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Diffusion MRI of Human Brain: Key Points and Innovations

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Diffusion MRI of Human Brain: Key Points and Innovations

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Abstract- **MRI-based investigations represent, to date, very powerful approaches for the study of the brain. One set of tools, provided by diffusion MRI, allows the non-invasive analysis of structural aspects of gray and white matter, by analyzing how water molecules diffuse within the brain. Although number of clinical studies employing diffusion MRI has grown in last years, some aspects still result poorly known or poorly understood by unfamiliar researchers and clinicians, due to their technical complexity. The main goal of the present work is to resume the main landmarks of diffusion MRI investigation and to show the current state as well as future perspectives of related methodologies.**

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I. Introduction

Diffusion MRI (dMRI) represents nowadays a powerful tool for the non-invasive investigation of the brain. It allows to perform both qualitative and quantitative evaluation of brain features as well as of its alterations, with particular regards to white matter ones. All diffusion-based techniques are dedicated to the analysis of signals provided by the diffusion process of water molecules within brain tissues. Goal of this manuscript is two-fold: firstly, we want to provide a summary of the state of the art for researchers unfamiliar with dMRI models and related techniques; secondly, we want to address some of future perspectives in the field.

II. Diffusion Models

Diffusion models consist in a set of algorithms attempting to estimate how water molecules diffuse within each voxel (imaging unit). The mostly known model is diffusion tensor, which is the basis of Diffusion Tensor Imaging (DTI) (Basser et al., 2000); however a cohort of other models which overperform DTI have been developed over the years, such as Q-ball imaging (QBI) (Tuch, 2004), Diffusion Spectrum Imaging (Wedeen et al., 2008), Constrained Spherical Deconvolution (CSD) (Tournier et al., 2007), multi-compartments models (see for instance Panagiotaki et al., 2012). All above mentioned techniques return back a geometrical object (e.g. the tensor for DTI) which encodes diffusion process for each analyzed voxel; the sensitivity as well as the type of information which can be extracted from such objects vary according to the algorithm/model used. Based on these objects, qualitative and quantitative analyses can be performed.

a) Qualitative analysis

One of the most explored applications of diffusion MRI is tractography (Soares et al., 2013), i.e. the reconstruction of the path followed by a given white matter bundle. This can be achieved by means of both deterministic (one direction assigned for each voxel) and probabilistic (the most probable path obtained after a given number of attempts) tractographic algorithms (Soares et al., 2013; Behrens et al., 2007). Tractography reconstruction outcomes strongly rely on the underlying diffusion model used In this context, several issues can affect the reliability of tractographic results, e.g. the presence of voxels with multiple fiber directions (Farquharson et al., 2013). DTI cannot handle multiple fiber directions, as it can only provide a unique diffusion direction. This is the reason why other more advanced approaches outperform DTI based tractography, like CSD (Tournier et al., 2008; Farquharson et al., 2013). An exemplificative case showing how tractographic output can be different according to the model used, namely DTI and CSD, is shown in Figure 1, where corticospinal tract and optic radiations were reconstructed with both methods.

