Super-resolution track-weighted functional connectivity (TW-FC): a tool for characterizing the structural-functional connections in the brain

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Introduction: 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. Similarly, 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 (e.g. [1-4]) 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 [5], to combine whole-brain fibre-tracking data (the so-called tractogram) with FC data, to generate *track-weighted (TW) FC maps* of a given FC network. The method was assessed on data from 8 healthy volunteers.

Methods: TWI was recently introduced [5] as a generalized framework to extend the principles of super-resolution track-density imaging (TDI) [6]. In TWI, a tractogram can be combined with a reference image to generate a super-resolution TW version of that image [5]. In our study, a network from the FC analysis is used as the reference image, thus generating a *super-resolution TW-FC map*. In brief, for each track traversing a given super-resolution grid element of the TWI map [5], the sum of the FC map intensities along the track was computed, and the mean of these values across tracks was assigned as the intensity of the TW-FC map for that grid element. This value corresponds to the mean total FC value for the tracks in the grid element.

Fig.1: Individual subject example. (a) Axial DMN map. For display purposes, the subset of fibre tracks connecting clusters from the DMN is displayed on sagittal (b) and axial (c) projections. Note: these tracks were isolated (using track-editing) from the whole-brain dataset; however, this information was not used for TWI, which is calculated from the whole-brain tractogram directly, without any track-editing.

MRI acquisition: Data from 8 healthy volunteers were acquired on a 3T Siemens scanner. FC data were acquired with a GE-EPI sequence (TE/TR= 30/3000ms, voxel size=3mm isotropic, 100 volumes). Diffusion MRI (DWI) data were acquired using a twice-refocused SE-EPI (60 diffusion directions, b=3000s/mm^2, voxel size=2.5mm isotropic). Reference EPI data with opposite phase-encoding polarities were acquired for both FC and DWI data to correct for susceptibility distortions [7].

FC analysis: Data were motion corrected; smoothed (FWHM=8mm); band-pass filtered (0.01-0.1Hz); and the motion parameters, mean white-matter, CSF, and whole-brain signals regressed out. For illustration purposes, the results for a seeded connectivity analysis of the default mode network (DMN) are shown here. To determine the seed coordinate, the data were normalized to MNI space; a group ICA was performed on temporally concatenated data; the maximal voxel in the precuneus/posterior cingulate cortex (PCC) from the group DMN component was identified (0,-52,31); and this co-ordinate was transformed back into each subject's native space. A correlation analysis was then carried out for a time course obtained from a spherical ROI (5mm radius) centered on this seed voxel. The individual DMN maps were thresholded at r >0.4, extent >30 voxels.

Diffusion MRI analysis: Whole-brain fiber-tracking was done using in-house software based on MRtrix (http://www.brain.org.au/), which includes constrained spherical deconvolution (CSD) [8] to model multiple fiber-orientations, and probabilistic streamlines [9]. Ten million tracks/dataset were generated.

Fig. 2: Individual subject examples (same subject as Fig. 1). Top: sagittal (a) and axial (b) super-resolution TW-FC maps. For anatomical detail, the bottom row shows the corresponding sagittal (c) and axial (d) TDI maps.

TW-FC: Following distortion correction [7] and image registration between FC and diffusion data, TWI maps were generated using a 500µm isotropic grid-size, normalized to a group template [10], and the group mean TWI map was then calculated.

Results: TW-FC maps show high intensity in white matter structures connecting the nodes of the FC network used as the reference image; the intensity of the map reflects the degree of FC associated with a given white matter pathway (see Figs. 1 and 2 for the results from a typical individual, and Fig. 3 for the group results). Consistent with the findings from previous studies (e.g. [2]), the cingulum bundles show the strongest FC values, due to their major role in the connection between medial frontal cortex (MFC) and PCC. Several other white matter pathways were also represented, including the superior longitudinal fasciculus, inferior fronto-occipital fasciculus, splenium and genu of the corpus callosum.

