From hodology to function

In 1993 Francis Crick and Edward Jones appealed to the scientific community with an editorial in *Nature* entitled ‘Backwardness of human neuroanatomy’. Their aim was twofold: to ‘make a wide audience aware’ of how little is known about human brain anatomy, and to highlight the urgent need for ‘new methods to solve this problem’ (Crick and Jones, 1993).

Around that time a group of researchers based at the NIH were working on a new magnetic resonance technique called diffusion tensor imaging (DTI) (Basser *et al*., 1994). Almost 15 years after publication of the Crick and Jones editorial, diffusion-based imaging methods represent perhaps the most concrete response to their appeal. Without doubt, diffusion-based imaging methods are revolutionizing the field of neuroimaging along two fronts: for the first time we are able to reconstruct white matter pathways in the living human brain and re-explore connectional anatomy after a long period of stagnation since the work of the early 19th century neuroanatomists; and diffusion-based imaging methods allow us to take a hodological (i.e. connectionist) approach to disorders of the brain, where a more narrow localizationist model has been found wanting (Catani and Ffytche, 2005).

In this issue of *Brain*, Schmahmann *et al.* (2007) report the results of a study where a recently developed diffusion-based imaging technique, namely diffusion spectrum imaging, is used to perform virtual dissections of a monkey’s white matter tracts. Their article contains spectacular images of the major association pathways and their virtual reconstructions appear to replicate the details of the monkey’s anatomy derived from tracing techniques. The reader might be surprised that *Brain* has overruled its editorial policy of rarely publishing normative data. However, the reason for this is that the article encourages the reader to reflect on two important issues in neurological science: the relevance of neuroanatomy to the understanding of brain function, and the importance of methodological developments for studying neuroanatomy.

The reasons for studying anatomy have recently been intensely debated (see reference to *The New Anatomist*) and the use of ‘expensive’ neuroimaging techniques has been harshly criticized by one of the most influential philosophers in contemporary cognitive neuroscience: ‘It isn’t, after all, seriously in doubt that talking . . . depends on things that go on in the brain somewhere or other.’ If the mind happens in space at all, it happens somewhere north of the neck. What exactly turns on knowing how far north?’ (Fodor, 1999). However, philosophers have not always shared Fodor’s opinion. For example, Aristotle, the father of comparative anatomy, held that ‘every bodily member subserves some partial end, that is to say, some special action’ . . . ‘The beaks of birds, as their feet, vary with their modes of life . . . straight in those who use it merely for eating; crooked in those that live on a raw flesh’ (Aristotle, 2004). Hence, ‘form and function go together for Aristotle. Anatomist and physiologist are integral components of Aristotle’s science’ (Blits, 1999).

In teleological terms it might be suggested that a unique form subserves a specific function; in evolutionary terms that the function has shaped the form. It follows that it is that modification of the form results in dysfunction, a corollary that applies in nature at any level and one which scientists have exploited to work out the causes of human diseases, moving—in a reverse logic—from functional deficits to structural modifications. Thus, in molecular biology the study of linear sequences of bases or amino acids and their ability to fold into relatively stable three-dimensional structures with unique transcriptional or enzymatic activities, has led to important insight into normal cellular processes and pathological conditions derived from substitution of a single base or amino acid.

At a macroscopic level the ‘Aristotelian’ principle has dominated Western culture since the Renaissance. Michelangelo’s obsession with the human body was driven by the hope of capturing the meaning of human existence through the representation of the perfect body. Leonardo’s physiology attempted to reveal the many facets of ‘human passions’ through the representation of facial expressions. Both Michelangelo and Leonardo practised human body dissections, a method of scientific inquiry that grew stronger over the centuries and culminated in the work of the greatest neuroanatomists of the 19th century—among them Bernhard Von Gudden and August Forel (Danek *et al*., 1989), Karl Meynert, Karl Wernicke and Jules Déjérine (Catani and Ffytche, 2005), all of whom shared a common faith in the value of clinico-anatomical correlation in exploring disorders of the brain, both in animals and in man. However, it soon became clear to them that, for the brain, the relationship between form and function—in the neurology clinic between brain lesion and
symptoms—was not to be interpreted in a narrow localizationist sense, but rather to be conceived as something occurring at a ‘supra-regional’ level, between patterns of connections and clinically assessed performance in specific aspects of behaviour and cognition. For them ‘any higher psychic process...could not be localized, but rested on the mutual interaction of fundamental psychic elements [e.g. sensory and motor activities as occurring in primary cortical areas] mediated by means of their manifold connections via the association fibres’ (Wernicke, 1885). ‘The anatomy of the central nervous system’ became ‘above all an anatomy of the texture’ (Déjerine, 1895); describing the details of association fibres the key to understanding brain function.

