Modeling Human Neural Systems: Insights from Brain Imaging

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Inter-regional connectivity is a fundamental aspect of brain organization for which powerful imaging probes have been developed, the most widely utilized being resting-state network (RSN) anslysis of BOLD fMRI (a functional connectivity measure) and diffusion tensor imaging (DTI) tractography (a structural connectivity measure). A problem facing both types of connectivity metric is that they are capable (at least in principle) of computing connection strength between any two points in the brain, generating extraordinarily large data sets and potentially sacrificing statistical power by requiring correction for multiple comparisons. A second problem facing these forms of connectivity analysis is that they do not carry information about function, being either purely structural (DTI) or acquired at rest (RSN). One strategy for overcoming these two limitations is to model the neural circuits of interest meta-analytically. To this end, we have developed meta-analytic approaches to connectivity mapping which have the distinct advantages of: 1) using very large, pre-existing, published datasets; 2) using behavioral meta-data to characterize the behaviors and mental operations supported by individual networks; and, 3) generating output very similar in format and results to per-subject connectivity mapping methods. The data input for meta-analytic connectivity modeling (MACM) are center-of-mass stereotactic location coordinates from published brain-activation or voxel-based morphometry studies and the study-associated meta-data, as stored in the BrainMap database (www.brainmap.org).[1] For MACM analyses, all data sets within BrainMap can be included, unlike "traditional" activation likelihood estimation (ALE) analyses, in which only datasets from similar tasks are grouped.[2] Similar to connectivity analyses of resting-state fMRI, MACM analyses can be region-seeded[3] (e.g., assessing amygdala connectivity) or be performed via independent components analysis[4] (ICA). In either application, behavioral meta-data can be used to characterize and filter connectivity results. For example, the functional role of specific pathways within the default mode network (DMN) can be discriminted meta-analytically, a type of analysis not possible using structural connectivity data or resting-state functional connectivity data.[5] A variety of MACM validations have been performed, including comparisons to resting-state fMRI analyses, to DTI tractography, and to primate tract tracing literature.[3,4,6] MACM can readily model connectivity patterns and behavioral functions throughout the human brain, providing a framework within which per-subject data can be analyzed in a more directed and statistically powerful manner. For example, we have used MACM to select the optimal imaging endophenotypes to assess genetic influences on working memory; prior modeling "limited the search space" and increased statistical power.[7] MACM can also be used to construct fully data driven starting models for causal modeling (e.g., structural equation modeling [SEM] and dynamic causal modeling [DCM]) and graph analytic modeling[8], a general requirement for using these methods. Collectively, MACM connectivity modeling approaches compliment per-subject approaches both by "limiting the search space" and by providing task-based behavioral information. We suggest that virtually all connectivity studies performed on per-subject data can be enhanced by doing prior modeling using MACM.

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