for these changes, and extend previous findings in the hippocampus by the same group (Gemmell et al., 2012, 2014).

What are the vascular mechanisms behind this neuronal volume loss? Such a selective change cannot be explained by a chronic failure of oxygen or nutrient delivery. However, brain blood vessels are also crucial for the delivery of trophic signals that link the viability of neurons and glia to that of vascular cells (Iadecola, 2013). Vascular damage may disrupt these interactions and affect specific neuronal populations. We can also speculate about the potential role of subcortical lesions, which are known to affect axon integrity. Such axonal changes may induce a loss of volume in cell bodies via a retrograde degenerative mechanism.

The work of Foster et al. raises important questions that now need to be addressed, in particular whether this specific vascular neuronal atrophy is an early or late event in the natural history of cerebrovascular disease. Further studies are also required to explore the clinical and imaging correlates of the selective neuronal changes, which may develop at sites remote from infarcts.

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The next step in modern brain lesion analysis: multivariate pattern analysis

This scientific commentary refers to ‘Human brain lesion-deficit inference remapped’, by Y.-H. Mah et al. (doi: 10.1093/brain/awu164).

A cardinal goal in neuroscience relates to mapping brain circuits to specific functions. Although progress towards this goal has been made using a range of measurement techniques applicable in healthy human subjects, the brain circuits that are necessary for a given function can only be ascertained by observing the behavioural consequences of brain injury (Rorden and Karnath, 2004). In the evolution of this domain, voxel-wise lesion symptom mapping (VLSM; Bates et al., 2003) represents a tremendous step forward. This statistical approach, as well as other inferential methods (e.g. Rorden et al., 2007), controls for regions that are not critical for the behavioural deficit under consideration; i.e. VLSM rules out regions of the brain that are simply vulnerable to damage and thus commonly damaged in stroke patients.

However, a limitation of this mass univariate approach is that it typically does not consider how multiple regions interact to produce a behavioural deficit. Indeed, in cases where function is tied to a distributed network of regions, two patients with the same symptom and with damage to the same functional network may have damage to distinct parts of the network, thus appearing as statistical counter examples to each other [cf. the ‘partial injury problem’ (Rorden and Karnath, 2004)]. To overcome this problem, Smith et al. (2013) used multivariate pattern analysis (MVPA) for lesion analysis, which uses machine learning algorithms (e.g. support vector machines) to train and then test predictive models based on the pattern of damage to multiple regions (Fig. 1). This seminal application of MVPA to lesion data addressed the multivariate patterns of damage predictive of spatial neglect. In a large sample of 140 patients with acute right brain damage, MVPA revealed two key findings: (i) leveraging information from multiple regions (both damaged and spared) provides superior predictive power for distinguishing neglect and control patients; and (ii) adding superior temporal cortex to other regions consistently improved predictive power. Yet, while Smith et al. (2013) focused

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on the predictive performance of various regions, the use of MVPA in lesion mapping may extend beyond prediction by examining how specific regions (or voxels within a region) are weighted to form the predictive model. In this issue of Brain, Mah et al. (2014) investigate whether the weights derived from MVPA offer enhanced anatomical precision over traditional univariate techniques.

Mah et al. (2014) hypothesized that univariate techniques systematically distort the true anatomical associations between functional impairments and the complex patterns of brain injury that arise from ischaemic stroke. Crucially, damage from ischaemic stroke follows stereotyped patterns that conform to the vascular tree, which could result in regions that are merely collateral damage, bearing no relationship with the function of interest. To examine this possibility, Mah et al. used an impressive database of lesion maps from 581 patients. This database created an opportunity for the authors to run a series of elegant simulations quantifying the direction and magnitude of mislocalization across the whole brain. Strikingly, the authors found that the results from standard univariate analyses are displaced by nearly 16 mm on average. As these spurious associations followed the underlying vasculature of the brain, the resultant error in localization cannot be ameliorated with additional patients or otherwise increasing statistical power. Instead, one would have to consider the entire pattern of damage—how each voxel is damaged in the context of all other voxels—which requires the MVPA approach (Fig. 1). Rather than examining the predictive performance of multiple regions, Mah et al. (2014) focused on how individual voxels were weighted in the learning algorithm (i.e. linear support vector machine). In a linear classifier, voxels with the largest weights have the greatest influence on the learning algorithm and are thus expected to have the closest association with the true underlying anatomy contributing to the functional deficit. Consistent with this observation, the authors found that the weights derived from MVPA overcome the inherent mislocalization issues that affect univariate techniques.

