<u>Diffusion Imaging Methods in Language Sciences</u>

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ABSTRACT

The field of neuroanatomy of language is moving forward at a fast pace. This progression is partially due to the development of diffusion tractography, which has been used to describe white matter connections in the living human brain. For the field of neurolinguistics this advancement is timely and important for two reasons. First, it allows clinical researchers to liberate themselves from neuroanatomical models of language derived from animal studies. Second, for the first time, it offers the possibility of testing network correlates of neurolinguistic models directly in the human brain. This chapter introduces the reader to general principles of diffusion imaging and tractography. Examples of its applications, such as tract analysis, will be used to explicate its potentials and limitations.

Keywords: diffusion imaging, tractography, white matter, networks, arcuate fasciculus, frontal aslant tract, uncinated fasciculus, aphasia, language recovery, stroke.

INTRODUCTION

Neuronal correlates of language have been investigated employing various methods over the last two centuries. These include traditional post-mortem clinical-anatomical correlations (Broca, 1865; Wernicke, 1874), measurements derived from computer tomography (Naeser & Hayward, 1978; Yarnell, Monroe, &

Sobel, 1976) and magnetic resonance imaging (MRI) to quantify damage to cortical and subcortical anatomy (DeWitt, Grek, Buonanno, Levine, & Kistler, 1985), as well as functional quantities obtained from electro- and magnetoencephalography (Friederici, von Cramon, & Kotz, 1999; Hari & Lounasmaa, 1989; Salmelin, 2007; Tikofsky, Kooi, & Thomas, 1960), functional MRI (McCarthy, Blamire, Rothman, Gruetter, & Shulman, 1993), and tomography methods for brain hemodynamics, such as single photon emission computerised tomography (Perani, Vallar, Cappa, Messa, & Fazio, 1987) and positron emissions tomography (Cappa et al., 1997; Wise, Hadar, Howard, & Patterson, 1991). These methods, albeit complementary to each other in terms of spatial and temporal resolution, are insufficient to investigate the structural connections supporting distributed language processing in the human brain. They are indeed limited in describing the origin, course and termination of white matter networks connecting language areas. Additionally, they are unable to provide quantitative measures of tract anatomy to study, for example, structural asymmetry between the two hemispheres in the same subjects or across groups.

Understanding the anatomy of language networks and its variability in the healthy population and patients is a pivotal step in modern neurolinguistics. First, by looking at tracts we can reconcile data on patients who present with aphasia and 'atypical' lesion location {Catani:2012fa}. These patients often have lesions which are distant from regions dedicated to specific language functions. The classical example is represented by patients presenting with Broca's aphasia with retro-rolandic lesions sparing Broca's area (Basso, Lecours, Moraschini, & Vanier, 1985). Secondly, and most importantly, a network approach emphasises the parallel and integrated nature of the cognitive processes underlying language. This network approach is a fundamental evolution away from static and rigid localisationist models of brain function and helps to broaden the disconnectionist approach to a wider range of language disorders in neurology and psychiatry (Catani & ffytche, 2005).

In the last fifteen years, diffusion tractography, has become an established non-invasive quantitative method to study connectional anatomy in the living human brain. When applied to language, tractography has proven to be a powerful tool

to gain new insights into the functional anatomy of language. For example, tractography has indicated that networks for language and communication are more complex than previously anticipated (Catani & Bambini, 2014; Catani, Jones, & ffytche, 2005; Turken & Dronkers, 2011) and extend to areas and connections that were not included in the classical Broca-Wernicke-Geschwind model (Geschwind, 1965). This complexity heterogeneous amongst the healthy population, with striking differences between the male and female brain (Catani et al., 2007) and across ages (Budisavljevic et al., 2015; Lebel, Walker, Leemans, Phillips, & Beaulieu, 2008). These inter-individual differences are beginning to explain the observed variance in language performances amongst healthy controls (Catani et al., 2007; Lopez-Barroso et al., 2013) and in the recovery of language after stroke (Forkel et al., 2014).

In this chapter we will discuss the principles of diffusion imaging and tractography alongside examples of how this method has informed our understanding of language development, variance in language performances, and language disorders.

