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SCIENTIFIC COMMENTARIES

A robust brain signature region approach for episodic memory performance in older adults

This scientific commentary refers to 'A robust brain signature region approach for episodic memory performance in older adults' by Fletcher *et al.* (doi:10.1093/brain/awab007).

A perennial challenge in the field of cognitive neuroscience pertains to how best to map and summarize associations between brain structures and behaviour.[1,2] One popular approach is to focus exclusively on brain structures that have previously been reported to show robust associations with the behaviour under investigation. Another common approach is to identify the combination of brain regions that associate with the behaviour of interest in a data-driven manner. On the surface, these approaches seem quite distinct and are more or less suitable dependent on cohort scale, placing the emphasis on either eschewing the multiple comparisons problem or mitigating systematic biases of the field.

In practice they often share some of the same limitations due to a common starting point, specifically, the application of an established atlas to segment the brain into functional or anatomical regions of interest. When the data are summarized in this way, subtle differences in brain–behaviour associations that span multiple predefined regions of interest or that subdivide them further may be missed, with consequences for sensitivity. Relatedly, different results may be observed dependent on arbitrary decisions made when choosing between atlases or segmentation methods.

The current pursuit of better models to track and predict behavioural aspects of age-related decline from brain metrics has brought this methodological issue to the fore.[3] Studies seeking to leverage the statistical power of large online datasets to improve such models are beginning to move beyond the limitations of predefined atlases by aggregating associations between brain structure and memory at the finer grained voxel level. In this issue of *Brain*, Fletcher and colleagues[4] explore the potential of a novel variant of the 'brain signature regions of interest' method for predictively modelling differences in episodic memory function, both cross-sectionally and longitudinally, based on imaging measures of grey matter density. At the heart of this method is a three-stage process that generates an array of regions of interest from voxel-wise associations in a data-driven manner. The regions of interest form the basis of a further regression model that is first fitted to the behavioural target measure and then cross-validated in independent datasets. Critically, as the segmentation is conducted voxelwise based on association with the target behavioural measure, it is not constrained by prior literature or standard functional–anatomical atlases.

The most notable results of this study are from the analyses of the predictive value of the signature regions of interest model. This was evaluated across three large independent datasets, each comprising healthy older adults as well as individuals with mild cognitive impairment (MCI) and Alzheimer's disease. For comparison, the performance is benchmarked against a set of predefined regions of interest that have previously been proposed as a standard atlas-derived correlate of impaired episodic memory function, comprising hippocampal and cortical grey matter volumes.

The results indicate that removing constraints imposed by atlas-based parcellation can produce improved predictive models of both baseline performance and longitudinal change in memory. This finding is counter to the current drive towards generation and application of standard atlases in neuroimaging research. There are pragmatic motivations for that drive. Combining voxels into functional networks or anatomical regions of interest provides a convenient form of data reduction. It can improve signal to noise via regression to the mean, partially mitigates the problem of statistical correction for multiple comparisons and can form a consistent framework complete with interoperable labels for summarizing results across studies. However, if such atlases are misaligned with patterns of pathology, or the functional systems of the brain that support cognitive and memory functions, then pragmatic advantages may come at a cost. In this respect the results of the current study have quite broad relevance.

The authors also report that the spatial patterns of high association with episodic memory are highly replicable across the three cohorts. These patterns include the temporal lobes,

