ABSTRACT

One of the basic principles underlying modern neuroscience is that of connectional specificity; that is, neurons in different regions of the brain do not form connections randomly but rather in a manner that facilitates the processing of information among regions with related functions. A full characterization of the connectional specificity of the human brain would require identifying all connections between individual neurons and mapping the trajectories of the axons that connect them. This neuronal connectivity diagram, referred to as the human connectome, is unknown and beyond the reach of current technologies. However, recent advances in diffusion and functional MRI have opened the way to the study of major pathways in the brain, which are formed by bundles of axons running in parallel and terminating in groups of neurons with architectonic and functional homogeneity. These advances have brought us excitingly close to the in vivo, non-invasive mapping of the human connectome at the aggregate level but several technical challenges remain to be addressed.

Diffusion MRI measures the diffusion of water molecules in different directions at each voxel in the brain to infer the orientation of the major white-matter pathways at each location. The simplest model of the diffusion process within a voxel, that of a single tensor, can be reconstructed from data acquired within a few minutes but can only represent a single pathway orientation at each voxel. Thus high angular resolution methods for diffusion MRI have been introduced to resolve the more complex architecture, consisting of multiple intersecting pathways, that is present in many locations in the brain. These complex models involve many more parameters per voxel than the simple tensor model. Consequently a much larger number of diffusion-weighted images needs to be acquired to estimate these parameters reliably, increasing the required scan time, sometimes up to several hours, and thus restricting the applicability of these methods in vivo. The number of images that can be acquired within reasonable scan times with current diffusion MRI sequences is not sufficient to capture all the complexity of white-matter pathways that can be observed in ex vivo samples. This creates the need for faster acquisition methods, including parallel and multi-slice approaches, that allow data to be acquired with more diffusion-weighting directions within the same amount of time. In addition to high angular resolution, data acquisition methods also need to achieve adequate spatial resolution for imaging pathways of high curvature (U-shaped), reduced imaging artifacts, and increased the signal-to-noise-ratio (SNR). These are competing requirements and a given pulse sequence can only achieve a trade-off among them. However, a sequence that reduces scan time can be combined with improvements in acquisition hardware, particularly gradient strength, to increase SNR.

Once the diffusion data is acquired, a tractography algorithm is used to reconstruct the shape of the white-matter pathways from this data. This is a challenging problem, even with high-quality data, because of the size of the solution space of all possible connections and the uncertainty introduced by the multiple true pathway orientations at every voxel. Deterministic approaches to tractography are faster and thus more practical for whole-brain analyses but less robust to noise than probabilistic methods. Local methods, either deterministic or probabilistic, that trace a pathway step-by-step using the data locally at each voxel, suffer from bias against shorter or longer connections. Global methods that optimize the entire pathway at once suffer from local minima and sensitivity to initialization due to the large solution space. Tractography methods can benefit from the use of appropriate side information based on prior anatomical knowledge to reduce the space of acceptable solutions. Specifically, anatomical context from structural MRI can be used to constrain the possible trajectories of white-matter pathways. In addition, path reconstructions from high-quality diffusion data can be combined with this anatomical context to inform tractography solutions obtained from data of routine quality. To utilize such prior information on path shape, images from a set of training subjects need to be registered to each other and to those of the test subject. Conventional affine registration cannot achieve accurate alignment of both the path terminations on the cortex and the path bodies through
the white matter. Instead surface-based registration is preferable for aligning the cortical folds and can be combined with intensity-based volumetric registration to align noncortical structures.

Diffusion tractography provides us with a blueprint of the brain’s wiring diagram. Additional information on the connectome can be derived from functional imaging, which allows us to probe the flow of information through this diagram. Connectivity maps derived from diffusion and functional data have complimentary strengths. Diffusion tractography is often challenging for longer paths, as well as paths with variable fiber density, where fibers fan out and then converge, such as in the internal capsule. On the other hand, resting-state functional MRI, which is used to map the temporal correlations of spontaneous BOLD time courses in different brain regions, can provide us with evidence of long-range connectivity. However, it cannot not determine whether correlation between two regions is due to a direct (monosynaptic) connection, an indirect (polysynaptic) connection via an intermediate region, or a common driving input from a third region. As a result, connectivity maps derived from functional and diffusion MRI differ, with the latter being sparser. Finally, conventional functional MRI cannot identify the direction of information flow within a given connection. This direction can be estimated from EEG and MEG, which measure electromagnetic field changes along the surface of the brain due to neuronal activity. The high temporal resolution of EEG and MEG allows us to infer on directionality of connections based on the relative phase of time courses from different brain regions.

Acquiring the aforementioned multi-modal data and transforming it into a common space is a challenging task in itself. Even after this is accomplished, however, how to combine the information provided by each type of data towards multi-modal inference on the connectome is an open problem. Approaches such as structural equation modeling and dynamic causal modeling, which have been applied to study isolated brain networks comprising only a few nodes, do not scale efficiently to the study of whole-brain connectivity. Graphical models hold promise in this direction but further work is needed to develop methods for the analysis of fully multi-modal graphical models that combine information on edges and weights from diffusion and functional MRI with information on directionality from MEG/EEG.

In this talk I will present an overview of the challenges discussed above and the efforts to address them that are currently underway at the Martinos Center and collaborating institutions.

**Index Terms**— Diffusion MRI, functional MRI, brain imaging.