (and uncertainty in this positional estimate) in which various clinical and neuroimaging events had occurred in one cohort of patients with Parkinson's disease, before validating their findings in a separate cohort (Fig. 1A and B). Although the dataset was cross-sectional, event order was inferred from the combinations in which the events occurred. If event A only ever occurred in the presence of event B, but B was often found without A, then event B would be estimated to precede A. Certainty in this inference would be reduced the more frequently A was observed

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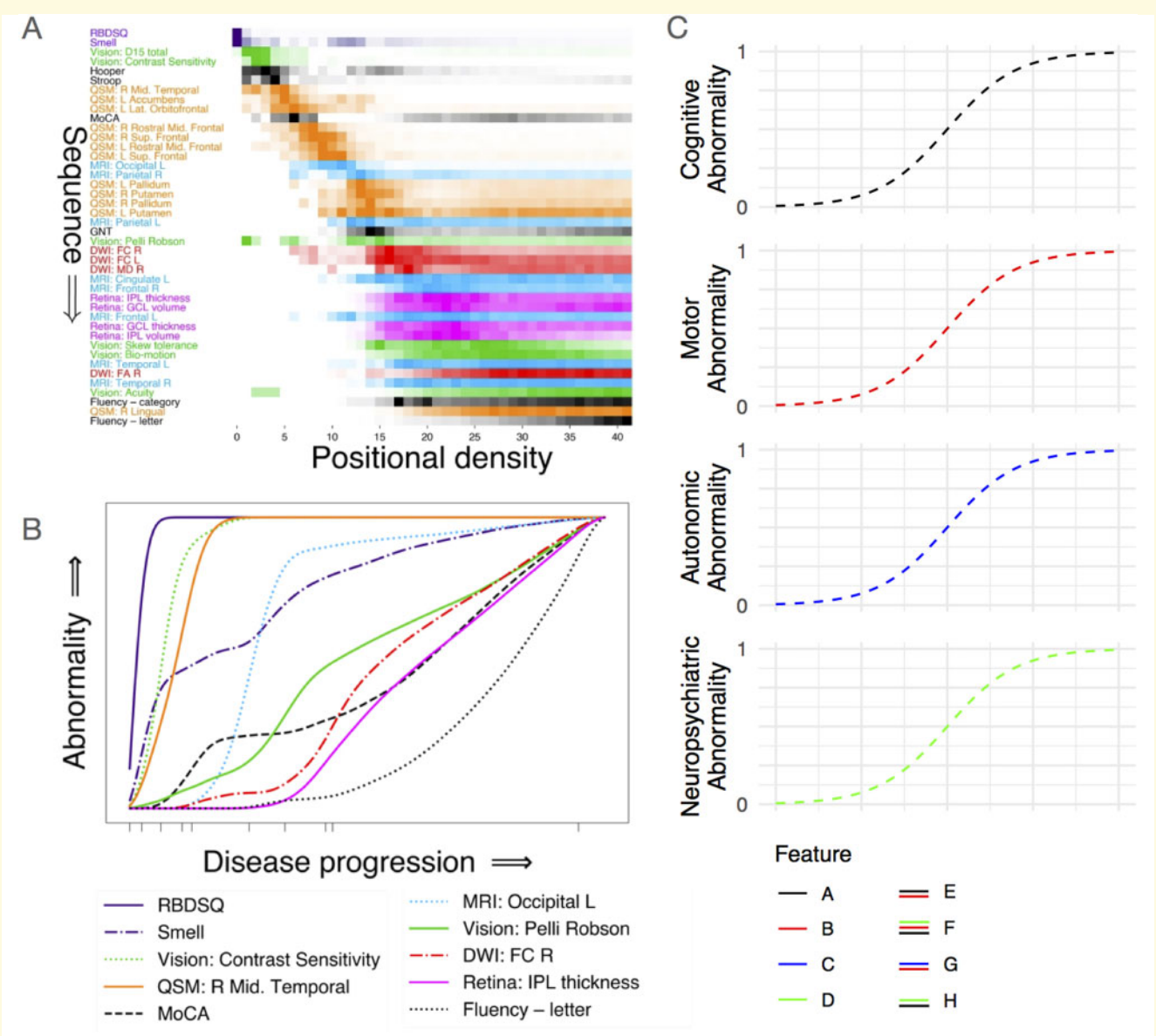

