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Track-weighted functional connectivity (TW-FC): A tool for characterizing the structural–functional connections in the brain

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ABSTRACT

MRI provides a powerful tool for studying the functional and structural connections in the brain non-invasively. The technique of functional connectivity (FC) exploits the intrinsic temporal correlations of slow spontaneous signal fluctuations to characterise brain functional networks. In addition, diffusion MRI fibre-tracking can be used to study the white matter structural connections. In recent years, there has been considerable interest in combining these two techniques to provide an overall structural–functional description of the brain. In this work we applied the recently proposed super-resolution track-weighted imaging (TWI) methodology to demonstrate how whole-brain fibre-tracking data can be combined with FC data to generate a *track-weighted (TW) FC map* of FC networks. The method was applied to data from 8 healthy volunteers, and illustrated with (*i*) FC networks obtained using a seeded connectivity-based analysis (seeding in the precuneus/posterior cingulate cortex, PCC, known to be part of the default mode network), and (*ii*) with FC networks generated using independent component analysis (in particular, the default mode, attention, visual, and sensory-motor networks). TW-FC maps showed high intensity in white matter structures connecting the nodes of the FC networks. For example, the cingulum bundles show the strongest TW-FC values in the PCC seeded-based analysis, due to their major role in the connection between medial frontal cortex and precuneus/posterior cingulate cortex; similarly the superior longitudinal fasciculus was well represented in the attention network, the optic radiations in the visual network, and the corticospinal tract and corpus callosum in the sensory-motor network. The TW-FC maps highlight the white matter connections associated with a given FC network, and their intensity in a given voxel reflects the functional connectivity of the part of the nodes of the network linked by the structural connections traversing that voxel. They therefore contain a different (and novel) image contrast from that of the images used to generate them. The results shown in this study illustrate the potential of the TW-FC approach for the fusion of structural and functional data into a *single quantitative image*. This technique could therefore have important applications in neuroscience and neurology, such as for voxel-based comparison studies.

Introduction

MRI provides an arguably unique and powerful tool for studying the functional and structural connections in the brain in vivo non-invasively. The technique of resting-state functional connectivity (FC) exploits the intrinsic temporal correlations of slow spontaneous signal fluctuations to characterise brain *functional* networks (Biswal et al., 1995). This is commonly done using blood oxygenation level-dependent (BOLD) contrast (e.g. Biswal et al., 1995; Damoiseaux et al., 2006), although similar studies have been also carried out by measuring the fluctuations on the perfusion-weighted signal using arterial spin labelling (e.g. Chuang et al., 2008; Liang et al., 2012) or the cerebral blood volume weighted signal (Magnuson et al., 2010). These studies have shown that the information contained in signal fluctuations can be used to identify distinct networks in the brain that are consistent with networks activated when performing common tasks.

Abbreviations: AC, anterior commissure; ALIC, anterior limb of the internal capsule; BOLD, blood oxygenation level-dependent; CC, corpus callosum; Cg, cingulum; Cgh, cingulum hippocampal part; CP, cerebral peduncle; CSD, constrained spherical deconvolution; CST, corticospinal tract; DMN, default mode network; DWI, diffusion MRI; EC, external capsule; EPI, echo-planar imaging; FC, functional connectivity; FOD, fibre orientation distribution; FWHM, full-width at half-maximum; Fx, fornix; gCC, genu of the corpus callosum; ICA, independent component analysis; iFOD2, 2nd order integration over fibre orientation distributions fibre-tracking algorithm; IFOF, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; IPL, inferior parietal lobules; ITG, inferior temporal gyrus; MCP, middle cerebellar peduncle; MPFC, medial prefrontal cortex; mTL, mesial temporal lobe; OR, optic radiation; PCC, precuneus/posterior cingulate cortex; PLIC, posterior limb of the internal capsule; sCC, splenium of corpus callosum; SCP, superior cerebellar peduncle; SLF, superior longitudinal fasciculus; SS, sagittal stratum; Tap, tapetum; TDI, track-density imaging; TE, echo time; TR, repetition time; TW, track-weighted; TWI, track-weighted imaging; Unc, uncinate; VBA, voxel-based analysis.

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Additionally, the technique of diffusion MRI fibre-tracking can be used to study white matter *structural* connections (e.g. Mori and van Zijl, 2002). Diffusion MRI data can be used to obtain an estimate of the white matter fibre orientations at each voxel (Basser, 1995; Tournier et al., 2011), which in turn can be used with a fibre-tracking algorithm to reconstruct a representation of the white matter pathways in the brain (Mori and van Zijl, 2002; Tournier et al., 2011). In the particular case of whole-brain fibre-tracking, a very large number of tracks (or streamlines) are generated by seeding throughout the brain, thus providing an overall representation of white matter pathways throughout the brain (the so-called 'tractogram').

In recent years, there has been considerable interest in combining these two techniques (e.g. Fernández-Espejo et al., 2012; Greicius et al., 2009; Hagmann et al., 2008, 2010a,b; Honey et al., 2009; Skudlarski et al., 2008; Supekar et al., 2010; Teipel et al., 2010; van den Heuvel et al., 2008, 2009) to provide an overall *structural–functional* description of the brain. In most studies, the results of one methodology are used to guide the other (e.g. the nodes of a FC network are used as seed/target regions for fibre-tracking). In this work, we applied a fundamentally different approach to this problem by using the recently proposed super-resolution track-weighted imaging (TWI) methodology (Calamante et al., 2012a), to combine the whole-brain fibre-tracking data (the tractogram) with a given FC network, to generate a *track-weighted (TW) FC map* of that FC network. The resulting image contains a different (and novel) image contrast from that of the images used to generate them, and allows for the fusion of structural and functional data into a *single quantitative image*. The method was applied to data acquired from 8 healthy volunteers. One of the advantages of the TW-FC technique is that a *single* tractogram can be combined with multiple FC networks (one at a time) to generate multiple TW-FC maps (one for each FC network). To illustrate the flexibility and potential of the method, example TW-FC maps were generated both from FC networks obtained (*i*) using a seeded connectivity-based analysis (seeding in the precuneus/posterior cingulate cortex, PCC, known to be part of the default mode network, DMN), and (*ii*) using FC networks generated using independent component analysis (ICA), in particular, the default mode, attention, visual, and sensory-motor networks.

