SCIENTIFIC COMMENTARIES

Setting new tracks: not just creating another pretty picture

Diffusion tensor imaging (DTI) has the lure that functional MRI had in the 1980s; it often yields beautiful pictures, whether or not it confirms your beautiful hypotheses. It is not that we haven’t learned much from both, indeed, functional MRI has revealed substantial insights into the networks of brain regions that work together to support cognitive functions; how these networks change to support recovery of function over time after stroke (Saur et al., 2006); and how these networks are altered in disease states—for example, Alzheimer’s disease, frontotemporal dementia (Zhou et al., 2010) and developmental disabilities such as dyslexia (e.g. Hu et al., 2010). Similarly, DTI, and particularly tractography, have provided important new information, for example, about the various connections of the superior longitudinal fasciculus, and how lesions affecting the separate connections might explain various types of language disorder (Catani and ffytche, 2005) or neglect (Bartolomeo et al., 2007). It has also helped in monitoring disease progression in diseases such as multiple sclerosis; and proved useful in evaluating recovery in a variety of neurological contexts. But the lure to be avoided is to use DTI merely to localize a previously well described behaviour. That is, the field is already full of voxel-based morphometry studies of the precise voxels most associated with performance on a particular published test. Adding another layer of localization—the white matter tracts where disruption is associated with impaired performance on that particular test—is not a sufficient advance unless the behaviour itself is interesting, or a specific hypothesis about the white matter tract or the disease of interest is being tested.

This issue of Brain remembers John Hughlings Jackson. In the 1860s Dr Hughlings Jackson wrote a large number of influential observations on language and epilepsy. These observations had a substantial impact on our understanding of disease and the brain, because they were new, well-described observations of behaviour. They often, but not always, were accompanied by some localization of the lesion. Dr Hughlings Jackson wrote about not only language, but everything related, from ‘Paralysis of the right half of the tongue and palate and right vocal cord’ to, ‘The psychology of joking’. His cases broke new ground. He described the case of left hemiplegia and aphasia in a patient with previous right hemiplegia without aphasia, indicating that not all individuals are left-hemisphere dominant for language. He wrote on ‘Language and thought—the duality of mental processes’, recognizing, perhaps for the first time, that people who cannot use language are nevertheless able to think in other ways. Hughlings Jackson also described the relationship between aphasia, right hemiplegia and valvular disease of the heart. Now we readily recognize this association as due to emboli from the heart to the left middle cerebral artery. But these early observations associating phenomena that have no clear common basis are what led to the understanding of cardioembolic stroke as well as vascular aphasia syndromes.

Two papers in this issue of Brain report novel imaging findings concerning three variants of primary progressive aphasia first reported by Gorno-Tempini et al. (2004). One is an elegant tractography study by the same group (Galantucci et al., 2011); the other is a study incorporating 11C-labelled Pittsburgh compound (PiB) PET imaging, which detects β-amyloid accumulation, a putative marker of Alzheimer’s disease pathology (Leyton et al., 2011). Like Dr Hughlings Jackson, Gorno-Tempini and colleagues first noticed an interesting pattern of language in neurological disease that was distinct from the patterns previously reported. For nearly two decades, there had been reports of patients with progressive impairment in speech articulation and grammatical sentence production (now called non-fluent/agrammatic variant primary progressive aphasia; Gorno-Tempini et al., 2011) and others with progressive impairment in word and object meaning (now called semantic variant primary progressive aphasia). However, these authors observed patients with progressive language production impairments, but not quite either of the previously reported patterns; rather, they made phonological paraphasias (e.g. ‘springing’ for earring) and had disproportionate errors in sentence repetition. Furthermore, mirroring the work of Hughlings Jackson, they reported that this newly described pattern of language impairment, which they called logopenic progressive aphasia, seemed to be associated with a distinct pattern of atrophy from the other two clinical variants (Gorno-Tempini et al., 2004). Recent studies have provided evidence that the three subtypes are also associated with distinct pathologies—logopenic variant primary progressive aphasia most commonly associated with Alzheimer’s disease pathology; semantic variant most commonly associated with ubiquitin pathology (also in frontotemporal lobar degeneration; FTLD); and non-fluent/agrammatic variant most associated with tau deposition (also in FTLD, progressive supranuclear palsy, corticobasal degeneration; Leyton et al., 2011).
Leyton and colleagues provide novel evidence for this proposal, by investigating the three variants of primary progressive aphasia, distinguished using recently published consensus criteria, with Philadelphia Compound B-Positron Emission Tomography (PIB-PET). They find that 96% of patients with logopenic variant primary progressive aphasia, but only 10% of those with semantic variant primary progressive aphasia and 25% of those with non-fluent/agrammatic variant primary progressive aphasia, have positive amyloid accumulation on PIB-PET. Their data confirm that the logopenic variant primary progressive aphasia has a distinct pathological basis, as well as a distinct localization and language profile.

