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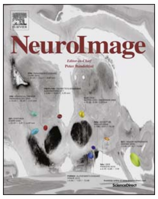

A graded tractographic parcellation of the temporal lobe

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ABSTRACT

The temporal lobe has been implicated in multiple cognitive domains through lesion studies as well as cognitive neuroimaging research. There has been a recent increased interest in the structural and connective architecture that underlies these functions. However there has not yet been a comprehensive exploration of the patterns of connectivity that appear across the temporal lobe. This article uses a data driven, spectral reordering approach in order to understand the general axes of structural connectivity within the temporal lobe.

Two important findings emerge from the study. Firstly, the temporal lobe's overarching patterns of connectivity are organised along two key structural axes: medial to lateral and anteroventral to posterodorsal, mirroring findings in the functional literature. Secondly, the connective organisation of the temporal lobe is graded and transitional; this is reminiscent of the original work of 19th Century neuroanatomists, who posited the existence of some regions which transitioned between one another in a graded fashion. While regions with unique connectivity exist, the boundaries between these are not always sharp. Instead there are zones of graded connectivity reflecting the influence and overlap of shared connectivity.

Introduction

The temporal lobe is a complex region that supports multiple cognitive domains including language (Cloutman, 2013; Price, 2010), semantic processing (Lambon Ralph, 2014; Lambon Ralph et al., 2017), memory (Scoville and Milner, 1957), audition (Kaas and Hackett, 1999) and vision (Goodale and Milner, 1992; Grill-Spector and Malach, 2004). In order to understand its roles in these diverse cognitive functions, researchers have attempted to map the precise anatomical organisation within the temporal lobe, revealing an intricate functional architecture and regions of specialisation throughout the temporal cortex. For example, within the temporal lobe, anteroventral and middle temporal areas have been found to be associated with semantic processing (Binder et al., 2009; Binney et al., 2010; Lambon Ralph et al., 2017), while medial areas have long been implicated in episodic memory (Scoville and Milner, 1957).

One way to understand the functional organisation of a region is to understand its structural composition. Traditionally, the exploration and mapping of structural/functional subdivisions within the cortex has been based primarily on cytoarchitecture but there has also been work on receptor distribution and other microarchitectural patterns. The laminar distribution of a given area, in conjunction with local microcircuitry and connectivity patterns determines its functional processing capabilities (c.f. Amunts and Zilles, 2015 for a full and in depth review). Indeed, the cortex does not exist as a detached entity and regions such as the temporal lobe are highly interconnected both locally and to other areas throughout the brain via white matter fibre bundles (Bajada et al., 2015; Catani, 2007; Catani et al., 2012; Catani and Thiebaut de Schotten, 2008; Déjerine and Déjerine-Klumpke, 1895; Duffau, 2015). These structural connections are assumed to be a determinant of the functional capabilities of a cortical area, governing the nature and flow of information to and from an area, and can influence both its underlying neural architecture and its functioning (Anwander et al., 2006; Cloutman and Lambon Ralph, 2012; Johansen-Berg et al., 2004).

While there has been a lot of research mapping function to structure within the temporal lobe and reconstructing the white matter fibre bundles that course through it, there has been relatively little exploration of the organising principles underlying connective similarity in the temporal lobe. Parcellation schemes identify core regions within the target area of interest where there is high intra-regional similarity in relation to some aspect of their anatomical or functional

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anatomy, but comparatively low similarity with areas outside the sub region. From these parcellations, researchers are able to delineate key regions of anatomical distinction, and by inference, areas of functional specialisation (Cloutman and Lambon Ralph, 2013). However, there is evidence to suggest that such hard parcels may not always describe the true underlying nature of the data (Brodmann, 1909 pp. 120–122; von Bonin and Baily). Brodmann himself noted that *"not all these regions are demarcated from each other by sharp borders but may undergo gradual transitions as, for example, in the temporal and parietal regions."* (Brodmann, 1909 p. 106).

In recent years with the advent of modern imaging techniques, researchers have begun to explore different ways to parcellate the cortex based on their patterns of connectivity described as connectivity-based parcellation (Eickhoff et al., 2015). Three main types of algorithms have been used. The first two are k-means clustering and hierarchical clustering (c.f. Eickhoff et al., 2015 for a full review). The third approach utilises principles of spectral graph theory to perform the parcellation (Cerliani et al., 2012; Devlin et al., 2006; Eickhoff et al., 2015; Haak et al., 2016; Johansen-Berg et al., 2004). The latter approach, often referred to as spectral reordering or a closely related Laplacian eigenmapping (Belkin and Niyogi, 2002; Cerliani et al., 2012; Johansen-Berg et al., 2004), allows for the investigation of the relationships between areas, whether these are graded or distinct, and hence is appropriate to investigate the organising principles of the temporal lobe.

Our aims were twofold. First, we wanted to establish whether the data supported graded regions within the temporal lobe. Second, we wanted to explore how connectivity similarity varied across the cortex.

