

# Diffusion Tensor Imaging to Study Brain Connectivity

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## Introduction

MRI has been a powerful tool to map anatomy and function of human brains. To assign functions of the cortex, fMRI has been playing important roles. Classically, anatomy – function correlation studies had relied on postmortem examination of patients with localized lesions. Now we have a tool to non-invasively investigate functional centers of the brain.

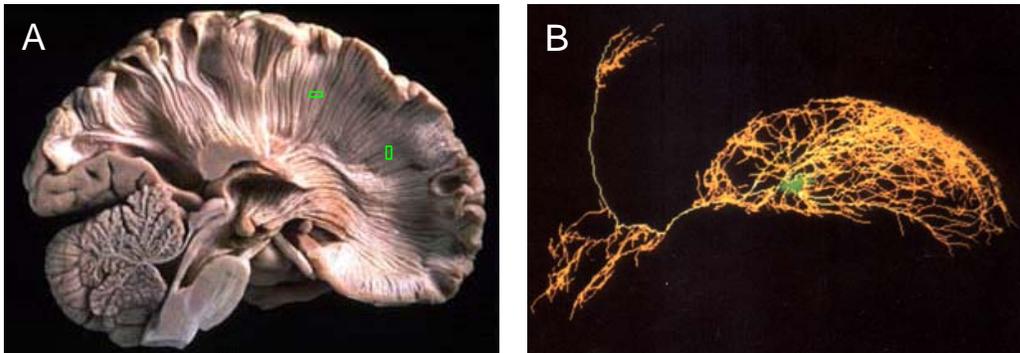
Compared to the cortical mapping, white matter mapping has been a challenging target. The white matter plays an important role to connect different regions of the brain. To understand brain functions, it is essential to understand brain connectivity. Interestingly, our understanding about brain connectivity is quite limited. One of the reasons could be its sheer complexity. In addition, we haven't had good tools to investigate brain connectivity either. All existing methods are based on invasive techniques, which can't be applied to human.

In addition to our scarce knowledge about the brain connectivity, conventional MRI has also been powerless in this front. In T1 and T2-weighted images, most white matter regions look homogeneous. This situation has changed since the introduction of diffusion imaging and diffusion tensor imaging (DTI) in '90s. (1-3) This technology can provide us with approximate orientations of axonal tracts within each pixel. (3-8) It has been also shown that trajectories of prominent white tracts can be three-dimensionally reconstructed based on DTI results. (9-16) There is a possibility that we can obtain much needed information about human brain connectivity. By combining with fMRI data, we can ask questions like, "how two fMRI-activated regions are connected?" Although this is a quite exciting technique, it is also becoming increasingly clear that great care is needed to interpret DTI and DTI-based tractography results. (17, 18) In this course, I would like to go over limitations of DTI technique and various techniques to study brain connectivity.

## Limitations of DTI

First of all, it is important to define what we mean by "connectivity". We are tempted to think that tractography results reveal cell-level neural connectivity, but what it gives us is not axonal connectivity, but the macroscopic anatomy of the white matter. In Fig. 1A, 1x3 mm boxes are placed on a postmortem specimen. This size of probe could delineate overall configuration of the white matter anatomy seen in Fig. 1A. In Fig. 1B, a result of single-neuron reconstruction in a rat hippocampus is shown. There are two important facts in this figure. First, with the current level of image resolution, it is impossible to reveal the single-cell level connectivity. Second, even if we could reconstruct the entire neuron, "connectivity" is not as simple as connecting two points.

Neurons have a dendrite network to communicate with nearby neurons. They have axons to communicate distant neurons, which could have many branches. If biological questions require information about the cell-to-cell level connectivity, DTI and tractography may not be the right tool. The real power of DTI is that it can delineate the entire white matter architecture within 10 min of scanning time, which is unthinkable to achieve by using invasive chemical tracer technologies. There must be many important biological and clinical questions that can be answered by DTI but not by the microscopic methods. We need to use right tools for right questions.



**Fig. 1: Comparison of a postmortem human sample that reveals the macroscopic white matter architecture (A) and single-cell reconstruction of a neuron in a rat brain using an invasive *in vivo* chemical tracer experiment (B). In (A), the approximate size of 1 x 3 mm pixel is shown by green boxes.**

In addition of the resolution problem, it is also known that tractography is sensitive to noise, partial volume effect, locations of seeding pixels, and crossing fibers. It is reasonable to assume that the result contains false positive and negative data. Despite of these limitations of DTI/tractography, it is also true that DTI can provide us new anatomical information about axonal architectures. Our task is to extract reliable and useful connectivity information from the DTI datasets. One important step toward this goal is to develop tools to quantitatively analyze the DTI-based connectivity data and statistically analyze the results. This approach at least gives us a platform to compare different groups and detect reproducible differences, which could give us important clues about brain connectivity and its pathology.

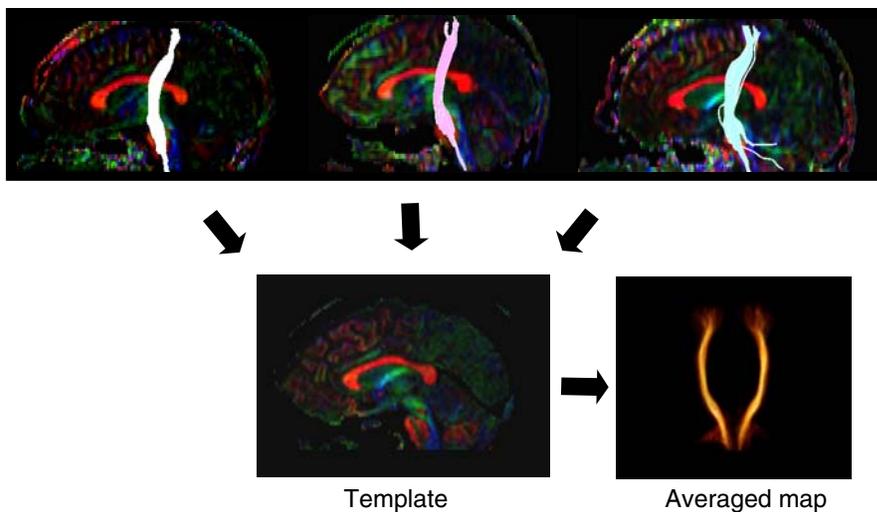
### **Techniques to study connectivity**

