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Towards a multi-function mapping of the cerebellar cortex

This scientific commentary refers to ‘Structural cerebellar correlates of cognitive and motor dysfunctions in cerebellar degeneration’, by Kansal *et al.* (doi:10.1093/aww327).

Anatomical evidence suggests that substantial portions of the cerebellum do not communicate directly with motor regions of the neocortex, but rather are connected to parietal and prefrontal association areas (for a review see, Strick *et al.*, 2009). Neuroimaging studies have provided the first detailed maps for a functional topography of the cerebellum. For example, activation associated with cognitive function is usually localized to lobules VI and VII while somatosensory and motor function is mapped to lobules I–IV in the anterior lobe and lobule VIIIb in the posterior lobe (for a review see Stoodley and Schmahmann, 2009). If these activations are functionally relevant, one would predict that lesion or degeneration in these areas would lead to specific deficits. Classically, however, the main clinical symptom of cerebellar damage has been the disruption of smooth motor function, resulting in ataxia, dysarthria, dysidiadochokinesia and dysmetria. Only more recently has it been acknowledged that cerebellar atrophy can lead to higher-order cognitive dysfunctions, including generalized cognitive impairment, deficits in executive function (planning, abstract reasoning, and working memory), and language deficits (for a

review, see Schmahmann, 2004). Previous studies have mapped cognitive and motor dysfunctions in cerebellar disease to specific cerebellar lobules in a one-to-one (Schmahmann and Sherman, 1998) fashion in an attempt to find direct associations between cerebellar integrity and both motor and cognitive performance. This approach is generally known as lesion–symptom mapping and has been successfully applied to the study of both patients with focal lesions caused by stroke or tumour resection, and to patient groups with cerebellar degeneration (for a review, see Timmann *et al.* 2008). However, a comprehensive mapping of clinical dysfunctions to different cerebellar subregions is currently missing. In this issue of *Brain*, Kansal *et al.* (2017) take a step towards this goal by studying a large and heterogeneous sample of patients with cerebellar degeneration across a wide range of clinical tests. Using elegant statistical techniques, the authors advance the traditional lesion–symptom mapping approach, and provide the first multi-domain mapping of cognitive and motor dysfunctions to atrophied cerebellar lobules.

This study uses two novel methodological features. First, the authors use a graph-cut based segmentation routine (Yang *et al.*, 2016), which allows for automated lobular segmentation along subject-specific cerebellar fissures. The many-to-many mapping achieved by this study was, in part,

facilitated by this optimized segmentation routine. Second, the authors use a more advanced statistical approach to address one of the main methodological challenges accompanying lesion–symptom mapping in patients with cerebellar degeneration: Even though individual patients differ in their specific patterns of degeneration, the loss of tissue in various lobules is usually highly correlated (Figure 1 in Kansal *et al.* 2017). This collinearity makes the structure-to-function assignment very difficult. The authors counter this problem by using an automated variable selection approach, termed sparse partial least squares (SPLS). Like normal linear regression, the approach seeks to explain the functional score by a certain combination of lobular volumes. However, it also imposes a sparsity constraint (implemented in the form of an L1-norm penalization) which biases the method to automatically ‘select’ only one or a few of the possible lobules. As compared to other variable-selection approaches, such as step-wise regression, SPLS provides a principled approach to deal with the issue of highly collinear predictors. Using this statistical method, the authors were able to obtain coefficients of the cerebellar volumes for each task (across motor, mixed and cognitive domains) and determine the lobule most closely associated with each. As a result, the authors were able to provide evidence for a functional involvement of the

Glossary

Lobules: Macro-anatomically well-defined subdivisions of the human cerebellum. The currently dominant nomenclature was devised by Larsell (1970), who divided the tightly folded cerebellar cortex (both in the hemispheres and vermis) into 10 lobules (I–X).

Regularization: Statistical method that reduces overfitting caused by ill-posed problems by including additional information in a regression model.

Sparse partial least squares (SPLS): Variable selection statistical method that produces fewer non-zero coefficients than a traditional least squares approach.

regions identified using functional neuroimaging. For example, tasks targeting higher-order cognition such as working memory and immediate and delayed recall were most strongly associated with posterior lobules (Crus I and II) while tasks that were predominantly motor in nature were linked to anterior lobules (I–IV).

While the statistical approach chosen by the authors was able to provide a meaningful multi-domain map of the human cerebellum, it by no means removes the fundamental statistical problem that the amount of degeneration across cerebellar lobules was highly correlated (Figure 1 in Kansal *et al.*, 2017). While the method provided a sparse solution in each case, such that it identified one or few regions as being important, the strong correlations between volumes make such solutions relatively unstable. However, the authors should be commended for acknowledging this problem and for quantifying the reliability of their method by bootstrapping. They randomly drew new subsets from their data with replacement, and repeated the process of variable selection 1000 times. Each time, the method selected slightly different lobules, and the frequency of associations between lobular volumes and test scores served as a measure of certainty of this association (Supplementary material of Kansal *et al.*, 2017). These results clearly indicate that some assignments were made with relatively high confidence (Table 1: 99.1% for lobule HVI and ICARS speech), whereas other associations were far less stable (Table 1: 25.9% for lobule HVI and noun fluency).