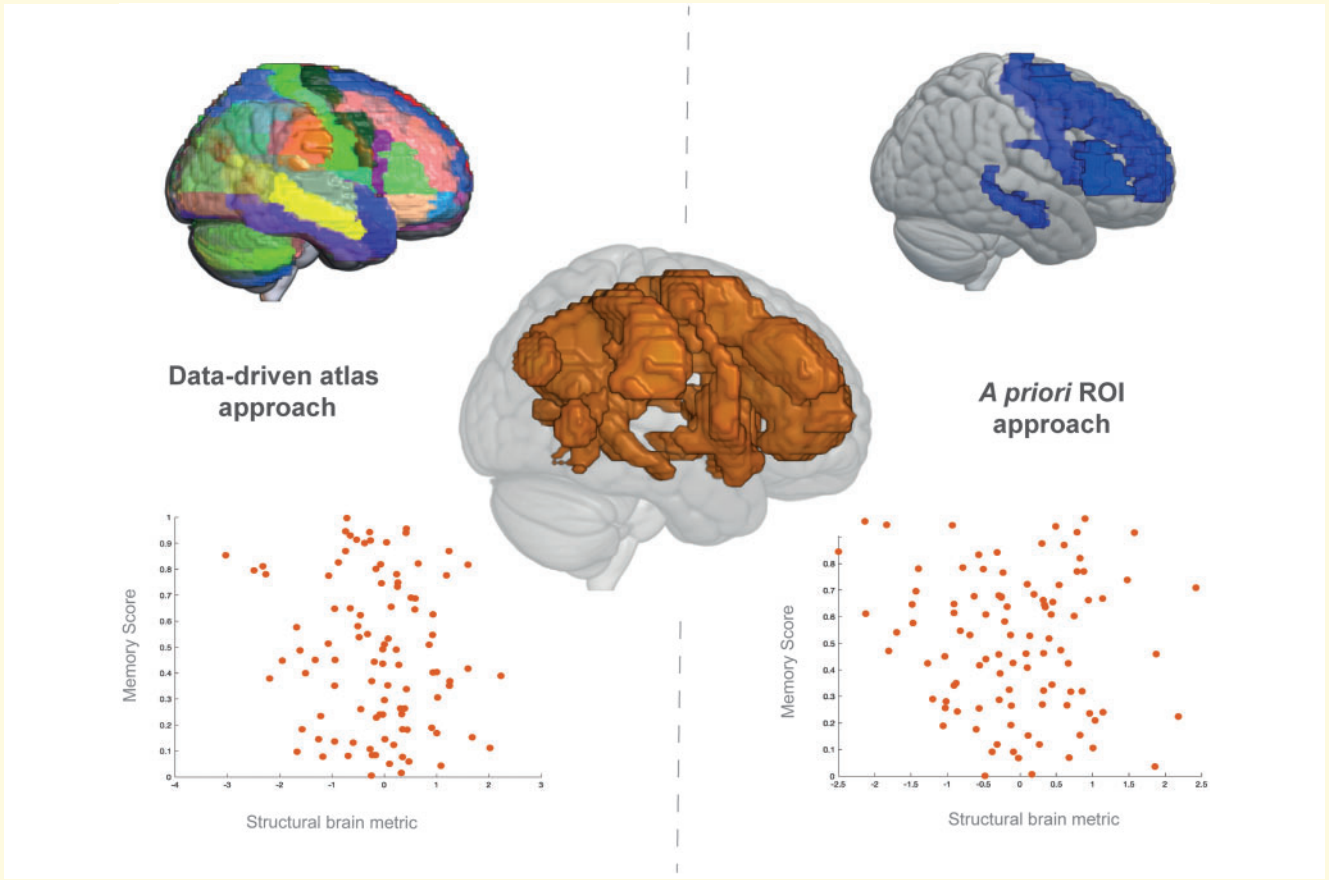

Figure 1 Potential impact of brain feature extraction approaches to investigate brain-behaviour relationships. In a given scenario, researchers may wish to investigate the relationship between brain metrics such as grey matter volume and memory. Here, researchers will often choose to explore such relationships by extracting features of brain structure using a data-driven approach, whereby a well established atlas (*left*) is applied, or by selecting a small number of regions of interest *a priori* (*right*), based on previous literature. Importantly, both methods can miss subtle patterns of associations that span the brain (orange) by omitting areas or summarizing patterns that span multiple predefined regions of interest in varying magnitude. Furthermore, differences between researchers in terms of arbitrary choices in feature extraction within the brain can lead to different results being obtained. ROI = region of interest.