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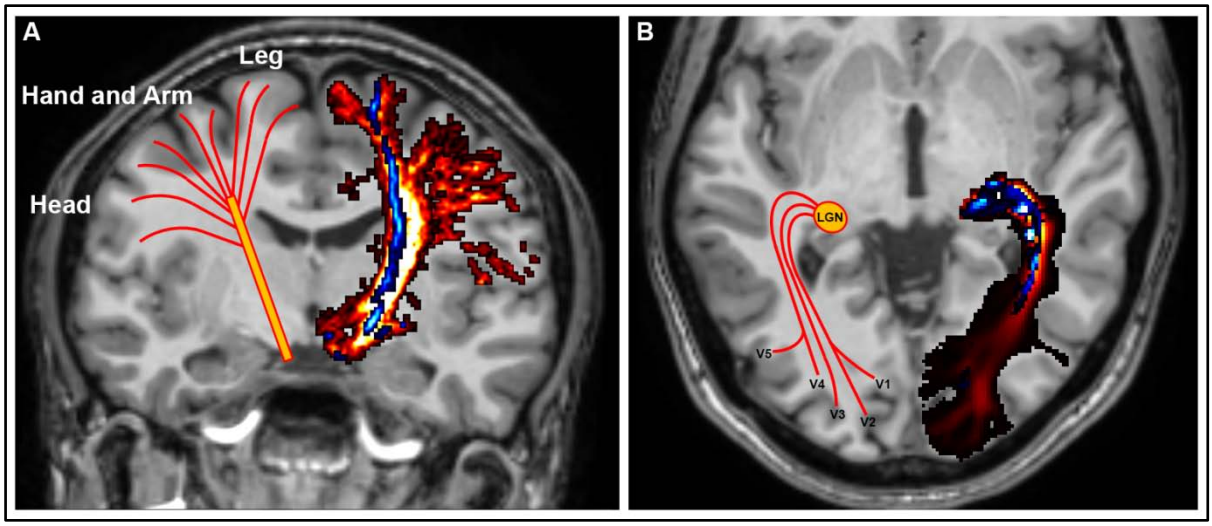

Figure 1 : Tractography of left corticospinal tract (A) and left optic radiations (B). Reconstructions of these two eloquent white matter bundles were obtained by means of probabilistic CSD model (red) and DTI one (blue), which were overlapped in order to show qualitative differences. On the right side, the schematic representation of anatomical features of these bundles, as well as their end points in the cortex, are shown.

b) Quantitative analysis

From each diffusion model a number of useful features can be extracted in a given voxel. Those features can be used to quantify WM and perform investigation both in normal and pathological conditions. It is important to clarify that nature and validity of features extracted depend on a number of factors, e.g. quality of scans used. Here we want however to keep focus on what different diffusion model can offer. If based on tensor model, quantitative analysis can provide information regarding how much anisotropic is the signal within a voxel, through a number of parameters among which fractional anisotropy (FA) and mean diffusivity (MD) are the most used (Soares et al., 2013). Those measures have been considered indirect measures of axonal integrity (Alexander et al., 2007; Soares et al., 2013). Due to the ability of other models to better reconstruct WM bundles, it was suggested to sample tensor features on voxels reached by tractographic reconstructions obtained by other methods, like CSD (Mormina et al., 2014; Arrigo et al., 2014; Mormina et al., 2015; Arrigo et al., 2015; Arrigo et al., 2016).

FA measures level of anisotropy in the voxel: the higher this number, the higher the probability that a single predominant fiber direction is appearing in that voxel. It has to be noticed however that (Jeurissen et al., 2013), if we were to compare FA values obtained by averaging within voxels sampled by means ofCSD-based tractographic reconstruction with the same average performed on the basis of DTI tractography, we would observe a FA reduction. This happens because, with CSD, voxels with multiple dominant fiber directions are involved; as result, water diffusion anisotropy is spread across different directions, and tensor model is able to fit an overall anisotropy decreasing. Due to the huge number of voxels showing this behavior in WM (Jeurissen et al, 2013), new features were developed to the better describe diffusion models. As an example, based on CSD, Apparent Fiber Density (AFD) (Raffelt et al., 2012), was developed to measure contribute of each dominant direction. Figure 2 illustrates the situation.