PRINCIPLES OF DIFFUSION TRACTOGRAPHY

The history of diffusion imaging and tractography spans about thirty years and can be broadly split into two halves. The first 15 years extent onwards from 1985, the year that the first diffusion weighted images of the brain were acquired, to 1999 when a handful of researchers proposed diffusion tractography as a method to study trajectories of white matter pathways in the living brain (Le Bihan et al., 1986; Conturo et al., 1999; Jones, Simmons, Williams, & Horsfield, 1999; Mori, Crain, Chacko, van Zijl, P. C., 1999). The second half (i.e., 2000 – 2015) has been characterised by a systematic application of diffusion methods, including tractography, to study the anatomy of connections in the healthy population and the impact of disorders to white matter organisation in patient cohorts. While novel methods for diffusion imaging are continuously proposed, here we focus on current mainstream methods which are widely employed.

Diffusion weighted imaging

Diffusion weighted imaging (DWI) is a non-invasive, in vivo MRI technique which quantifies water diffusion in biological tissues. In neuronal tissue, the displacement of water molecules is not random due to the presence of biological structures such as cell membranes, filaments, and nuclei. These structures reduce diffusion distances in the three-dimensional space. In the white matter, the overall displacement is reduced unevenly due to the presence of axonal membranes and myelin sheets which hinders water diffusion in a direction perpendicular to the axonal fibres. The water diffusion measured in a voxel can be described geometrically as an ellipsoid (the tensor) calculated from the diffusion coefficient values (eigenvalues, λ_{1-3}) and orientations (eigenvectors, ν_{1-3}) of its three principal axes (figure 1). A detailed analysis of the tensor can provide precise information about not only the average water molecular displacement within a voxel (e.g., mean diffusivity), but also the degree of tissue anisotropy (e.g., fractional anisotropy), and the main orientation of the underlying white matter pathways (e.g., principal eigenvector or colour-coded maps). These indices provide complementary information about the microstructural composition and architecture of brain tissue.

Mean diffusivity (MD) is a rotational invariant quantitative index that describes the average mobility of water molecules and is calculated from the three eigenvalues ($\lambda 1$, $\lambda 2$, $\lambda 3$) of the tensor (MD= [($\lambda 1$ + $\lambda 2$ + $\lambda 3$)/3]). Voxels containing grey and white matter tissue show similar MD values (Pierpaoli, Jezzard, Basser, Barnett, & Di Chiro, 1996). MD reduces with age within the first years of life and increases in those disorders characterised by demyelination, axonal injury, and oedema (Beaulieu, 2009).

The fractional anisotropy (FA) index ranges from 0 to 1 and represents a quantitative measure of the degree of anisotropy in biological tissue. High FA values indicate a more anisotropic, e.g. non-equal, diffusion (figure 1). In the healthy adult brain, FA varies between 0.2 (e.g., in grey matter) and \geq 0.8 in white matter. FA provides information about the organisation of the tissue within a voxel (e.g., strongly or weakly anisotropic) and the microarchitecture of the streamlines (e.g., parallel, crossing, kissing fibres). FA reduces in pathological tissue (e.g., demyelination, oedema) and is therefore commonly used as an indirect index of microstructural organisation.

Perpendicular $[(\lambda 2 + \lambda 3)/2]$ and parallel diffusivity ($\lambda 1$) describe the diffusivity along the principal directions of the diffusion. The perpendicular diffusivity, also indicated with the term radial diffusivity (RD), is generally considered a more sensitive index of axonal or myelin damage, although interpretation of their changes in regions with crossing fibres is not always straightforward (Dell'Acqua & Catani, 2012). The principal eigenvector and the red-green-blue (RGB) colour-coded maps are particularly useful to visualise the principal orientation of the tensor within each voxel (Pajevic & Pierpaoli, 1999; Figure 1).

Tractography-based reconstruction of white matter pathways

Compared to previously established methods for tracing fibre pathways, such as those used in animal axonal tracing studies, diffusion tensor tractography offers the unique advantage of being a completely non-invasive technique and therefore its use is not restricted to non-human primates but it can be applied to the living human brain. Furthermore, the data required to obtain tract reconstructions with tractography can be readily acquired on standard clinical MRI systems with scanning times typically ranging between 5–20 minutes. Recently, methodological advancements enable shorter acquisition times, which makes tractography a suitable tool for clinical populations, including children with developmental language disorders (Rimrodt, Peterson, Denckla, Kaufmann, & Cutting, 2010), adults with stroke (Forkel et al., 2014), and neurodegenerative disorders (Catani et al., 2013; D'Anna et al., 2016).