posterior cingulate cortex and precuneus. The comparison of these associations to previous data-driven and hypothesis-led models illustrates where findings converge, although there are some notable discrepancies. For example, hippocampal areas do not show the strong associations with longitudinal change that some models would predict, although it is important to note that this may be a consequence of using mixed cohorts. These results are interesting because there has been some concern regarding the lack of reproducibility in brain structure and behaviour relationships across cohorts[2] and the varied patchwork of models and proposed regions implicated in such cognitive processes in ageing and neurodegeneration.[5–7] The multiple levels of reproducibility achieved at scale in the current study indicate that historic inconsistencies may in part have a basis in the application of parcellation methods that are suboptimal, being misaligned with the spatial pattern of pathology, but might also reflect studies that have focused on specific predefined anatomical regions or smaller population samples.

Achieving accurate model-based prediction and quantification of long-term outcomes in both healthy ageing and neurodegeneration remains a major outstanding research challenge. The signature regions of interest approach appears to be a promising avenue for improving the sensitivity of such models. Improving associations between brain metrics and memory function has research potential for studies investigating the role of cognitive reserve and resilience in older adults. The approach may also be useful in intervention studies. Indeed, it has been proposed that pharmacological interventions targeting dementia often fail because of the damage already incurred at the point of obvious cognitive decline.[8] More sensitive identification of atrophy patterns associated with memory may help in the early stratification of patients for treatment and quantification of intervention efficacy at the level of brain metrics.

A notable limitation of this study is the exclusive focus on grey matter density measures. Nevertheless, the method could readily be extended to

include multimodal imaging data. Furthermore, given the stepwise approach, there is also the potential to examine the degree to which the application of more sophisticated modelling of the associations between behavioural measures and regions of interest derived in this manner might improve sensitivity in terms of predicting and quantifying decline in memory function. More generally, the approach may have utility in other clinical populations that are characterized by subtle but widespread abnormalities in brain structure that are not neatly aligned with standard brain parcellation atlases.

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Competing interests

The authors report no competing interests.

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Is clinical assessment enough? Moving towards early differentiation of neurodegenerative parkinsonisms

This scientific commentary refers to 'Identification of multiple system atrophy mimicking Parkinson's disease or progressive supranuclear palsy' by Miki *et al.* (doi:10.1093/brain/awab017).

Multiple system atrophy (MSA) is a sporadic neurodegenerative condition characterized by a variable combination of parkinsonism, autonomic failure, cerebellar ataxia and pyramidal features.[1] Confirmation of the diagnosis still requires direct pathological examination, although the differentiation of probable and possible MSA remains clinical, often requiring the consideration of non-supporting features and red flags. Despite advances in neurology, the diagnostic accuracy of experts in identifying MSA and differentiating it from other neurodegenerative conditions, such as Parkinson's disease, progressive supranuclear palsy (PSP) and dementia with Lewy bodies (DLB), remains suboptimal. Besides a lack of diagnostic biomarkers, the heterogeneity of these conditions and the presence of variants further complicate a reliable diagnosis.

These obstacles have led to considerable efforts to develop more accurate diagnostic criteria, including the ongoing revision of the second consensus statement from 2008 by the International Parkinson and Movement Disorder Society, which is expected to be published soon. Appropriately diagnosing and categorizing such conditions not only provides patients and their families with a better understanding of the disease course and expected prognosis, but also allows a more refined patient selection for epidemiological studies and clinical trials. In this issue of *Brain*, Miki and colleagues[2] explore some of the limitations of the current diagnostic approach to MSA, and highlight particular clinical pointers that may assist clinicians in reaching a more reliable diagnosis when faced with challenging or hybrid cases.

In this large retrospective clinicopathological study, Miki *et al.*[2] concentrated their analysis on MSA patients who had been misdiagnosed in life as having Parkinson's disease or PSP. Of the 218 patients with a neuropathological diagnosis of MSA included in the study, 177 (81.2%) had received a correct clinical diagnosis of MSA ('typical cases'), while most of the