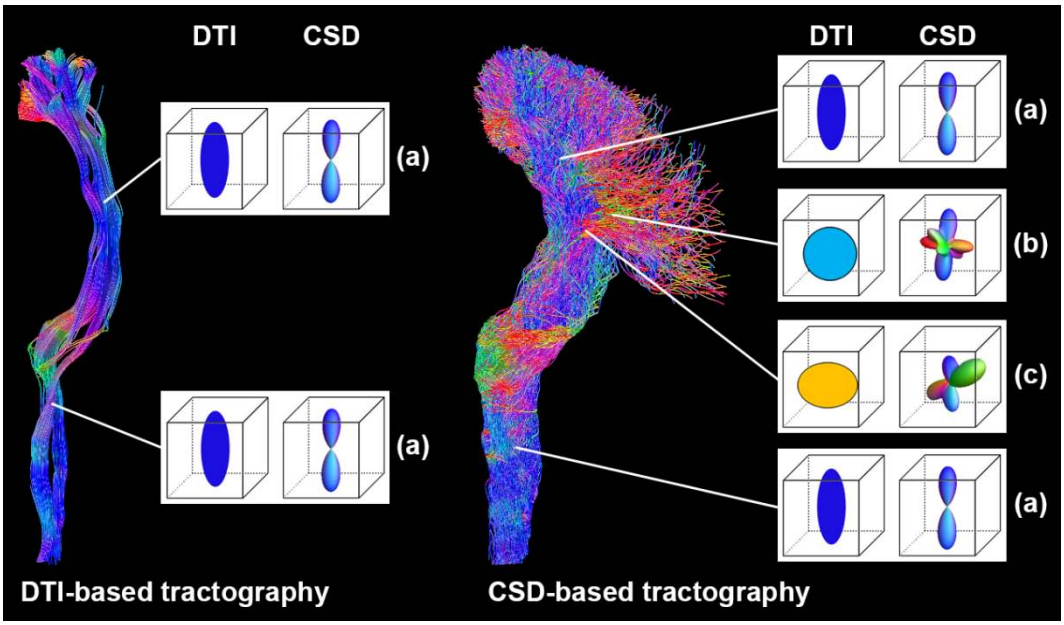

Figure 2 : Tractography of the left corticospinal tract obtained by means of DTI and CSD models. Some exemplificative voxels showed differences regarding calculation of diffusion signals, if using tensor model or CSD, in the following cases: monodirectional (a), multidirectional (b) and crossing fibers (c) voxels. The presence of (b) and (c) affects tensor model, thus causing poor qualitative reconstruction. Moreover, also quantitative analysis is affected, since only voxels with a well-represented principal direction are considered.

III. Limitations, Validations and Future Perspectives

Diffusion MRI results, particularly tractography, are often criticized due to a number of limitations potentially affecting outputs. Moving beyond the intrinsic limitation represented by the impossibility to discriminate directionality of afferent or efferent signal transmission (Parker et al. 2013; Chung et al. 2011), as previously described, tractographic output strongly depends on the algorithm used for diffusion signal modelling (Farquharson et al., 2013).Several inaccuracies caused by possible artefactual effects as well as false positive tracts should be also taken into account (Jones and Cercignani, 2010). Furthermore, since tractography represents the reconstruction of white matter paths provided by a mathematical computation (deterministic or probabilistic), it is often criticized by declaring that dissection is preferable due to its ability to definitely assess the real existence of a given connection. However, a number of studies have validated DTI tractographic output through histological investigations (Seehaus et al., 2013; Gao et al., 2013; Seehaus et al., 2015). The adoption of more advanced algorithms have allowed a better detection of white matter bundles; those techniques have obtained histological validations as well (Dirby et al., 2007; Azadbakht et al., 2015). Recently, in vivo neurite orientation dispersion and density imaging (NODDI) (Zhang et al., 2012) was proposed: this technique allows a multi-compartmental analysis of the brain, i.e. separately considering glial, axonal and extracellular components, thus restituting a detailed profile of brain microstructure. Although technical requirement are not easily reachable, this represents a promising investigative technique for a deeper study of the brain both in healthy and pathological conditions.

Interesting future perspectives will be to make more feasible these innovative approaches for clinical settings as well as to integrate them with other investigative techniques, such as electrophysiology and transcranial magnetic stimulation.

IV. Conclusion

In this paper the main key points of diffusion MRI investigations have been neatly described. We wanted to provide a brief and simplified description of the complex methodological aspects, in order to offer necessary pills for better understanding diffusion-based studies.

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