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Introduction

The human brain is profoundly self-connected. Its hundred billion or so nerve cells, or neurons, communicate with one another by means of around a quadrillion synapses; and this mass intraconnectivity, as it were, is undoubtedly essential for the array of information processing tasks that it is required to perform. The grey matter of the brain's cortex—which is composed primarily of neuron cell bodies—is often thought of as the part of the brain most specialised for particular tasks, and therefore the tissue most likely affected when brain damage impairs the ability of an individual to complete specific kinds of tests. This view became popular in the early twentieth century due in part to the work of Korbinian Brodmann and Alfred Walter Campbell, who divided the cortex into regions according to their microstructure (see ffytche & Catani, 2005)—thereby displacing the connectionist school, primarily attributed to Carl Wernicke, which came before it. It was the American neurologist Norman Geschwind who, in 1965, reemphasised the role of white matter and the likely effect of its interruption, cutting off normally connected cortical areas from one another (Geschwind, 1965a,b). Given appropriate white matter lesions, Geschwind argued, this disconnection effect could lead to a range of impairments such as aphasias (difficulties with speech), agnosias (failures of recognition), or apraxias (problems with voluntary movement). The gist of Geschwind's thesis has come to be known as the **disconnection hypothesis**.

Almost simultaneously, in the mid-1960s, the foundations of a method called diffusion magnetic resonance imaging (dmri) were being laid, a technique which could be used to characterise the diffusion of water in living tissue. This technique, in common with all magnetic resonance imaging (mri) methods, made use of an earlier discovery about the behaviour of certain types of particles in a very strong magnetic field: the nuclear magnetic resonance

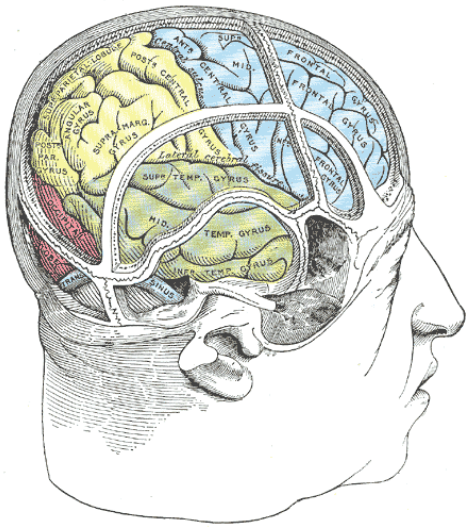

Figure 1.1: Engraving showing the gross anatomy of the brain, relative to features of the skull and face. The frontal lobes are coloured blue, the parietal lobes yellow, the temporal lobes green, and the occipital lobes red. Reproduced from Gray (1918).

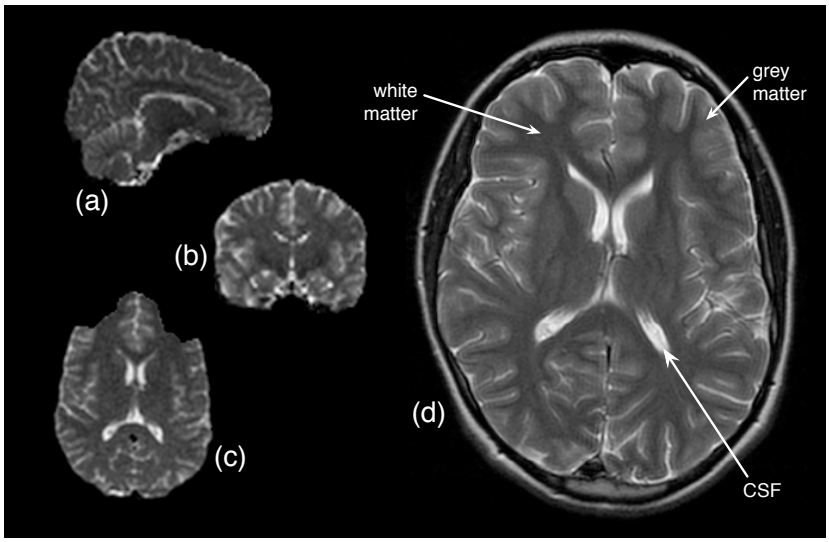

Figure 1.2: Magnetic resonance images of the brain, shown in sagittal **(a)**, coronal **(b)** and axial **(c)** planes, perpendicular to the left–right, anterior–posterior and superior–inferior directions respectively. The high resolution axial image **(d)** shows clear contrast between the three main tissue types. By radiological convention, the left side of the brain from the patient's perspective is shown on the right side of all images.

(NMR) phenomenon, which had been used for chemical analysis for some time before imaging methods reached maturity. Both NMR and MRI won their respective pioneers Nobel prizes. Felix Bloch and Edward Mills Purcell shared the 1952 physics prize for their work on the former; while Paul Lauterbur and Peter Mansfield were awarded the prize in medicine in 2003 for developing MRI, despite outstanding controversy over whether they were truly the first to demonstrate the technique.

