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Education

Extending the frontiers of neuroimaging: an introduction to Diffusion Tensor Imaging Tractography

EDUCATION

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ABSTRACT

Summary:

The use of Diffusion Tensor Imaging (DTI) tractography has exploded over the past two decades, proving to be a major advancement in the current methods for exploring the architecture of white matter tracts in the living human brain. Despite making up 50% of brain tissue, investigations into the function of white matter have long remained in the background of medical research. Consequently, white matter pathology cited in neuropsychiatric disease remains a heavy burden of human illness. Nonetheless, with novel diffusion MRI techniques, including DTI tractography, we are able to visualise areas of the brain better than ever before, furthering our understanding of white matter beyond the crude depictions offered by conventional MRI.

Relevance:

It is important that medical students have an understanding of DTI tractography because it has the potential to illuminate mechanisms that underpin cognition and emotion through the creation of connectional maps. Furthermore, advances in MR technology should not be restricted to the territory of academics. Instead, both medical students and clinicians should be able to draw upon the current research methods to improve the care and understanding of patients with white matter pathology.

Take-Home Messages:

1. Diffusion Tensor Imaging is a diffusion MRI technique that depicts the movement of water molecules along major white matter pathways in the living brain
2. Using information from DTI, tractography software virtually reconstructs white matter tracts and can be used to make dissections of major fasciculi in vivo.
3. DTI tractography remains the only non-invasive method to study white matter tracts in the living human brain
4. Results from tractography are increasingly being used in neuropsychiatric research
5. Despite its potential, DTI tractography still faces a number of challenges. The most prominent of these being its inability to accurately map crossing fibres within a voxel.

Neuroanatomists have worked to delineate the architecture of the human brain from as early as the 19th century. (1) Such techniques have ranged from classical studies of histological sections and post-mortem dissections, to the use of peroxide tracers that can be actively transported along axons. (2,3) Nonetheless, Diffusion Tensor Imaging (DTI) tractography, (4-7) a novel neuroimaging technique developed in the early 1990s, remains the only non-invasive method for exploring white matter connections in the living human brain. (8, 9)

Advances in Neuroimaging

Owing to recent advances in technology, clinicians now have access to an array of neuroimaging techniques that can explore brain structure. One of the earliest examples of this is computed tomography (CT). CT uses X-rays to visualise gross structures in the head such as bone and soft tissue. Whilst indispensable in emergency settings, CT is increasingly being replaced by magnetic resonance imaging (MRI). Unlike other scanning techniques, MRI is able to create contrast between soft tissue, allowing the naked eye to distinguish between white and grey matter. DTI is an MRI-based neuroimaging technique developed specifically to visualise myelinated tracts and macroscopic connectivity of the brain.

How does DTI work?

In order to understand DTI, its first important to know the basics of diffusion and how it varies across biological tissue.

In simple liquids and some homogenous solid materials water molecules are free to move equally in all directions. This is known as isotropic diffusion and is represented in figure 1.

However, due to the structure of axons, diffusion in the white matter of the brain is anisotropic, meaning the direction of diffusion is unequal. As the myelin surrounding axons is relatively impermeable to water, we can assume it acts as a barrier to diffusion. Therefore, whilst water is able to diffuse at high rates along the long axis of axons through the cytoplasm, diffusion perpendicular to the long axis is restricted. This is demonstrated in figure 1.

Diffusion Tensor Imaging works by tracing the motion of water molecules along axons; therefore the scanner is able to pick up diffusion in one direction. This is called setting a diffusion gradient. (10)

In 1994, Basser et al. (11) demonstrated that by utilising multiple diffusion gradients, DTI can be used to compute the principal 3D trajectory of white matter fibres in each MR voxel - known as a diffusion tensor. The diffusion tensor made it possible to display the orientation of major fasciculi in vivo (1) and a number of methods have since been developed to achieve this. (12-16) Colour coded 2D images produced in conjunction with priori knowledge of white matter anatomy have been favoured to detail the orientations of major white matter tracts (see figure 1.1).

