Specialty area: *Connectomics: A New Frontier in Neuroscience*

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Highlights: Significant methodological improvements are attained in neuroimaging methods for studying connections among gray matter regions of the human brain, yielding new and novel results.

Title: *Innovations in Multi-Modal Imaging for Mapping a Comprehensive Human Connectome*

Target Audience: Researchers interesting neuroimaging and applications of neuroimaging towards understanding brain function in heath and disease.

Outcome/Objectives: Human Connectome Project (HCP), an ambitious effort initiated by the 16 National Institutes of Health (NIH) Institutes and Centers that support the NIH Blueprint for Neuroscience Research, to map the neural pathways that underlie human brain function. The purpose of this lecture is to describe the results of a ~2.5 years of work undertaken by a large consortium of HCP investigators, led by Washington University and the University of Minnesota (the "WU-Minn" consortium), with a major contribution from the University of Oxford.

Purpose: The HCP aims to generate a comprehensive description of the connections among gray matter locations in the human brain at the millimeter scale. Three complementary MR methods are employed to achieve this goal. These are: 1) resting state functional magnetic resonance imaging (R-fMRI), which uses correlations in the temporal fluctuations in an fMRI time series to deduce '*functional connectivity*'; 2) diffusion weighted imaging (dMRI) that provides the input for the reconstruction of the complex axonal fiber architecture so as to infer '*structural connectivity*' between gray matter regions; and 3) task based fMRI (T-fMRI) to identify functional parcellations in the human brain directly and thus assisting analyses of data obtained with the first two methods. A growing number of studies have revealed important insights through systematic studies of whole-brain connectivity using the aforementioned MR methods. Realizing significant new methodological developments to overcome or ameliorate limitations of these techniques are considered imperative for the success of the HCP.

Methods: Improving signal-to-noise ratio (SNR) by minimizing T_2 decay during the diffusion encoding period, and accelerating the data acquisition rate to increase SNR per unit time of data acquisition are key to obtaining more informative dMRI data for tractography analysis. Such gains, achieved using 100 mT/m maximum amplitude gradients and slice accelerated whole brain imaging sequences, have been exploited to reduce voxel size to 1.25 isotropic in 3T WU-Minn HCP protocol and to permit finer sampling of the diffusion encoding space (i.e. 3 shell acquisition with 90 diffusion weighted direction per shell, acquired twice). These data acquisition gains are complemented with new methods developed for eddy current, distortion and motion correction. Slice accelerated imaging methods with 8-fold acceleration have been developed and rigorously evaluate for R- and T-fMRI to attain 0.7 s whole brain EPI imaging with 2 mm isotropic resolution at 3T. These methods, together with anatomical imaging, are currently being used at 3 Tesla to acquire data on 1200 subjects involving twins and non-twin siblings, to be augmented with behavioral and genetic analyses. This 3T effort will be complemented with studies at 7 Tesla subsequent to the ongoing optimization phase at this magnetic field strength.

Results: Faster rate of data sampling without compromising volume coverage permitted the detection of larger number of Resting State Networks (RSNs) with greater statistical significance and allowed the development of new analysis approaches to evaluate the temporal dynamics of the RSNs. In dMRI, the orientation of white matter fiber bundles was more accurately determined aided by the unprecedented spatial resolution achieved in HCP dMRI studies, allowing visualization of connections with significantly improved clarity. Further improvements for the R-and T-fMRI are expected at 7 Tesla because, in fMRI, spatial resolution is also by the spatial relationships associated with neurovascular coupling, and coupling between functional mapping signals and underlying vasculature; the latter is field dependent.

Conclusions: Methodological advances in acquisition and processing has allowed us to obtain very high-quality in-vivo MRI data at 3T, while achieving the aim of scanning a very large number of subjects. These advances result from two years of intensive efforts in optimizing many aspects of data acquisition and processing during the piloting phase of the project. A similar optimization effort is expected to yield equally significant gains for the 7 Tesla component of WU-Minn