MRI is now routinely used to create images of almost every part of the body for clinical diagnosis and prognosis, but it is particularly valuable for imaging the brain, whose details are obscured for x-rays by the bone of the skull. (The major regions, or *lobes*, of the brain are shown relative to the skull in Fig. 1.1.) Since the method involves no ionising radiation, it can also be used repeatedly on a single subject without fear of tissue damage. Imaging using magnetic resonance not only allows clinicians and researchers to visualise brain structure at a respectable resolution—on the order of 1 mm in each dimension—it can also be tailored to enhance contrasts between different tissue types, or between healthy and unhealthy tissue. In Fig. 1.2, for example, the distinction is quite clear between grey matter, white matter, and the cerebrospinal fluid (CSF) in which the brain is bathed. With diffusion MRI, image contrast is related to the local magnitude of water diffusion.

The potential of DMRI for studying white matter in particular was not immediately realised, and it was not until Peter Basser, James Mattiello and Denis Le Bihan described a way of measuring not just the magnitude but also the orientational structure of diffusion using NMR (Basser *et al.*, 1994a)—a method called diffusion tensor imaging—that this potential began to be fully realised. With this new development established, methods for virtual reconstruction of white matter structures—or **tractography**—quickly followed.

It has been possible for decades to examine the structure of connective tissue at the individual neuron level. Santiago Ramón y Cajal, often called one of the fathers of modern neuroscience, created superbly detailed and quite beautiful drawings of a great variety of complex neurons more than a hundred years ago (see Fig. 1.3), thereby earning him, and the inventor of the staining technique he used, Camillo Golgi, the 1906 Nobel prize for medicine. Moreover, histological methods have since improved to the point where tracing the routes of axons—the projections of neurons which bundle into larger connective structures—can be performed effectively and with impressive accuracy. Nonetheless, the development of a method for probing the connectivity of *living* brains was no small achievement, despite its far coarser

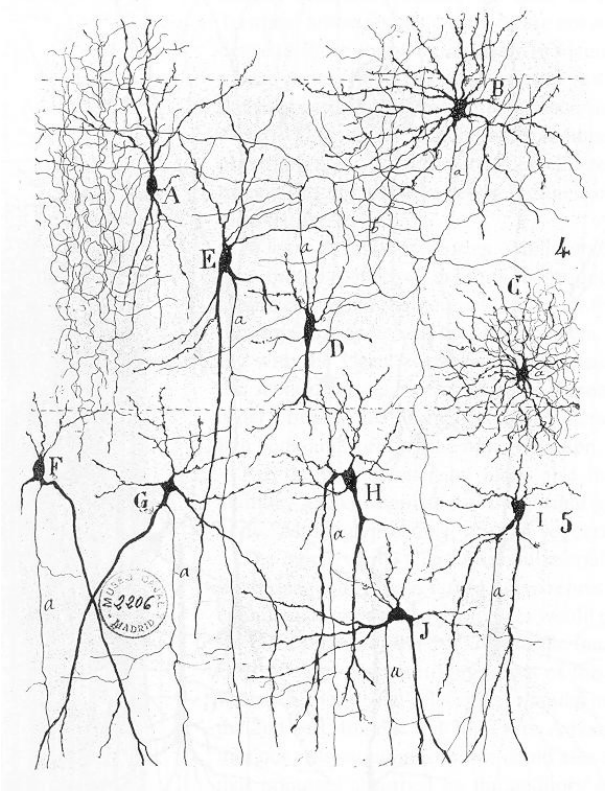

Figure 1.3: Drawing of Golgi-stained neurons in auditory cortex by Santiago Ramón y Cajal. A considerable variety of cell morphologies is visible. Reproduced from *Texture of the nervous system of man and the vertebrates*, translated and edited by Pedro and Tauba Pasik.