***Pixel-based approach:*** Without resorting to tractography, we have a fair amount of knowledge about white matter connectivity. For example, we can clearly identify the pyramidal tract in the pons, which is known to contain a high concentration of the corticospinal tract. Assuming that the size of tract is correlated with strength of functional connectivity, we can investigate status of specific connectivity by measuring a tract size at pre-determined regions. Pixel-by-pixel information about the fiber orientation is crucial to delineate the tract size. There are several types of quantification approaches. Advantages and disadvantages of each approach will be discussed.

***Tractography-based approach:*** Tractography can be used to identify a specific pathway that connects regions of interest. Tractography is an inevitable choice if one wants to study connections which haven't been described before and, thus, we don't have *a priori*

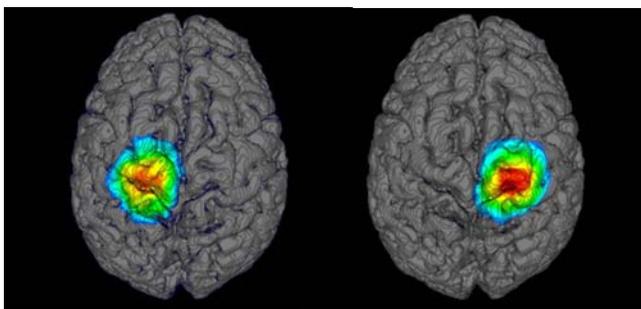
knowledge about the trajectory. We need to assess reproducibility of its trajectory among subjects. Reproducible placement of ROI locations (intra and inter-subjects) is also an important issue. Identification of the same ROI locations across subjects could be performed by using fMRI or anatomical landmarks. Once fibers are reconstructed, we need to quantify their coordinates. In this presentation three types of quantification approaches will be discussed. These are;

- 1) Trajectory probabilistic map: Once fibers are reconstructed in each subjects, they can be normalized into a template. As shown in Fig. 2, this creates a probabilistic map of the tract. If a high reproducibility is found, it suggests that the authenticity of the tract. By comparing the results between different populations, the status of the tract can be investigated.



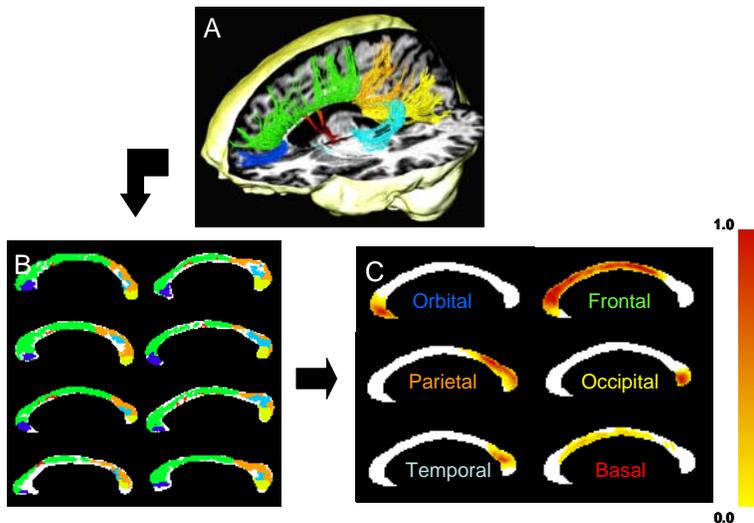
**Fig. 2: An example of a probabilistic map of tracking results. In this example, the corticospinal tract is reconstructed in each subject and the coordinates are transformed to a template. By adding all transformed results, an averaged map can be created.**

- 2) Connectivity map: It is also possible to extrapolate the tracking results to identify cortical regions that are associated with a specific white matter tract. Again, the key is to statistically analyze the results from multiple subjects. Fig. 3 shows an example in which the results in Fig. 2 are registered in the Talairach coordinates.



**Fig. 3: An example of cortical connectivity map. Results of corticospinal tract reconstruction are extrapolated to identify associated cortical regions in each subjects and the results are registered in the Talairach coordinates.**

- 3) Parcellation map: By using tractography in a systematic way, we can parcellate various brain structures such as the cortex, the thalamus, and the white matter. This idea is explained in Fig. 4. This is a new parcellation method that is based on brain connectivity.



**Fig. 4:** An example of quantification of connectivity information. From tractography (A), the corpus callosum is divided into regions connected to the orbital (blue), frontal (green), parietal (orange), occipital (yellow), temporal (cyan), and basal ganglion / thalamus (red). Images in (B) show results from 8 subjects. The results are registered to a common template, from which probabilistic maps of connectivity to each cortical lobes can be calculated (C).

## Conclusion

In this presentation, various approaches to study brain connectivity based on DTI are discussed. Because it is often difficult to validate the DTI-based connectivity information, it is essential to quantify the results and test the reproducibility of the results across subjects. Most importantly, we need to define what type of brain connectivity we are interested in and assess if DTI is the most appropriate modality to characterize the connectivity.

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