The main assumption underpinning diffusion tensor tractography is that the diffusion of water molecules can be described mathematically by a diffusion tensor whose principal axis aligns with the predominant orientation of the fibres contained within each voxel (Basser, Mattiello, & Le Bihan, 1994). Based on this assumption, the tractography algorithms permit to track white matter pathways by inferring continuity of fibre paths from voxel to voxel (figure 1). In simple terms, this process is achieved by following the direction of maximum diffusion from a given voxel into a neighbouring voxel (Basser, Pajevic, Pierpaoli, Duda, & Aldroubi, 2000; Conturo et al., 1999; Jones et al., 1999; Mori et al., 1999; Poupon et al., 2000). How to piece together discrete estimates of water diffusion

between contiguous voxels depends on the algorithm used and the choice of some tracking and stopping parameters. Most tractography algorithms adopt angular and FA thresholds to avoid unrealistic fibre bending or tracking outside white matter regions.

Diffusion tractography can be used to generate indirect measures of tract volume and microstructural properties of fibres. Common measures of tract volume are the overall number of streamlines that compose a single tract or the total volume of voxels intersected by those streamlines (Dell'Acqua & Catani, 2012). Tractography-derived inter-hemispheric differences in tract volume are widely reported in the literature, especially for language pathways (Catani et al., 2007), although their exact interpretation is not straightforward. Histological properties that are likely to determine larger tract volumes are increased axonal diameter and myelination, high axonal density and fibre dispersion, presence of fibre crossing and branching.

In addition to tract volume, for each voxel intersected by streamlines, other diffusion indices can be extracted and the total average can be extrapolated from these. Examples include the fractional anisotropy, mean diffusivity, parallel and radial diffusivity. These can provide important information on the microstructural properties of fibres and their organisation. Asymmetry in fractional anisotropy, for example, could indicate differences in the axonal anatomy (intraxonal composition, axon diameter, and membrane permeability), fibre myelination (myelin density, internodal distance, and myelin distribution) or fibre arrangement and morphology (axonal dispersion, axonal crossing, and axonal branching) (Beaulieu, 2002; Concha, 2014). Other diffusion measurements may reveal more specific fibre properties. Changes in axial diffusivity measurements, for example, could be related to intraxonal composition, while radial diffusivity may be more sensitive to changes in membrane permeability and myelin density (Song et al., 2002). These in vivo diffusion-based measurements allow connectional anatomy to be defined at different scales during development and in the adult brain.

TRACTOGRAPHY-BASED MODELS OF LANGUAGE NETWORKS

In the past 15 years, tractography has greatly contributed to contemporary revisions of anatomical models of language networks. New connections, which were not previously described in animal models, have been identified by tractography (Figure 2) {Catani:2005bf}{Lawes:2008cg}{Catani:2012eq}.

In general, tractography identified two sets of white matter connections for language and social communication: a *core network* encompassing classical perisylvian language regions, and an *extended network* connecting perisylvian regions to other cortical and subcortical hubs (Catani & Bambini, 2014; Catani & Mesulam, 2008). The paragraphs that follow do not represent a comprehensive account of the literature on the tracts forming the core and extended language networks but are intended to provide examples of how tractography has been used to address specific research topics in healthy cohorts and in patients with language disorders.

The core language network

The *arcuate fasciculus* is a dorsal perisylvian tract connecting Wernicke's region in the posterior temporal lobe to Broca's region in the inferior frontal lobe (figure 2A). Early tractography studies have shown that the classical Wernicke-Broca arcuate model was an oversimplification of the real anatomy (Catani et al., 2005, figure 2B). Indeed, two parallel pathways within the arcuate fasciculus have been identified: the medial, direct pathway connecting Wernicke's with Broca's region (i.e. the arcuate fasciculus *sensu strictu* or long segment), and the indirect pathway consisting of an anterior segment linking Broca's to Geschwind's region (encompassing the angular and supramarginal gyrus in the inferior parietal lobe) and a posterior segment between Geschwind's and Wernicke's region. There is evidence that this anatomical division has also important functional implications (Catani & Mesulam, 2008).