An important question for further studies is how best to segment the cerebellum into functionally

meaningful subdivisions. In agreement with current convention, the authors subdivided the cerebellum with respect to lobular boundaries. However, it is not clear that the functional boundaries in the cerebellum respect the macro-anatomical folding of the cerebellar cortex. Indeed, recent imaging studies (Buckner *et al.*, 2011; Diedrichsen and Zotow, 2015) suggest that functional modules in the cerebellum span multiple lobules, and often are more clearly defined in their medio-to-lateral location on the cerebellar cortex. The intention of the group to conduct analyses of cerebellar function free from lobular constraints in the future will therefore constitute an important step forward.

It is also worth mentioning that functional lateralization was not accounted for in this study. While the authors acknowledge the importance of left-right differences, especially in the context of verbal fluency, the decision was made to amalgamate both hemispheres in an attempt to reduce collinearity. Ideally, future work would consider lateralization when mapping cognitive and motor deficits to cerebellar disease.

Despite these limitations, Kansal *et al.* provide an important contribution to clinical and cerebellar research. Their study is the first to map a comprehensive battery of motor, affective and cognitive tasks to the degeneration of specific cerebellar lobules in a large and heterogeneous patient sample. While this many-to-many mapping could be more easily achieved using functional neuroimaging approaches (Stoodley and Schmahmann, 2009), the study of clinical deficits is absolutely essential to understand the functional relevance of the observed activations. Real insight into the functional role(s) of

the cerebellum will likely emerge from further advances in high dimensional function-to-structure mapping, using both neuroimaging and patient-based approaches.

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Refining Alzheimer's disease diagnosis with MRI

This scientific commentary refers to 'Heterogeneity of neuroanatomical patterns in prodromal Alzheimer's disease: links to cognition, progression and biomarkers', by Dong *et al.* (doi:10.1093/brain/aww319).

A revolution in Alzheimer's disease clinical diagnosis will be required to target upcoming, potentially disease-modifying therapies early in the course of the disease, when they are most likely to work and maintain good quality of life (Gauthier *et al.*, 2016). Well-defined, homogeneous patient cohorts will need to be identified, preferably before the onset of dementia. Currently, in stark contrast, many patients in the UK are never diagnosed and, of those that are, around half are identified relatively late in the course of the illness (Hodge and Hailey, 2015). Basic principles of current diagnosis stem from knowledge about neuropathological staging of disease; for example, clinicians look for hippocampal atrophy on MRI scans because we know from post-mortem studies that the hippocampus is affected by tau pathology relatively early in the disease process (Braak and Braak, 1995). In this issue of *Brain*, Dong and colleagues characterize the patterns of atrophy in Alzheimer's dementia and mild cognitive impairment (MCI) using a data driven, unbiased algorithm for the analysis of structural MRI that is not constrained by our existing neuropathological framework for diagnosis (Dong *et al.*, 2017).

Using a dataset of 1243 participants from the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort, followed up for around 2–4 years, Dong and colleagues beautifully

demonstrate the heterogeneity of patients diagnosed with Alzheimer's dementia and MCI, even those carefully selected on the basis of fairly standard amnesic presentation in the ADNI protocol (Box 1). The paper explores the possibility of stratifying individuals objectively according to patterns of tissue loss, taking into account covariates such as age and gender. The brain images were analysed using a new program named CHIMERA to find 'clusters' that best described the data. Four such clusters were identified (Box 2). These are suggested to represent not just different stages of neurodegeneration, but different categories of pathology, demonstrating the inherent heterogeneity of cognitive decline.

The four clusters were each associated with distinct CSF biomarkers, neuropsychological profiles and levels of white matter hyperintensity (WMH) (Box 2 and Fig. 1). By following the cohort for 2–4 years, the progression rates for each cluster could also be interrogated, demonstrating that clusters 2 and 3, with more widespread involvement and

more severe cognitive symptoms, progressed more readily from MCI to Alzheimer's disease with a faster overall rate of decline in cognitive and executive function (Fig. 1).

Such striking differences between clusters in parameters other than those used to define the clusters tantalizingly suggest that this method of classification may be probing dimensions of Alzheimer's disease overlooked by neuropathologically-driven diagnostic algorithms. Most notably, the presence of WMH in cluster 2 is intriguing, particularly given accumulating evidence that hypoperfusion of the white matter is an intrinsic component of Alzheimer's disease progression (Lee *et al.*, 2016). Do these data suggest that hypoperfusion is more relevant in a subset of patients? Of course, cluster 2 could also be conceptualized as a group with a tendency to independent, but mixed, Alzheimer's disease and vascular pathology, a group in whom interventions to target both vascular and Alzheimer pathology may perhaps be particularly helpful. In contrast,

Box 1 Alzheimer's Disease Neuroimaging Initiative (ADNI)

- A major strength of the paper is use of the ADNI dataset.
- ADNI is an international collaborative observational study where healthy older participants as well as those with mild cognitive impairment (MCI) and Alzheimer's disease undergo a systematic set of tests including structural MRI, PET scanning, cognitive tests, blood tests and CSF biomarkers and are then followed over time to monitor for cognitive change.
- There have been several phases of ADNI—ADNII, ADNIGO, ADNI2—and together these now include several hundred participants.
- Data are made freely available to authorized investigators and this has resulted in over 300 publications so far.
- ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering and industrial partners.
- Study coordination is through the Alzheimer's Disease Cooperative Study at the University of California, San Diego.