Tractography Methods

Whilst novel, the poor visualisation of tracts in DTI led to the development of fiber tractography. Using tractography software, such as ExploreDTI (17), alongside the information obtained in Diffusion MRI, it is possible to employ algorithms that virtually reconstruct the 3D trajectories of neuronal fibre pathways in vivo. (18) These trajectories are often referred to as '*streamlines*.' (See figure 1.2)

There are currently two major classes of algorithms used in tractography. The first class, known as deterministic algorithms, (7,19,20) work on the assumption that the principal direction or eigenvector (PEV) of the diffusion tensor is parallel to the direction of most fibres running within a voxel. In this method, a number of seed points (starting voxels) are placed within the brain and the PEV is measured. Deterministic algorithms are then used to calculate how closely the orientations of neighboring voxels match the seed. Voxels with similar PEVs to the seed are subsequently connected bidirectionally to form streamlines.

Whilst deterministic algorithms have been shown to produce major reconstructions faithful to classic neuroanatomy; (1, 21, 22) this mode of tracking remains susceptible to false positives and often fails to account for branching fasciculi.

To overcome these limitations, a second class of probabilistic algorithms have since been developed for use in tractography. (23-26) Instead of relying upon the PEV, probabilistic tracking applies an orientation density function (ODF). This calculates the probability of multiple fibre pathways projecting from the seed points and again at each step along reconstructed streamlines. Not only does a probabilistic approach account for branching fasciculi but it is also able to quantify the confidence of each reconstructed pathway. (8) An example of streamlines produced by probabilistic tracking is shown in figure 1.2.

Potential clinical applications of DTI tractography

DTI has generated enormous research interest due to its ability to evaluate pathological changes in brain tissue. For example, diffusion MRI has been identified as a promising biomarker in neurodegenerative conditions such as Alzheimer's disease (AD). AD is defined by widespread cognitive impairments including

executive function failure, emotional instability and psychosis. (27) A longitudinal study (28) comparing imaging data of AD patients with controls showed that anisotropic diffusion was significantly reduced in those with AD. This was also associated with disease progression. Therefore, DTI not only has the potential to aid pre-symptomatic detection of AD, but it may also help to differentiate between mild cognitive impairment and early signs of AD. (29)

Another example of its potential use is in patients with Multiple Sclerosis (MS). Similar to AD, MS lesions are associated with reduced anisotropic diffusion. Some studies have therefore suggested that DTI can be used as a biomarker of disease activity in MS and will further enable clinicians to monitor disease progression. (27)

The challenges facing DTI tractography: Mapping the Superior Longitudinal Fasciculus

Despite its potential, DTI tractography still has a number of significant limitations. These become apparent when reconstructing complex association fibre bundles such as the superior longitudinal fasciculus (SLF). Thought to be involved in important cognitive processes such as attention, memory and language; the SLF has posed a particular challenge to researchers using tractography and this is reflected in the medical literature. For example, studies describing its cortical connections are often confusing or contradictory. (9, 30-32) As DTI has conventionally used a single tensor of diffusion per voxel, it is therefore unable to account for multiple fibres crossing or diverging within a voxel. (33) This becomes a major problem when mapping the SLF.

We know from classical post mortem studies that the SLF intersects the fronto-occipital fasciculus at the level of the frontal operculum. (34) As a result, dissections are often inaccurate as crossing fibres artificially deviate reconstructed trajectories towards closer endpoints. (35) Furthermore, DTI-tractography is not yet sensitive enough to distinguish between separate fascicles in areas where tracts run parallel, resulting in numerous false positives. Running closely alongside both the optic radiations and the inferior fronto-occipital fasciculus, (1,34) the SLF again offers an important example of this.

Ultimately the inability of tractography to map complex white matter pathways, such as the SLF, call into question whether tractograms reflect true neuroanatomy, let alone their use as a tool for quantitative analysis.

Conclusion: The future of DTI tractography

Albeit, more research is needed to overcome the shortcomings of tractography, it is undeniable that Diffusion MRI has the potential to revolutionise the way in which we study white matter. In particular, a number of studies have highlighted its promise as a biomarker in neurodegenerative disease. Ultimately, this can help pave the way for new, much needed treatments and improved patient care.