Discussion: This study describes a methodology for super-resolution TW-FC mapping, and illustrates the potential of this approach for the fusion of structural and functional data into a *single quantitative image*. The TW-FC maps highlight the white matter connections involved in a given FC network (e.g. the DMN in the figures), and their intensity in a given voxel reflects the mean total FC value for the white matter fibre-tracks traversing that voxel. They therefore contain a different (and novel) image contrast from that of the images used to generate them. The methodology can naturally be extended to other FC analysis methods (e.g. ICA-based methods) and even to traditional paradigm-driven fMRI studies. A potential important application of this methodology is for quantitative voxel-wise group comparison. We hypothesize that these maps could have increased sensitivity, since both a change to the structural connections and/or a change in FC will affect the TW-FC maps.

References: [1] Skudlarski P et al. *NeuroImage* 2008;43:554. [2] van den Heuvel MP et al. *HBM* 2009;30:3127. [3] Honey CJ et al. *PNAS* 2009;106:2035. [4] Greicius MD et al. *Cereb Cortex* 2009;19:72. [5] Calamante F et al. *NeuroImage*; doi:10.1016/j.neuroimage.2011.08.099. [6] Calamante F et al. *NeuroImage* 2010;53:1233. [7] Holland D et al. *NeuroImage* 2010;50:175. [8] Tournier JD et al. *NeuroImage* 2007;35:1459. [9] Tournier JD et al. *ISMRM*, 2010;18:1670. [10] Raffelt D et al. *NeuroImage* 2011; 56:1171.
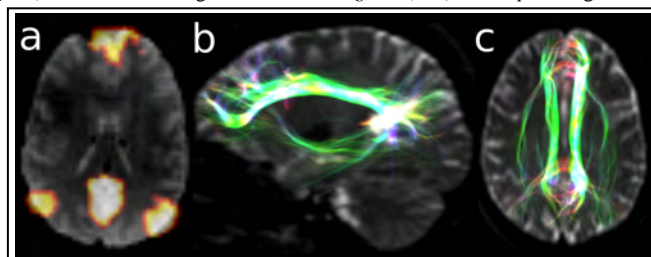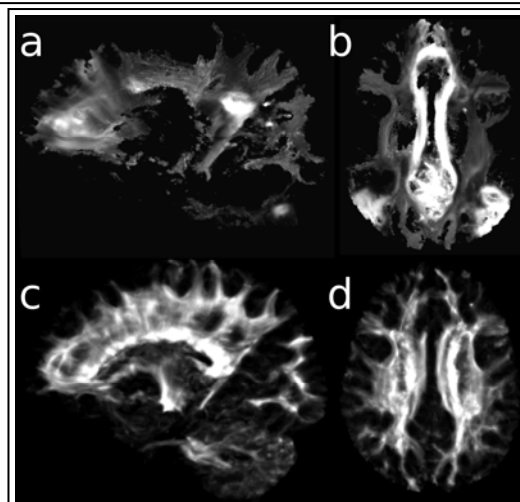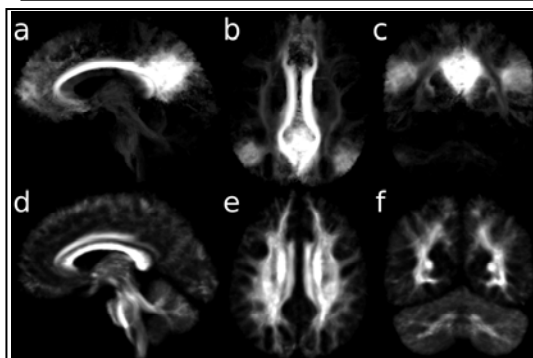
Fig. 3: Group mean results. Top: sagittal (a), axial (b) and (c) coronal super-resolution group TW-FC maps. Bottom: corresponding group TDI maps for anatomical reference.