The ability to correlate structural properties of individual segments with performance in specific language tasks allows for the identification of distinct functional correlates for the direct and indirect arcuate pathways. Lopez-Barroso et al. (2013) demonstrated that performance in word learning correlates with microstructural properties (as measured with DTI) and strength of

functional connectivity (as measured with fMRI) of the direct segment (López-Barroso et al., 2013). In addition, the long segment tends to myelinate later in childhood and its maturation is associated with the acquisition of syntactic abilities (Brauer, Anwander, Perani, & Friederici, 2013). These studies indicate that our ability to learn new words and develop syntax relies on an efficient and fast communication between auditory temporal and motor frontal regions. The presence of a less prominent long segment in non-human primates might explain our linguistic specialisation (López-Barroso et al., 2013; Thiebaut de Schotten, Dell'Acqua, Valabregue, & Catani, 2012).

While the direct pathway may support auditory-motor integration, which is crucial during early stages of language acquisition, the role of the indirect pathway and the Geschwind's region could be more complex and related to linking semantic and phonological processes (Newhart et al., 2012) for tasks that require verbal working memory to understand complex sentences (Jacquemot & Scott, 2006). In addition, the temporo-parietal regions connected by the posterior segment activate in tasks for the comprehension of ambiguous sentences (e.g. garden-path paradigms) {denOuden:2016hl}, metaphors (Bambini, Gentili, Ricciardi, Bertinetto, & Pietrini, 2011) and indirect speech acts (Bašnáková, Weber, Petersson, van Berkum, & Hagoort, 2014), as well as for tasks that involve the representation of discourse and the protagonist's perspective in narratives (Mason & Just, 2009). These studies suggest that the posterior network supports complex integration and inferential mechanisms that reach several layers of meta-representations for the attribution of beliefs and emotional states to conversational partners (Catani & Bambini, 2014).

Among all tracts of the human brain, the arcuate fasciculus displays the greatest degree of inter-hemispheric and inter-individual asymmetry. By extracting volumetric measurements of the three segments of the arcuate fasciculus, it was possible to demonstrate that the long segment is strongly left lateralised in 60% of the population, whereas the remaining 40% show a bilateral pattern. The bilateral pattern seems to be more prevalent among the female population (60%) as compared to males (15%). Moreover, the pattern of asymmetry correlated with performances on the California verbal Learning test (CVLT), a verbal memory

task that relies on semantic clustering for word retrieval; the correlation indicated that a more bilateral representation was advantageous for the retrieval of word lists (Catani et al., 2007). A better understanding of the pattern of asymmetry of the long segment has important implications. First, it offers a neuroanatomical explanation the evidentially observed for superior performances of females over males on verbal learning tasks (Kramer, Delis, & Daniel, 1988). Second, the high variability of asymmetry in the general population can help to identify different trajectories to language recovery in patients with aphasia after left hemisphere stroke. This was demonstrated employing tractography in a longitudinal study of aphasia recovery in which the volumetric measurements of the of the long segment in the right hemisphere were predicative of aphasia recovery six months after stroke (Forkel et al., 2014). Tractography measurements of the volume of the right long segment improved the predictive value for recovery above and beyond models accounting for demographics by explaining up to 57% of the observed variance in recovery at six-months post symptom onset.

The extended language network

The extended language network is composed of several tracts, including the uncinate fasciculus, the frontal aslant tract and the fronto-insular tracts (figure 2C).

The *uncinate fasciculus*, which connects the anterior temporal lobe to the orbitofrontal region and part of the inferior frontal gyrus (Catani, Howard, Pajevic, & Jones, 2002) is classically considered as a major pathway of the limbic system (Catani, Dell'Acqua, & Thiebaut de Schotten, 2013). In addition to its role in emotion processing and behaviour, the uncinate fasciculus has been associated with tasks involving lexical retrieval, semantic association, and naming (Heide, Skipper, Klobusicky, & Olson, 2013). The uncinate fasciculus is severely damaged in patients with the semantic variant of primary progressive aphasia and the severity of its degeneration correlates with scores on tests for naming and single word comprehension (Catani et al., 2013).