In order to address these questions, the current study used spectral reordering, a data transformational technique, to explore the temporal cortex's connectivity. While not a clustering technique in the formal sense, the approach is well-established in the literature and its results have been validated (Anwander et al., 2006). We extended the method by projecting the reordered voxels into brain space. This allows one to elucidate the spatial pattern of connectivity across the cortex. We applied this technique to the temporal lobe and found that connectivity changes occur along a medial to lateral as well as anteroventral to posterodorsal axis. The tracts that underlie these axes were then explored. We finally discuss the possible functional processes that these gradations underpin. Throughout this paper we have referred to the current approach as a 'graded' parcellation. It is important to note that this is not to imply a presupposition about the underlying anatomical structure (indeed, the method allows both transitional and more discrete boundaries to emerge), but to differentiate it from more traditional methods which impose the delineation of hard boundaries.

Materials and methods

Image acquisition

A dataset containing structural (T1 and T2-weighted), and diffusion-weighted MR images from 24 healthy participants (mean age 25.9 years, range 19–47 years; 11 females) was used. All participants were right handed, as determined by the Edinburgh Handedness Inventory (Oldfield, 1971). The study was approved by the local ethics committee and all participants gave their informed consent. The images were acquired on a 3 T Philips Achieva scanner (Philips Healthcare, Best, The Netherlands), using an 8 element SENSE head coil. Diffusion-weighted images were acquired with a pulsed gradient spin echo echo-planar sequence with TE=59 ms, TR ≈ 11884 ms (cardiac gated using a peripheral pulse monitor on the participant's index finger (n=21), or using electrocardiography (n=3)), Gmax=62 mT/m, half scan factor=0.679, 112×112 image matrix reconstructed to 128×128 using zero padding, reconstructed in-plane voxel resolution 1.875×1.875 mm^2, slice thickness 2.1 mm, 60 contiguous slices, 61 non-collinear diffusion sensitization directions at b=1200 s/mm^2 (Δ=29. ms, δ=13.1 ms), 1 at b=0, SENSE acceleration factor=2.5. In order to correct susceptibility-related image distortions, two volumes were obtained for each diffusion gradient direction with inversed phase encode directions, with distortion correction carried out using the method described in Embleton et al. (2010). In order to obtain a qualitative indication of distortion correction accuracy, a co-localized T2-weighted turbo spin echo scan (in-plane voxel resolution of 0.94×0.94 mm^2, slice thickness 2.1 mm) was obtained. A high resolution structural T1-weighted 3D turbo field echo inversion recovery scan (TR ≈ 2000 ms, TE=3.9 ms, TI=1150 ms, flip angle 8°, 256×205 image matrix reconstructed to 256×256, reconstructed in-plane voxel resolution 0.938×0.938 mm, slice thickness 0.9 mm, 160 slices, SENSE factor=2.5), was acquired in order to obtain high accuracy anatomical data on individual subjects which were used to define individualised anatomical seed regions

Tractography

A temporal lobe region of interest was created which included all voxels within the temporal lobe at the boundary between the grey matter and the white matter (Anwander et al., 2006). To do this, each participant's skull stripped (FSL BET; Smith, 2002) T1-weighted image was co-registered to the distortion-corrected diffusion images using FSL's linear affine transformation (FLIRT) (Jenkinson et al., 2002; Jenkinson and Smith, 2001). The interface between the grey and white matter of the co-registered T1 image was then obtained using FSL's FAST algorithm to obtain a partial volume map of white matter, which was binarised with no threshold to ensure that the map overlapped the edge of the grey matter – the grey matter to white matter interface (GWI). The perimeter voxels of this map (the GWI) were extracted using an in-house MATLAB script. The GWI was then masked to include only those voxels within the temporal lobe. A temporal mask was first defined in MNI space using the MNI structural atlas within FSL (Collins et al., 1995; Mazziotta et al., 2001). This mask was then normalised and co-registered to each participant's native diffusion space. In order to ensure full temporal lobe coverage, the original probabilistic temporal mask was leniently thresholded. This resulted in the region of interest encroaching (or 'bleed') into other lobes (for example the frontal lobe across the sylvian fissure). In order to ensure that only the temporal lobe was used as a region of interest, the masks were all manually reviewed in native space. The corrected temporal mask was then used to mask the GWI to create the temporal GWI seed regions of interest used for tracking.

Unconstrained probabilistic tractography was performed from every individual voxel in the temporal lobe GWI using the probabilistic index of connectivity (PICo) algorithm (Parker and Alexander, 2005; Parker et al., 2003), which sampled the voxel-wise diffusion probability distribution functions (PDFs) generated via the constrained spherical deconvolution (Tournier et al., 2007) and model-based residual bootstrapping method (Haroon et al., 2009a; Haroon et al., 2009b; Jeurissen et al., 2011). During tracking, 10,000 streamlines were propagated from each seed voxel, with step size for streamline propagation set to 0.5 mm. An exclusion mask was created and used to avoid path propagation through the grey matter and tracts anomalously jumping sulcal boundaries and gyri. The streamlines were set to stop if they hit the exclusion mask, if the path length of the streamline was greater than 500 mm, or if the curvature of the streamline was greater than 180°. For each individual seed voxel within the temporal lobe GWI (approx. 3000), the number of streamlines originating from the seed which reached a given voxel in the brain was recorded, generating a tractographic connectivity profile for each temporal GWI seed voxel.