Although MVPA has clear potential for advancing our understanding of the functional deficits incurred by brain injury, it is important to emphasize that lesion mapping studies are plagued by a crucial confound. Specifically, larger lesions are simply more likely to include a key region, meaning that the deficit of interest (e.g. spatial neglect or aphasia, etc.) will be correlated with lesion size. Standard VLSM techniques attempt to account for this confound by including lesion size as a nuisance regressor (Karnath et al., 2004; Schwartz et al., 2012; Kümmerer et al., 2013). While Mah et al. used standard VLSM techniques to create their estimates of mislocalization, it should be noted that lesion size was not included as a regressor in their model. Whether this analytical decision affected their estimates of mislocalization remains unclear; however, the absence of a lesion size control does not appear to have negative consequences on the localization of key weights derived from MVPA. Nevertheless, it should be noted that the predictive performance of MVPA would be artificially enhanced by lesion size, given its strong association with the deficit of interest. To control for this issue, Smith et al. (2013) included lesion size as a feature in their MVPA model. By using a combinatorial approach (Clithero et al., 2009), they were able to quantify how the addition of various regions improves predictive performance over and above lesion size alone.

Despite these caveats, MVPA applications to lesion data are rapidly advancing. Although both these MVPA lesion studies used simple binary classifiers, such as ‘spatial neglect present versus absent’ (Smith et al., 2013) or ‘affected versus unaffected’ (Mah et al., 2014), the approach could be extended by examining simplified schematic of MVPA applied to lesion data. Here we show an example of MVPA applied to brain injury maps to predict the presence or absence of spatial neglect as employed by Smith et al. (2013). The schematic outlines key components of MVPA, which principally involves both training and testing a predictive model. The training procedure employs machine-learning algorithms (support vector machines) to construct a model of how distributed patterns of lesion data indicate the presence or absence of spatial neglect. The constructed model is then tested on new data (i.e. not used to train the model). This testing procedure was repeated for each individual in the data set, meaning each individual was tested on a model that was built independently of that individual’s data. The average of those predictions is the predictive performance of the model (cf. the cross validation rate). The algorithm can be trained on various features (e.g. voxels from different regions of the brain) to predict the presence or absence of spatial neglect. Crucially, the features are differentially weighted by the learning algorithm: features with the largest weights have the most influence on the learning algorithm. From Smith et al. (2013).
continuous measures. It is evident that most neuropsychological phenomena exhibit a continuous spectrum of severity desiring of quantification. Indeed, this extension of MVPA in lesion mapping has recently been undertaken by Zhang et al. (2014), who investigated semantic as well as phonological error rates in object naming in 106 patients with aphasia after left hemisphere stroke. They used a regression-based MVPA approach to understand the brain–behaviour relationship contributed by multiple brain regions to these two (continuous measures of) aphasic errors. Their analysis reproduced the essential pattern of previous anatomical findings identified by VLSM but showed higher sensitivity than VLSM for identifying the lesion-behaviour relations.

Taken together, the recent results by Smith et al. (2013), Zhang et al. (2014), as well as the present study by Mah et al. (2014), indicate that MVPA indeed has the potential to improve localization of lesion-behaviour relations and identify predictive models of neuropsychological deficits arising from stroke with higher sensitivity. Analysing brain injury data using MVPA provides us with a method for simultaneously considering the influence of multiple regions or voxels and thus extends our understanding of both brain function and stark behavioural deficits incurred by brain damage. In addition to leveraging spatially distributed regions critical for a task, multivariate methods are also sensitive to regions where injury predicts normal performance on a specific task. By combining (noisy) information on regions that predict both the presence of impaired performance and the retention of performance after injury, a multivariate approach should become more accurate.

Beyond spatial neglect after right hemisphere damage (Smith et al., 2013) and language disorders after left hemisphere damage (Zhang et al., 2014), MVPA has broad implications for a wide spectrum of other cognitive functions and clinical disorders. Indeed, this method will be a useful tool for all neurological disorders where—as in spatial neglect and in language processing—similar symptoms can be observed following discrete injury to portions of a larger network. However, application of MVPA to lesion analysis not only provides an opportunity to gain greater insight into small- and large-scale network-driven behaviour, but also has the potential to become an important tool for long-term prognosis. The method could help triage individuals who will spontaneously recover from those who will need focused rehabilitation. As MVPA becomes more accessible to the larger community, its potential applications in both basic neuroscience research as well as behavioural neurology and neuropsychology will continue to grow and improve. We expect that its use and future development within the domain of lesion mapping will complement our current knowledge and eventually usher in a new inferential framework relating brain injury to specific human functions.

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