The *frontal aslant tract* is a recently described pathway connecting Broca's region with dorsal medial frontal areas including the pre-supplementary motor area and cingulate cortex (Catani et al., 2012; Ford, McGregor, Case, Crosson, & White, 2010; Lawes et al., 2008). Medial regions of the frontal lobe facilitate speech initiation through direct connection to the pars opercularis and triangularis of the inferior frontal gyrus. Patients with lesions to these areas present with various degrees of speech impairment from a total inability to initiate speech (i.e. mutism) to mildly altered fluency. The frontal aslant tract is damaged in patients with the non-fluent/agrammatic form of primary progressive aphasia (Catani et al., 2013; Mandelli et al., 2014).

The frontal operculum is connected to the insula through a system of short U-shaped *fronto-insular tracts* (Catani et al., 2012). Direct insular inputs to Broca's region from the insula provide visceral and emotional information for speech output modulation according to internal states. Lesions to these insular connections may result in motor aprosodia (e.g. flat intonation) in the right hemisphere {Witteman:2014ba}, while in the left hemisphere it may be associated to apraxia of speech (Dronkers, 1996).

Limitations and future directions

The advent of diffusion tractography signified a fundamental advancement of our understanding of networks underlying language functions. The ability of tracking connections in the living human brain offers the possibility to move above and beyond network models based on axonal tracing in monkeys. Despite the obvious advantages, tractography has several limitations, some of which will be briefly discussed below.

Compared to classical axonal tracing studies, tractography is unable to differentiate anterograde and retrograde connections, detect the presence of synapses, or determine whether a pathway is functional. In addition, whilst injected tracers are able to follow the termination of single axons, tractography follows the principal axis of the diffusion tensor, which is obtained by averaging the MRI signal within a voxel. Typically, the voxel resolution is too low to identify small fibre bundles. Also the level of noise in the diffusion data and the intrinsic

MRI artefacts constitute important factors that affect the precision and accuracy of the diffusion measurements and as a consequence the quality of the tractography reconstruction (Basser et al., 2000; LeBihan et al., 2006). Finally, diffusion tensor tractography assumes that fibres in each voxel are well described by a single orientation estimate, which is a valid assumption for voxels containing only one population of fibres with a similar orientation. The majority of white matter voxels, however, contain populations of fibres with multiple orientations; in these regions fibers cross, kiss, merge, or diverge and the tensor model is inadequate to capture this anatomical complexity. More recent tractography developments based on HARDI (high angular resolution diffusion imaging) methods (Frank, 2001; Dell'Acqua, 2010) and appropriate processing techniques are able to partially resolve fibre crossings (Tournier et al., 2004; Tuch, 2004; Wedeen et al., 2005; Alexander, 2005; Behrens et al., 2007). Among the HARDI methods, Spherical deconvolution algorithms (figure 3), have been used to dissect white matter pathways in regions with multiple fibre orientations, such as in the triangle between the corpus callosum, the superior longitudinal fasciculi, and the cortico-spinal tract (Thiebaut de Schotten et al., 2011).

All these limitations may lead to tracking pathways that do not exist (false positive) or fail to track those that do exist (false negative). A few studies have so far dealt with the issue of validating the tractography results with neuronal tracers (Dauguet et al., 2007; Dyrby et al., 2007) or performing reproducibility analysis on human subjects using post-mortem blunt dissections or diffusion datasets acquired at high resolution (Heiervang, et al., 2006; Lawes et al., 2008; Wakana et al., 2007).

It is evident from all the considerations above that interpretation of tractography results requires experience and a priori anatomical knowledge. This is particularly true in the diseased brain where alteration and anatomic distortion due to the presence of pathology, such as brain oedema, haemorrhage, and compression, generates tissue changes likely to lead to a greater number of artefactual reconstructions (Catani, 2006; Ciccarelli, Catani, Johansen-Berg, Clark, & Thompson, 2008). Despite the above limitations tractography is the only technique that permits a quantitative assessment of

white matter tracts in the living human brain. The recent development of MRI scanners with stronger gradients and multi-band acquisition sequences represents one of many steps towards a significant amelioration of the diffusion tractography approach. The possibility of combining tractography with other imaging modalities will provide a complete picture of the functional anatomy of human language pathways.

