Connectivity

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Connectivity in the brain has been explored by MR on a functional level using fMRI as well as on a structural level using DTI.

Functional connectivity. Brain regions do not act in isolation and fMRI can be used to explore how regions of the brain communicate one with the other. This has been assessed, by studying time course correlations of signal during a given task or during resting period. This 'resting-state fMRI' is based on the assessment of spontaneous, rather than task-induced, synchronous low-frequency BOLD fluctuations (LFBFs). The signal characteristics are similar to BOLD, rather than flow or other hemodynamic contrast (1-3) and the functional contrast is limited to the frequency domain 0–0.1 Hz (4). These LFBFs have been taken to be reflective of functional connectivity in the human brain since their first observation more than a decade ago (5), and since then have been applied in an increasing number of studies (6).

Although functional connectivity reveals temporal signal correlations, it does not allow any conclusions on the hierarchical relationships between these functionally connected zones. This information can be assessed using effective connectivity. While functional connectivity can be directly computed from experimental data, determination of effective connectivity relies on the definition of a cognitive model using prior knowledge based on neuroimaging studies or animal models. This approach aims to identify connection strengths that best predict the observed variance– covariance structure of the data with respect to the model, by means of the structural equation modeling (SEM). The resulting path coefficients represent the change of activity of a target area for a unit change in activity of a source area. (7). These methods have given new insights into a better understanding of cognitive networks in healthy subjects such as the auditory system (8), the working memory network (9), attention (10) and the visual systems (11). In CISS MS patients, effective connectivity, assessed with structural equation modeling and fMRI, can contribute to a better understanding of the impact of diffuse tissue damage onto large brain network and to a better characterization of functional reorganization mechanisms. In patients performing PASAT, modulation of effective connectivity is present inside the executive systems of working memory and could be related to adaptive cognitive control processes. (12)

Structural connectivity. The structural status of WM bundles belonging to a specific network can be assessed using DTI tractography, a powerful non-invasive technique which makes it possible to track WM bundles connecting distant cortical areas. There is evidence to suggest that DTI measures are specific to the details of the axonal damage present in diseased tissue. Transverse diffusivity correlates with demyelination in animal models of axonal injury and demyelination whereas longitudinal diffusivity correlates with axonal damage demonstrated by amyloid precursor protein (APP) measurements (9, 13-15)

Although it is assumed that functional connectivity reflects the brain's structural connectivity (i.e. the anatomical connections between brain regions) the exact relationship between structure and function is not necessarily straightforward. Functional connectivity is also observed between

regions where there is little or no structural connectivity. This could be related to BOLD signal correlations mediated by indirect structural connections (i.e. via a third region), to false negatives in DTI, to near-distance spatial fMRI effects (noise, hemodynamic or vascular artifacts) or to greater likelihood to complete short fibres in DTI/tractrography. (16)

To reliably track white matter pathways in the presence of lesions can be challenging. Tracking is therefore often limited to regions of NAWM. However, different approaches to tractography enable tracking even in areas of severe axonal damage. Improved tracking methodology include atlas-based approaches (17) and high-angular resolution diffusion imaging (HARDI)-based fiber orientation distribution function (FODF) estimation (18). This FODF estimation procedure permits the use of probabilistic tracking methods that allow tracking to progress across regions of fiber inhomogeneity that are not appropriate for the single-tensor model (9).

In MS, various white matter tracts have been investigated. These include the optic radiation, the corticospinal tract and the transcallosal pathways. In patients affected by optic neuritis the reconstructed optic radiations was localized more laterally in the posterior part of the tracts and more inferiorly than in the control group (19). A strong correlation was also detected between transverse diffusivity and changes in visual evoked potentials, suggesting that DTI is sensitive to underlying pathological changes leading to delayed conduction (20). A significant increase in transverse diffusivity has been shown in MS along the transcallosal pathway connecting the bilateral supplementary motor areas (SMA) (21). Taken together, all these results indicate that DTI is an excellent surrogate marker for disease burden and axonal injury in MS

A different approach to assess structural connectivity is to calculate grey matter density or perform cortical thickness measurements(22-24). However, correlations between such grey matter measures do not necessarily imply structural connectivity. They could arise from shared function, or shared genetic influence. It is however interesting to note, that in general, the various connectivity measures are in agreement with each other (16).

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