Neuronal substrate of cognitive impairment in post-stroke dementia

This scientific commentary refers to ‘Pyramidal neurons of the prefrontal cortex in post-stroke, vascular and other ageing-related dementias’, by V. Foster et al. (doi: 10.1093/brain/awu172).

Post-stroke dementia is a frequent cause of loss of independence following stroke, whereas post-stroke cognitive decline affects an even greater number of stroke survivors. The burden of post-stroke dementia and cognitive decline is likely to increase because of falling mortality rates after stroke, the ageing of Western populations, and longer life expectancies in developing countries. However, the pathological processes that increase vulnerability to cognitive decline in previously non-demented stroke survivors are unknown. In this issue of Brain, Foster et al. provide new clinico-pathological evidence that selective regional pyramidal neuron atrophy in the dorsolateral prefrontal cortex, rather than a change in neuronal density per se, is associated with executive dysfunction in post-stroke dementia and vascular dementia (Foster et al., 2014).

The neuropathology of vascular cognitive impairment remains controversial for several reasons. First, cerebrovascular lesions are heterogeneous in nature (vessel wall modifications, perivascular tissue alteration, myelin loss in white matter, infarcts or haemorrhages, etc.), in size (from microscopic cortical infarcts to large territorial infarcts), and in location, being widely distributed throughout the brain (cortex, deep or periventricular white matter, basal ganglia, hippocampus). Each cerebrovascular lesion may have an impact on cognition through various mechanisms including altered blood flow and oxygen supply, chronic inflammation, disruption of axonal tracts, or altered cortical connectivity (Iadecola, 2013). Second, the link between chronic cerebrovascular lesions and cognition is still disputed, especially when frequent reports of neuroimaging abnormalities attributed to vascular mechanisms in the brains of cognitively normal subjects. Finally, the exploration of clinico-pathological correlations in vascular cognitive impairment suffers from the absence of a reliable, harmonized and widely accepted protocol for quantification of the cerebrovascular burden in post-mortem brains, despite recent attempts to create one (Deramecourt et al., 2012).

Although dysexecutive syndrome has long been regarded as the predominant feature of vascular cognitive impairment, and has been linked to the disruption of frontal-subcortical neuronal circuits, the precise mechanisms and pathological changes underlying dysexecutive syndrome remain unclear. White matter changes, globally and regionally assessed with quite simple imaging rating scales, were associated with executive dysfunction and reductions in processing speed in several subtypes of mild cognitive impairment (Debette et al., 2007). However, such rating scales may lack validity for explaining cognitive performance. More detailed analyses of grey and white matter, using voxel-based morphometry and diffusion tensor imaging, are needed. Coupled with cognitive assessment, these approaches have produced convergent results, revealing widespread structural alterations in the frontal and parietal lobes of patients with early brain microangiopathy (Quinque et al., 2012). Changes in processing speed, one of the main components of executive function, have been related to disruption of frontal-subcortical circuits, particularly in dorsolateral prefrontal and anterior cingulate areas, in patients with the small vessel disease, CUDASIL (Ouering et al., 2012). These subcortical alterations were recently found to correlate with a significant frontal cortical thinning and atrophy in the thalamus, putamen and globus pallidus, suggesting degeneration of neurons in these regions (Thong et al., 2014).

Foster et al. now reveal pathological changes related to executive dysfunction in three main clinical variants of vascular cognitive impairment: post-stroke dementia, subcortical ischaemic dementia and mixed Alzheimer’s disease and vascular dementia. Their work extends the pathological spectrum of cerebrovascular lesions, to include neuronal atrophy (Foster et al., 2014). Using thorough stereological methods and robust cell morphometric analysis, they show reduced cell volume (but not reduced density) of pyramidal neurons in layers III and V of the dorsolateral prefrontal cortex in patients with vascular cognitive impairment, compared to post-stroke non-demented patients and controls. Notably, the changes in cell volume correlated with the degree of post-stroke cognitive impairment. Their observations suggest a vascular base...
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

References