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Figure Legends

Figure 1. The principle of Diffusion Tensor Imaging (DTI) Tractography.

- A) Visualisation of the diffusion tensor as an ellipsoid. The size and the shape or the tensor are defined by the three eigenvalues ($\lambda 1$, $\lambda 2$, $\lambda 3$ in red) while the spatial orientation is described by the three eigenvectors (v1, v2, v3 in blue).
- B) In biological tissues, the tensor can vary between three possible configurations: i) isotropy (equal diffusivity along the three eigenvalues) is commonly observed, for example, in the grey matter; ii) planar anisotropy is common in voxels containing, for example, two groups of crossing or diverging fibres; iii) axial anisotropy is typical of voxels containing parallel fibres (unequal diffusivity along all eigenvalues). C) Exemplified indices extracted from diffusion data, such as mean diffusivity (MD), fractional anisotropy (FA), principle eigenvector, and colour-coded FA maps. Streamline tractography is based on the assumption that in each white matter voxel the principal eigenvector (red arrows) is tangent to the main trajectory of the underlying fibres (black). Starting from a region of interest (blue circle) the tractography algorithm propagates, voxel by voxel, a streamline (blue) by piecing together neighbouring principal eigenvectors (in this example v1 and so on). This voxel-wise tensor estimation can be visualised in a eigenvector map and streamlines (blue) can be virtually reconstructed. An example is shown in the neighbouring panel where the

streamlines are tracked on a principle eigenvector map with the tractography reconstruction of the streamlines visualised as 3D tubes (arcuate fasciculus) on the right.

Figure 2. The language network

A) Classical language model with the arcuate fasciculus connecting Broca's area in the inferior frontal gyrus and Wernicke's area in the superior temporal gyrus. B) Extension of the classical arcuate fasciculus sense strictu to include the anterior segment, connecting inferior frontal to inferior parietal lobe, and the posterior segment linking the inferior parietal and the temporal lobes. C) Current model of an extended language network beyond the three segments of the arcuate fasciculus. The frontal aslant tract (FAT) connects the inferior frontal gyrus to the supplementary motor cortex. The ventral network includes the uncinated fasciculus between the anterior temporal lobe and the orbital frontal cortex, the longitudinal intratemporal fasciculus (LIT) between the anterior temporal and posterior superior temporal gyrus, the inferior fronto-occipital fasciculus (iFOF) connecting the ventral frontal cortex to the occipital cortex, and the inferior longitudinal fasciculus (ILF) between the occipital and ventral temporal cortex.

Figure 3. Advanced Diffusion Tractography exemplified: Spherical Deconvolution

A) Reconstruction of two crossing fibres in a voxel with different crossing angles (50°, 70°, and 90°) using Diffusion tensor imaging (DTI) and spherical deconvolution (SD, here shown under fibre response). Spherical deconvolution can better differentiate between two fibre populations where the tensor model reconstructs the average orientation within a voxel. B) Eigenvector map visualisation of the white matter organisation of the corpus callosum and the corona radiata based on the tensor model (left) and fibre response map of spherical deconvolution (right). In voxels with one fibre population, such as the

corpus callosum (red arrow), both models describe orientations that are consistent with the known anatomy. However, in regions with more than one population of crossing fibres (yellow arrow), the tensor model gives an average representation of the water diffusion, whereas the spherical deconvolution model separates different fibre components and describes their individual orientations. C) Virtual dissections of the corpus callosum based on diffusion tensor tractography (top panel) reconstruct only the most central part of the callosum (red), while spherical deconvolution (bottom panel) tractography shows several streamlines of the corpus callosum that cross the streamlines of the corticospinal tract (yellow) and reach the lateral cortex. Mapping diffusion indices along crossing white matter tracts. The arcuate fasciculus and the lateral projections of the corpus callosum cross at the level of the corona radiata. The hindrance modulated orientational anisotropy (HMOA) index, which is unique to spherical deconvolution tractography, shows distinct diffusion characteristics for the two crossing tracts, lower HMOA for the callosal projections and higher HMOA for the arcuate fibres. DTI FA measurements on the other hand are voxel-specific rather than tract-specific and would only indicate on overall reduction in FA within a given voxel.