The aforementioned words resonate in contemporary behavioral neurology: ‘Nothing defines the function of a neuron better than its connections...Understanding these patterns of cortical connectivity is absolutely essential for understanding the relational architecture, and therefore function, of large-scale neurocognitive networks’ (Mesulam, 2006). Real connectivity of the human brain, however, has remained an enigma for more than a century and despite advancements in our understanding of animal anatomy, little progress has been made since Déjerine. Hence, not surprisingly, diffusion imaging tractography is of great appeal to neuroanatomists as a method for in vivo virtual dissections (Catani et al., 2002) to narrow the gap between simian and human connectional anatomy, and to clinicians as a non-invasive tool to perform clinico-anatomical correlation in disorders where white matter changes are not visible with more conventional imaging (e.g. neurodevelopmental disorders). Thanks to diffusion-based imaging we are able, for the first time in humans, to study intraspecies variability in connectional anatomy (Fig. 1), delineate developmental white matter trajectories in normal and diseased brains, and identify behavioural correlates of different patterns of lateralization of white matter tracts.

I have little doubt that hodology, the science of connectional anatomy (Catani and ffytche, 2005), being revitalized by recent developments based on diffusion-based imaging and computational analysis of effective connectivity (e.g. Lee et al., 2006), will become the ‘next frontier in neurosciences’ (Mesulam, 2005). However diffusion-based imaging is not without limitations, but people seem to have been mesmerized by those ‘pretty pictures’ (Johansen-Berg and Behrens, 2006) and have lost sight (more or less consciously) of the underlying pitfalls and shortcomings. For example, in regions where fibres cross, kiss, splay, branch or twist, the tensor model does not perform so well and artefactual reconstructions of pathways and false negatives are likely to occur (Basser et al., 2000) (Fig. 2). This limitation of the tensor model has prompted the development of alternative approaches to analyse the diffusion weighted signal, including diffusion spectrum imaging (Wedeen et al., 2005), q-ball imaging (Tuch, 2004), probabilistic PAS-MRI (Parker and Alexander, 2005), spherical harmonic deconvolution (e.g. Tournier et al., 2004), and probabilistic diffusion tractography with multiple fibre orientations (Behrens et al., 2007). But these approaches are not a complete solution to the problem and still suffer from topological ambiguity, e.g. they are unable to differentiate between fibres crossing, kissing or bending within a voxel.

Schmahmann et al. are the first to have attempted validating in vivo tractography with previously published autoradiographic tracing reconstructions of white matter pathways. Beautiful as are the images, they fall short of representing the definitive validation for two reasons: first, tractography dissections and autoradiographic tracing are not performed in the same brain; secondly by focusing on association pathways they have lost a good opportunity to show whether their tractography method truly outperforms other diffusion-based methods in reconstructing those
tracts whose anatomy represents a real challenge for faithful in vivo reconstructions (e.g. projection and commissural pathways). The latter remains the real test for the tractography algorithms of the next generation.

While reading the paper by Schmahmann et al., the words from Dejeérine’s preface to his 1895 textbook of neuroanatomy come to mind: ‘to follow the fascicles, their origin, trajectory and termination, this is the goal of those who, after Vicq d’Azyr, have studied this branch of the anatomy [hodology]...despite the improvement of the techniques available to us nowadays, there is still...more than one obscure point to clarify’ (Dejeérine, 1895). A caveat to bear in mind in the journey to come.

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