Session Title: Methods for Assessing Functional Connectivity: TMS, ERP, MEG, Statistical Analyses
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Proposed Discussion Questions:

- What are the pros and cons of these methods for assessing functional connectivity?

- How sensitive are these methods to learning-based changes in connectivity?

Functional connectivity must be distinguished from anatomical connectivity.

Anatomical Connectivity:
Diffusion tensor imaging (DTI) is a technique based on diffusion weighted imaging (DWI) that allows an evaluation of the integrity of white matter tracts by virtue of its ability to visualize water diffusion along axonal pathways. Fiber tractography (FT), which is a three-dimensional visualized derivative of DTI data, permits visualization of the architecture and integrity of neuronal tracts.

Pros:

1. DWI is more sensitive to underlying microstructural events of water molecules in biologic tissues than conventional MRI, which is largely limited to the macroscopic assessment of cortical and subcortical structures.
2. By examining directional diffusion, DTI allows the evaluation of the orientation of white matter fibers determined from the primary vector of the diffusion tensor and can show the three-dimensional FT.
3. Quantitative measures such as mean diffusivity and fractional anisotropy are available with DTI. These measurements are not available from conventional MRI.
4. DTI can be used to visualize the white matter pathway, even prior to myelination. On the other hand, conventional T1- and T2-weighted signal intensity changes in white matter are strongly dependent on the presence of myelin.
5. Allows the probing of direct physiological connections when combined with other techniques such as TMS (M1 is stimulated and the corresponding motor response recorded in contralateral hand).

Cons:

1. FT. Poor specificity in terms of identifying the type of fibers that are quantified.
2. FT is also not reliable in regions where there are several fiber crossings.
3. DTI provides information concerning the average orientation of fibers at the voxel level, and if this volume-averaged information is used to reconstruct a pathway, false positive projections may be observed.

By comparison with the structural concept of anatomical connectivity is the more functionally relevant concept of functional connectivity.

Functional Connectivity:
Functional connectivity refers to correlative relationships that might exist between the activations of distinct and often well separated neuronal populations, without any reference to physical connections or an underlying causal model. In contrast, analyses of effective connectivity are based on statistical models that make anatomically based assumptions and limit their inferences to networks comprising a number of pre-selected regions. Sometimes these two terms are used interchangeably. The electrophysiological techniques (MEG/EEG) have superior temporal resolution and are able to measure functional or effective connectivity in ways that have greater physiological meaning (rather than just statistical meaning), but suffer from the inverse problem (i.e., the fact that any single electrophysiological pattern can be generated in an infinite number of ways, thus making it difficult to infer the sources without additional constraints or information). Functional connectivity can be defined in terms of activity that occurs during a given cognitive/motor task or during “rest” (the absence of a specific task) and is measured with several different analysis techniques including seed-voxel analyses, independent component analyses (ICA), dynamic causal models, structural equation modeling, granger causality, etc.

<u>Pros:</u>

1. Dynamic causal models (DCMs) incorporate a model of the neuronal level that aims to relate fMRI activity to theoretical activity at the neuronal level.
2. DCM uses Bayesian model comparison; therefore, one can compare non-nested network models.
3. In contrast to the majority of univariate statistics, functional connectivity analyses are not dependent on amplitude differences.
4. If functional connectivity is measured during rest, then one can potentially eliminate confounds between different patient groups that are a result of differences in behavioral performance.
5. There appears to be converging evidence from three different areas of imaging regarding a similar “default-mode” network (Raichle’s hypermetabolism at rest studies, Binder’s deactivation during a task (fMRI) and independent component analyses).

<u>Cons:</u>

1. These fMRI methods are analyses of functional connectivity, which make no inferences about the actual anatomy of the connections involved.
2. A current limitation of DCM is that model fitting is computationally demanding.
3. Another limitation of DCM is that neuron-dynamics in each region are characterized by a single state variable (neuronal activity). Thus, the method does not incorporate a model of different neurotransmitter systems.
4. Normal-appearing functional connectivity does not necessarily mean that normal coupling between brain regions exists.
5. One prominent confound in functional connectivity measurements is physiological noise in BOLD signal activity, which can influence correlation measurements.
6. It is not clear what “rest” really means in terms of underlying cognitive processes and whether this is just another task.
7. The relationship between neurovascular uncoupling following a stroke and how this affects the BOLD response has not been determined.

During motor learning processes, there are changes in neuronal network activity, which may be partially related to the development of new synaptic connections or to the unmasking of silent synapses. Although imaging methods can be sensitive enough to detect changes in neuronal network activity before and after an intervention, the nature of these changes requires careful interpretation. Functional connectivity is a measurement of the spatiotemporal synchrony or correlations of the BOLD fMRI signal between anatomically distinct brain regions of cerebral cortex. In the resting state, low-frequency fluctuations of the BOLD signal, which are related to neuronal spontaneous activity, can be used to identify functional connectivity among different brain regions. Then, the study of functional connectivity using resting state fMRI data may provide an opportunity to detect different aspects of plastic changes associated to motor learning processes, such as the appearance of compensatory plasticity; increased functional connectivity could indicate the dominance of a compensatory mechanism. However, one of the problems of using functional connectivity studies based on resting state fMRI is how to interpret these results in terms of active task performance.

Summary of the discussion:

Connectivity research can generally be classified into imaging techniques that are based on anatomical connectivity (DTI, fiber tracking) and those that are based on functional (fMRI, EEG and MEG) or effective (EEG and MEG) connectivity. The primary benefit of anatomical connectivity studies is that the underlying anatomy and physiology of the system is well characterized. Functional connectivity may hold great promise for understanding of network disruptions in the brain following trauma to the central nervous system, but more works needs to be done to quantify what these different techniques are measuring. Perhaps the single greatest benefit of true resting state data is that the clinician does not have to be concerned about differences in behavioral performance that necessarily confound studies examining functional activation during a task. Perhaps the greatest weakness of current connectivity techniques is the uncertainty regarding underlying physiological mechanism (i.e., what is rest?), the reliability of connectivity analyses and subsequent results, and the potential differences in connectivity in local penumbral/lesioned tissues compared to more unaffected regions following trauma. Finally, both fMRI and MEG/EEG techniques have their respective limitations in either being able to measure effective connectivity (MEG but not fMRI) or having ill-posed solutions for localization (MEG but not fMRI).

Synthesis / Recommendations:

Overall in this session, different imaging methods to study anatomical and functional connectivity between brain regions were described. Network models are important tools that can provide a common framework for describing connectivity of distinct brain areas at the level of anatomy and function. However, currently, there is no consensus on the most accurate or efficient method of detecting or measuring functional connectivity using fMRI. Importantly, during interpretation of the results, it is critical to consider that in all cases, even for anatomy, the network descriptions are only approximations of the real systems.