Materials and methods

Track-weighted functional connectivity (TW-FC)

The technique of TWI was recently introduced (Calamante et al., 2012a) as a generalized framework to extend the principles of track-density imaging (TDI) (Calamante et al., 2010). TDI converts the information contained within the tractogram into an image with high anatomical contrast (Calamante et al., 2012b,c) by counting the number of streamlines traversing each voxel (the larger the number of streamlines traversing that voxel, the higher the TDI intensity). TDI maps have been shown to have spatial super-resolution properties, in that the TDI voxel size can be chosen to be much smaller than that of the acquired diffusion MRI data[1] (Calamante et al., 2011). In the TWI technique, the tractogram can be combined with an associated map to generate a super-resolution TW-version of that map. In the current study, a network generated from the FC analysis is used as the associated map, thus generating a *super-resolution TW-FC map* (see Fig. 1 for a flow chart illustrating the processing steps involved in our implementation of the TW-FC methodology).

There are a number of ways in which the information contained in the FC network can be combined with the tractogram to generate the TW-FC map (see the Discussion section for more details regarding this issue). To demonstrate the principles of TW-FC and the type of information that can be encoded in these maps, we use the following approach in this study, due to its simple interpretation (see Fig. 2): for each track j traversing a given super-resolution grid element at position r of the TWI map, the sum (or integral, for a continuous representation of the streamline) of the FC map intensities along the track (tFC_j) was computed:

$$tFC_j = \int_0^{\lambda_j} FC\left(\varepsilon_j\right) d\varepsilon_j \tag{1}$$

where ε_j indicates the coordinate along streamline j, and λ_j its length; each track has therefore an associated *tFC* value. The mean of these values over all tracks passing through the grid element was then computed, and assigned as the intensity of the TW-FC map for that grid element:

$$TWFC(r) = \frac{1}{K(r)} \sum_{j=1}^{K(r)} tFC_j = \frac{1}{K(r)} \sum_{j=1}^{K(r)} \left[\int_0^{\lambda_j} FC\left(\varepsilon_j\right) d\varepsilon_j \right] \tag{2}$$

where $K(r)$ corresponds to the number of streamlines in the grid element at position r that have a non-zero *tFC* value (this is to avoid counting tracks that are unrelated to the FC network when computing the mean). By definition, this value of the TW-FC map corresponds to the mean total FC value associated with the tracks in the grid element (i.e. it is related to the functional connectivity of the nodes of the network linked by the structural connections traversing that grid element), and therefore can be used as a measure of the structural-functional connection of that grid element (see Discussion section for more details on interpretation of these maps).

By being a specific case of the TWI technique, the TW-FC maps display super-resolution properties; for example, 500 μm isotropic resolution TW-FC maps are shown in this study, which are constructed from 3 mm isotropic BOLD data and 2.5 mm isotropic DWI data (see Results section). Due to the spatial extent of the tracks (several voxels in length), each track will have a different *tFC* contribution, because each track will have a different value depending on its specific path (Note also that the streamlines do not take the discretised FC values from each voxel traversed, but they take interpolated FC values at the precise streamline points). Due to this extra information brought in by the tracks, the voxel can be sub-divided into small (super-resolution) 'grid elements' (i.e. the voxels of the TW-FC map).

To show the relevant anatomical structures in more detail, the corresponding TDI map was also constructed by counting the number of streamlines in each grid element (Calamante et al., 2010). A standard map (where all the streamlines contribute to the count, regardless of their *tFC* value) was created for this purpose. In addition, a modified TDI map (referred to as TDI_{nz_tFC}) was also created where only the streamlines with nonzero *tFC* value were counted (i.e. the intensity of TDI_{nz_tFC} is $K(r)$). The latter TDI map enables the masking of regions with no (or minimal) tracks contributing to the TW-FC map (e.g. if a grid element has too few streamlines contributing to Eq. (2), the TW-FC intensity of that grid element will be unreliable due to the probabilistic nature of the fibre-tracking algorithm used — see TW-FC analysis section).

Data acquisition

Data from 8 healthy volunteers (subjects *S1–S8*) were acquired on a 3T Siemens Trio scanner (Erlangen, Germany). FC data were acquired with a gradient-echo echo-planar imaging (EPI) sequence (TE/TR = 30/3000 ms, voxel size 3 mm isotropic, 200 volumes). Diffusion weighted imaging (DWI) data were acquired using a twice-refocused spin-echo EPI sequence (60 diffusion-encoding directions, $b = 3000$ s/mm^2, voxel size 2.5 mm isotropic). To correct the EPI for susceptibility distortions, reference spin-echo EPI volumes with opposite phase-encoding polarities

[1] The key feature to understand the origin of the super-resolution property is that information must be brought in from outside the voxel to 'disentangle' the *intra*-voxel information. Due to the extra information brought in by the continuity of the tracks, the acquired imaging voxels can be sub-divided into small (super-resolution) 'grid elements' (i.e. the voxels of the final TDI map).