Figure 1 Modelling Parkinson's disease progression. (**A**) Estimated order of events in Parkinson's disease by Oxtoby et al. The density of colour represents when the change in that feature is happening, and features are ordered from earliest at the *top* to latest at the *bottom*. For example, changes in cortical quantitative susceptibly mapping (QSM) all happen early on in disease progression. In contrast, changes in letter fluency happen later. (**B**) Cross-validated onset event cumulative positional densities by Oxtoby et al. This further illustrates the temporal nature of how features change, with some features, such as visual contrast sensitivity, showing a sharp early change, and other features such as the Montreal Cognitive Assessment (MoCA) gradually deteriorating over time. It should be noted that the spectrum of abnormality for each feature is constrained by the observed data, and may well be markedly worse with further (unmeasured) disease progression: for example, the lowest MoCA score here is 18. (**C**) Progression in Parkinson's disease should be viewed as occurring along multiple dissociable axes, including cognitive, motor, autonomic, and neuropsychiatric. Features may be specific to a single axis, or common to several of the axes. The dotted lines represent progression within a given axis, which will be indexed by a particular collection of features (e.g. A, E, F and H for cognitive). These features could be any disease relevant measure, from clinical testing to physiological markers. Relative progression along each axis will vary from patient to patient. Panels **A** and **B** from Oxtoby et al.[1]

without B. This model was applied across the full range of included events, which the authors selected as 'any observable dynamic measure that potentially contains disease information'.[1] The broad categories of measures included were prodromal states; performance on neuropsychological tests; assessments of vision, visual processing and retina; and imaging metrics including estimation of brain iron accumulation, white matter integrity, and atrophy at multiple subcortical and cortical sites. The dataset was 'enriched' with older

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(defined as age greater than 65 years) patients, who are known to progress at a faster rate, thus potentially increasing the variability across the spectrum of events. Furthermore, the inclusion of controls, and specific statistical treatment of their performance within a mixed modelling approach, grounded the model outputs within a spectrum from normality to progressive Parkinson's disease.

The results indicated much greater certainty in the position of earlier as compared to later events. Prodromal features (REM sleep behaviour disorder, anosmia) came first, followed by deficits in visual processing, a measure of executive function, widespread brain iron accumulation and posterior brain atrophy. The order of the remaining approximately two-thirds of events was estimated with much less precision, and spanned all categories aside from prodromal features. Some important assumptions of the model are worth highlighting before interpreting these results. All patients with Parkinson's disease were assumed to be progressing towards Parkinson's disease dementia—although the cross-sectional nature of the analysis means the end point of progression is in fact somewhat arbitrary (the ability of the model to predict cognitive performance was not tested). The model also assumes an orderly, stepwise progression, whereas many of these features would be changing simultaneously, often in a non-independent manner.

Probably most important though is the selection of features. The model can only play the hand it is dealt—in this case biomarkers with a neuropsychological, visual, structural imaging and brain iron emphasis. Neuropsychiatric (e.g. anxiety, hallucinations, apathy, depression), autonomic and motor features were not included, nor were more functional brain measures. Similarly, biomarkers reflecting neuropathological change (e.g. CSF neurofilament light chain levels or markers of astrocyte activation) were not included either. Thus, the outputs of this model must be interpreted as the ordering of a subset of potentially relevant biomarkers in Parkinson's disease progression, rather than a comprehensive assay of changes.

With these caveats in mind, in addition to the modelling method itself, Oxtoby and colleagues' study contributes important evidence regarding the sequence of brain changes in Parkinson's disease. Measures of brain iron accumulation were estimated to occur early—before most other MR metrics had changed substantially—in both subcortical and cortical regions. This early occurrence aligns with growing evidence implicating disordered iron homeostasis as a crucial step in Parkinson's disease pathogenesis, as well as a potential biomarker (via detection techniques such as quantitative susceptibility mapping) and therapeutic target.[8] Additionally, the finding of very early disordered visual processing is of significant interest. Previous studies have demonstrated the predictive power of disrupted visuospatial function for developing Parkinson's disease dementia.[5,9] The current work demonstrates that at least some of these changes may occur very early in the disease course. If these specific features can be shown to predict subsequent dementia (rather than being a more ubiquitous marker of Parkinson's disease in general), visual assessment could provide a relatively simple method for identifying those at higher risk of future cognitive decline, and targeting preventative strategies.

Building on this work, longitudinal studies are the most crucial next step. These could be used to validate the predictions of order based on this cross-sectional data, but also, in theory, extend the event-based model to include within subject changes over time. Additionally, careful consideration should be given to the features incorporated into future models. An overarching model, encompassing features that span physical and psychiatric clinical states, cognitive function, neuropathology including pathological protein accumulation, multimodal imaging, and other physiological markers of neural and astrocytic activity and dysfunction, would be of significant interest to the field, in much the same way that such models have aided in understanding of Alzheimer's disease.[10] However, with expansion of feature types, a reduction in representatives for each feature—ideally restricted to a single critical one—will be important to limit cross-correlation between variables and model complexity. Thought should also be given to how variations in the sensitivity of assessing different features affects the final model outputs. Additionally, the field needs to consider not just the multiple variables that may predict worsening of disease, but also the multiple axes upon which progression can occur (Fig. 1C). Particular combinations of feature changes may be associated with the dissociable ways that patients with Parkinson's disease progress: the trajectory (in terms of ordered steps) towards Parkinson's disease dementia is likely very different from that towards an endpoint of severe motor fluctuations with preserved cognition. In time, these developments may allow us to provide a more certain estimate of what the future holds for the individual patient in front of us in the clinic.

Competing interests

The authors report no competing interests.

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