RESTING-STATE SIGNALS: IDENTIFICATION, CLASSIFICATION & RELATION TO BRAIN CONNECTIVITY

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Resting-state networks: background

FMRI data acquired with the subject 'at rest' shows temporal correlations across the brain, with multiple functional networks 'spontaneously' activating without explicit external input (e.g., sensory stimulation). Different networks have distinct spontaneous timeseries, and, conversely, all voxels/regions within any given network by definition have similar timeseries. With data of sufficiently good quality, each large-scale network can be subdivided into sub-networks and ultimately individual functional 'nodes', all of which will have similar but distinct timeseries. The aim is to estimate functional connections between nodes (based on their timeseries) in order to identify the full set of functional networks. The dimensionality of a given network analysis is given by the number of functional nodes. A major distinction between this and a simple low-dimensional analysis of the original data is that connections *between* large-scale networks can be characterised with much greater functional/spatial specificity.

RSN characteristics

Given that such 'resting-state networks' (RSNs) are generally believed to represent spontaneous activity in the brain's functional networks, it is not surprising that they are only seen in grey matter, similar to activation maps in task FMRI. Indeed, RSNs have been shown to correspond very closely to known explicitly-activated functional networks (derived, for example, from maps of co-activation generated from thousands of different task FMRI studies). Some early work expressed concern that RSNs might be caused by non-neural physiological sources (e.g., cardiac and respiratory fluctuations), but there is now much evidence that this is not the dominant source of the correlations found by careful RSN analyses. Temporally, RSNs have been described as 'low frequency' or '1/f', although there is some evidence that the reduction in RSN amplitude at higher frequencies may simply be due to the smoothing effects of the haemodynamic response to neural activation. In practice, the ability to identify RSNs from signal fluctutations between 0.01-0.1Hz is well established.

RSN analysis

The two most widely-used analysis techniques for resting FMRI data are seed-based correlation and independent component analysis (ICA). With a seed-based correlation analysis, the timeseries from a given voxel (or region) is correlated against every other voxel's timeseries, producing a spatial map representing the functional network that includes the seed point. With ICA, all voxels' timeseries are considered simultaneously, and 'clustered' into distinct components. Each component represents either a functional network (with low-dimensional ICA) or functional region (high-dimensional ICA), along with its associated spontaneous timeseries. Various approaches for the analysis of multiple-subject resting FMRI data have been proposed, and have to address the significant challenge of identifying equivalent (and hence comparable) networks in all subjects while achieving within-session artefact/noise modelling/removal.

Brain networks

The identification of functional nodes and the estimation of functional connections between those nodes is becoming a powerful tool for mapping the brain. For example, this will be one of the primary modalities+methodologies utilised in the $40m NIH "Human Connectome Project" started in 2010, a major collaborative project attempting to provide leading-edge *in vivo* mapping of human brain connectivity. However, there are many outstanding methodological issues that require further research. For example, it is not yet clear what the best analysis method is that will take the nodes' timeseries and estimate the *direct functional connections* between the nodes. The most widely-used method, simple correlation between any two timeseries, is unlikely to make the best use of all of the information in the FMRI timeseries, and many more sophisticated approaches are being developed. Further, it is not clear how robustly the *directionality* of the network connections can be estimated from FMRI timeseries alone (or even if this is biologically a well-defined question). Here as well, several different methodologies are being developed and compared, and it is not clear which (if any) of these will be able to provide directionality, or whether other data modalities (such as EEG and MEG) will need to be utilised for this. Finally, once the brain 'network' has been estimated, there is much interest in summarising the organisation of the network, for example, identifying the different (if potentially overlapping) 'communities', or clusters, of functional nodes within the network, identifying functional nodes that are the major information 'hubs', and developing summary statistical measures of the whole network's efficiency.

Other and future work

Other exciting areas of research touching the field of resting FMRI connectivity include: studying the *temporal nonstationarity* of resting connectivity (the extent to which connections are changing over time); relating resting networks' variation across subjects with other *modalities*, such as structural connectivity estimated by diffusion imaging; comparing resting connectivity across *different species* or *ages*; investigating the effect of *sleep and anaesthesia* on resting networks; investigating the effect of *pathologies* on resting networks, and finding useful disease *biomarkers*; estimating the interaction between *genetics* and functional networks. Finally, of course, there will continue to be much work attempting to relate resting FMRI timeseries and connectivities to the underlying *neural dynamics*, and to understand as fully as possible their biological basis.