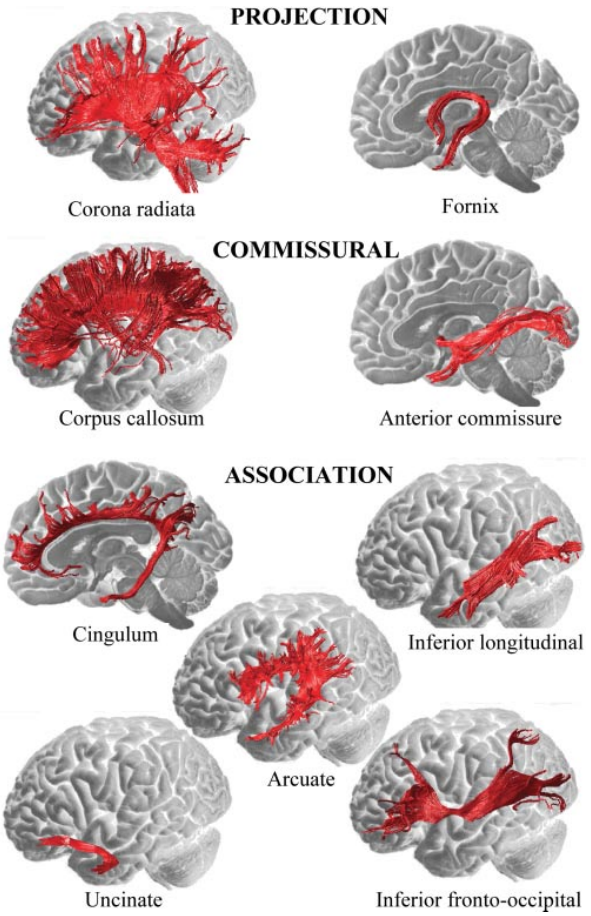

Figure 1.4: Illustration of some major white matter fasciculi, visualised using tractography and categorised after Meynert. Reproduced from Catani & ffytche (2005).

resolution, since all the alternatives oblige the researcher to wait for his subject to die, or to study animals which can be sacrificed. For the first time, it may be possible to test the disconnection hypothesis in patients with appropriate disorders.

Theodor Meynert, a nineteenth century neuropathologist, was the first to distinguish white matter structures, or **fasciculi**, into projection fibres, which connect cortical and subcortical grey matter together; commissural fibres, which link the two brain hemispheres; and association fibres, which connect distal cortical regions within a hemisphere. Fig. 1.4 shows examples of important tracts in each category. The corpus callosum, in the commissural class, is the largest white matter structure in the brain, connecting all the main lobes between hemispheres. Whatever principle one uses to categorise the various fasciculi, it is to be expected that interrupting different types of connection will have different effects; and so, conversely, it might be anticipated that different diseases affect different fasciculi. Indeed, Meynert described psychiatry as simply the study of diseases of the forebrain.

Despite its relative immaturity, tractography already offers the possibility of examining tract-specific effects of disease during the course of the illness; and at some point in the future it may become possible to use this kind of dMRI-derived information to inform the prognosis of patients with white matter diseases. At present, however, the robust location and characterisation of specific white matter tracts between subjects remains elusive. Tractography algorithms are able to segment particular tracts, but they are typically very strongly dependent on their initialisation, and principles for guiding the choice of starting condition are lacking. This thesis aims to take steps in that direction.

1.1 Problem statement

In order to establish whether a certain disease may be detrimentally affecting a particular white matter structure, it is typically constructive to compare the MR-visible characteristics of healthy and unhealthy examples of the tract in question. Since there is usually substantial variability in such characteristics even between normal individuals, due to imaging noise and genuine biological disparity, the comparison needs to be performed statistically between groups of subjects with similar clinical statuses. If a clear distinction is found, on aggregate, then this information can be used to estimate how likely it is that a new subject falls into one or other of the groups.

Under these circumstances, it is important to strive to minimise the impact of uncontrolled factors which may mask or exaggerate the true differences between the groups (or lack thereof). In statistical terms, an additional source of variance within the groups may lead to a falsely negative outcome, while a similar effect between groups may produce a falsely positive conclusion, suggesting that there is a group difference when in fact there is not.

One potentially large source of variance in the comparative analysis of white matter comes from segmentation. In order to compare a particular tract between groups, one must first identify it in each individual brain volume; and this should be done as consistently as possible to avoid introducing bias. Secondly, once comparable tracts have been identified in each brain volume, it is desirable that measures used to quantify differences between the groups be sensitive to white matter degradation whilst being relatively invariant to other nuisance factors. Improvement of segmentation consistency and examination of within-group and between-group variability in dMRI-derived measures of white matter integrity are the joint aims of the new work described in chapters 6–9.

The structure of the thesis is as follows. After outlining the general principles of probability (in chapter 2) and the physics of nuclear magnetic resonance (in chapter 3), we go on to discuss the nature of water diffusion in the brain. It is also explained, in chapter 4, how and why dMRI can be useful for probing white matter structure. Chapter 5 provides a survey of the tractography literature, thereby giving a sense of the potential diversity of segmentation methods, even within the general fibre tracking approach. Tractography is compared to other segmentation approaches in the early part of chapter 6, after which we begin to describe our novel take on the problem, whereby a reference tract is defined in advance to epitomise the topology of the white matter structure of interest, and a segmentation is chosen from among a

number of candidates in each brain volume by comparing them algorithmically to the reference and selecting the best match. The technique is demonstrated on healthy young and (in chapter 7) agèd and unhealthy subjects and shown to improve segmentation consistency compared to a simpler alternative strategy. Certain limitations come to light, however, and so in chapter 8 the method is further developed, and its principles are formalised using a probabilistic model. Techniques from machine learning are then applied to fitting the model parameters from data and performing segmentation in complete data sets. Finally, in chapter 9, we describe an attempt to compare a proxy measure for tract integrity between groups at a fine spatial scale, and investigate how the measure varies between and within populations.