Figures

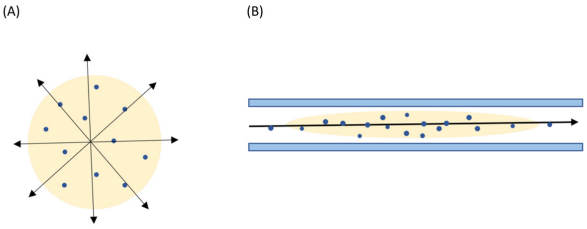

Figure 1: (A) Showing isotropic diffusion. As there are no barriers, water molecules are free to diffuse in all directions. Diffusion in the CSF and grey matter is primarily isotropic. (B) Showing anisotropic diffusion. The myelin sheath surrounding axons acts as a biological barrier to diffusion. Diagram based on Wilde et al. 2017.

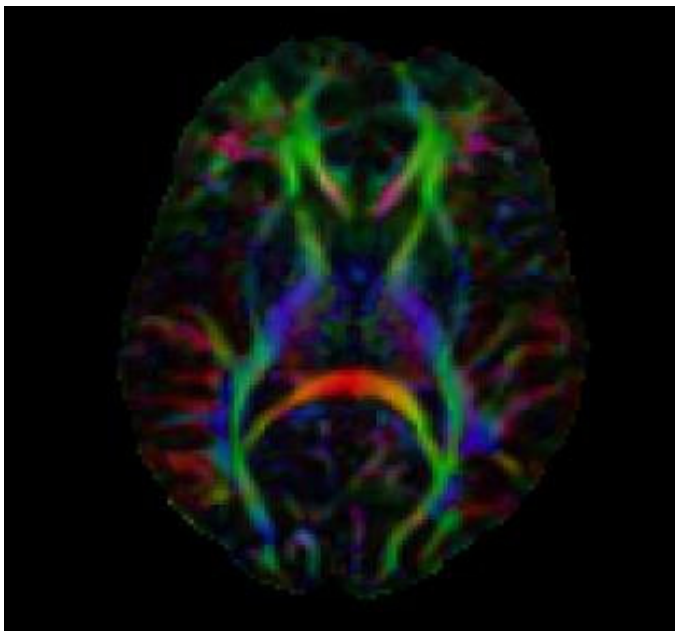

Figure 1.1: showing a Diffusion Tensor. It is colour coded to show the principal direction of white matter tracts. Red represents left to right, blue shows cranial to caudal and green depicts tracts running anterior to posterior. Data courtesy of the University Medical Centre Utrecht Explore DTI Workshop.

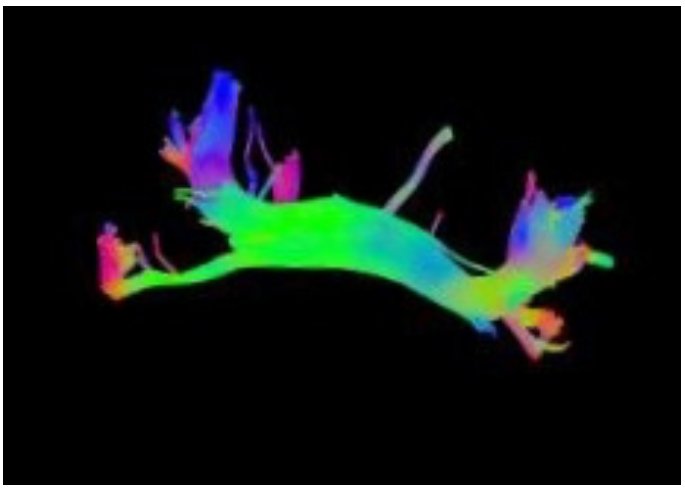

Figure 1.2: showing a reconstruction of the SLF 1 using probabilistic tractography. Data courtesy of the University Medical Centre Utrecht Explore DTI Workshop.

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