The paper by Galantucci et al. (2011) goes on to provide new data on the white matter tracts associated with these distinct patterns of language impairment. Importantly, their study reveals some interesting information not only about the anatomy, but also the nature of the disease and language and behaviour networks underlying these syndromes. Patients with semantic variant primary progressive aphasia show bilateral damage in all DTI metrics in the ventral tracts that connect the temporal lobe to the occipital lobe and to the orbitofrontal cortex, as well as left-sided tracts that connect the temporal lobe to the parietal and the frontal lobe. Dorsal frontoparietal tracts that do not involve the temporal lobes are spared bilaterally. Disruption of the ventral language network, with relative sparing of the dorsal network, explains the observation of impaired word and object meaning and preserved phonology and grammar. Furthermore, they show disruption of the uncinate fasciculus that might account for behavioural changes often observed in the semantic variant primary progressive aphasia; and its close relationship to frontotemporal dementia (and the shared ubiquitin pathology in many cases). In stark contrast, patients with the non-fluent/agrammatic variant primary progressive aphasia show significantly lower fractional anisotropy than controls in the dorsal tracts that are spared in the semantic variant primary progressive aphasia—the entire left superior longitudinal fasciculus and in all three of its left-sided components, i.e. tracts that connect the frontal lobe to the inferior parietal and posterior superior and middle temporal lobe. Disruption at these sites can account for the progressive impairment in grammar (sentence production and complex sentence comprehension) as well as speech articulation and phonology. Interestingly, no tract is more damaged in the logopenic variant than the other variants. Compared with controls, only the left temporoparietal portion of the superior longitudinal fasciculus shows significantly lower fractional anisotropy, consistent with the area of focal atrophy in these patients, and with the underlying pathology of Alzheimer's disease, which often affects temporoparietal cortex, relatively sparing white matter and frontal lobes until late.

Thus, the paper by Galantucci et al. (2011) illustrates the continued value of detailed observations of behaviour, coupled with careful localization (either by modern imaging or by autopsy as in Hughlings Jackson's day). Because of writers like Hughlings Jackson, we now recognize that effortful, poorly articulated speech frequently co-occurs with agrammatic, telegraphic speech and writing, as well as impaired use of the right arm. When these problems occur suddenly, we are concerned about a stroke in the distribution of the superior division of the middle cerebral artery. When they occur gradually, we are concerned about non-fluent variant primary progressive aphasia. Studies like that reported by Galantucci et al. (2011) reveal that the disease is not just cortical; unlike the logopenic variant of primary progressive aphasia, non-fluent variant primary progressive aphasia and semantic variant primary progressive aphasia run deeper. These language syndromes, which are usually due to FTLD pathology, affect white matter tracts that connect the frontal and temporal lobes (the uncinate, as well as inferior longitudinal fasciculus in semantic variant; and the arcuate fasciculus, as well as other components of the superior longitudinal fasciculus in non-fluent/agrammatic variant primary progressive aphasia). We hope that discovering the white matter tracts and the remainder of the neural networks underlying these well-characterized syndromes, along with the pathology and genetics will ultimately lead to effective treatment. But the discovery must start with careful observation and documentation of co-occurring behaviours or deficits as taught and so effectively achieved by John Hughlings Jackson.

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