INTEGRATION OF FMRI AND PROBABILISTIC TRACTOGRAPHY FOR CEREBRAL NETWORK ANALYSIS

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ABSTRACT

We present a data acquisition and analysis methodology for generating anatomical connectivity matrices using fMRI and diffusion MRI tractography. We describe a protocol for distortion-free, high spatial resolution diffusion MRI suitable for probabilistic tractography in the presence of complex fibre architecture and distortion-free, geometrically-matched fMRI. We then demonstrate that probabilistic tractography may be initiated from a set of functionally-defined regions to generate a matrix representation of the anatomical substrate of functional networks.

1. INTRODUCTION

Diffusion weighted MRI (DWI) allows the routes of connection between cortical and subcortical areas via white matter fibre bundles to be defined. The recent development of probabilistic fibre tracking methods additionally allows an estimate of the confidence that may be assigned to an observed connection [1-4].

One attractive application for probabilistic tractography measurements is in the understanding of functional networks. Cognitive function relies on networks of cortical regions rather than single units. Thus it is imperative to delineate the entire network to understand normal and abnormal function.

Much effort has gone in to defining network connectivity using functional imaging, leading to concepts such as functional and effective connectivity (see for example [5]). Characterization of the interplay between functional nodes using such methods requires the application of computational models that are constrained by cerebral anatomical connections. Neuroanatomical information can be incorporated to improve model behaviour (see for example [5, 6]); therefore, a method that is able to provide independent evidence for the existence of inter-nodal anatomical connections and a measure of the confidence with which connection has been identified would be invaluable in functional network characterization. Probabilistic tractography, through its provision of estimates of confidence in observed connections (determined using a model relating the diffusion weighted signal to fibre architecture and to the effects of noise) may, at least in part, fulfill this role. If so, these methods will become invaluable to those with an interest in network modeling or in comparing networks between individuals or groups to investigate disorders associated with connectivity abnormalities (see for example [6]).

Here we present initial work into the application of probabilistic tractography using crossing fibre information defined using the q-ball method [7] to extract inter-nodal patterns of anatomical connection in the example of language/semantic networks. The underlying concept is that functional nodes identified using fMRI can be used as the seed regions for probabilistic tractography [8] and that the anatomical interaction between these nodes may then be extracted by definition of an anatomical connectivity network, which may be expressed diagrammatically or in matrix form [9].

2. METHODS

We employ distortion correction techniques for both DWI and fMRI acquisitions to achieve two key aims. First, our combined fMRI and tractography experiment requires good geometrical matching of the two acquisitions as we aim to initiate the tractography using the fMRI loci (small artefactual perturbations of start point position can have large effects on a tracking experiment). Second, we wish to avoid the detrimental effect of geometric distortions on tractography [10] and of signal drop out on fMRI sensitivity [11]. These effects are particularly accentuated in the frontal and temporal lobes and become more severe at increasing magnetic field strength.

Our second aim requires us to use spin-echo echo planar imaging (SE-EPI) for our fMRI acquisition as gradient-echo EPI (GE-EPI) does not allow for full recovery of signal lost due to susceptibility-induced intra-voxel magnetization dephasing. This generates a useful secondary benefit for our study, as evidence suggests that SE-EPI provides better localization of functional activation to the grey matter than GE-EPI, which has greater contamination from draining veins (see for example [12]).

Once the fMRI and DWI data are suitably processed we use the individual fMRI loci to initiate probabilistic fibre tracking. We then combine the results of these experiments to generate inter-nodal anatomical connectivity matrices.

2.1. Data acquisition

Imaging of a single right-handed healthy volunteer was performed on a 3T Philips Achieva scanner using an 8 element SENSE head coil with a sense factor of 2.5 and phase-encoding in the left-right orientation. Whole brain DWI was performed using a SE-EPI sequence with TE = 54 ms, TR = 11884 ms, no signal averaging, G = 62 mTm−1, 112 × 112 matrix reconstructed to 128 × 128, reconstructed in-plane resolution 1.875 × 1.875 mm², slice thickness 2.1 mm, 60 slices, 61 diffusion sensitization directions at b = 1200 smm−² (Δ, δ = 28.5, 13.5 ms), and 1 b = 0 acquisition.

For the b = 0 acquisition and for each diffusion encoding direction a pair of acquisitions with identical diffusion gradient directions but with opposite direction k space traversal was acquired to allow distortion correction (see below). Total imaging time was 28 min for the entire DWI acquisition.
For fMRI a whole brain 30 slice SE-EPI sequence with TE = 75 ms, TR = 3200 ms, 112 × 112 matrix reconstructed to 128 × 128, reconstructed resolution 1.875 × 1.875 mm², and slice thickness 4.2 mm was used. The fMRI acquisition consisted of a 10 volume pre-scan with interleaved reversed k space traversal (again to allow distortion correction) and the subject at rest, followed by the main sequence of 160 time points with a single k space traversal direction over which the fMRI task was performed.

2.2. Distortion correction

Geometric and intensity distortion corrections were performed using an algorithm based on the reversed k space traversal method of Bowtell et al [13-15]. This method requires that the members of the image pairs are well aligned in the frequency encode direction, as misregistration in this direction will be detrimental to the quality of the restored image. Conventional image registration techniques are not satisfactory as images with opposing k space traversals show opposite distortions. Instead, image pairs were registered to subvoxel accuracy in the frequency encode direction using the standard deviation of signal intensity of the resultant distortion-corrected images as the cost function for the registration process.

For the fMRI data the closest matching image pair (particularly in respect to vascular and CSF inflow effects) from the opposing k space traversal pre-scans was manually chosen and corrected for distortion as above. A matrix of pixel shift required to correct the images was derived. Each fMRI series volume was then affine-registered to the chosen uncorrected pre-scan volume (FLIRT/FSL (FMrib, Oxford)). Distortion in the registered fMRI series was then corrected using the pixel shift maps.

Figure 1 shows examples of pre- and post-distortion correction diffusion generalized fractional anisotropy (GFA) [16] and fMRI time series images. The correction method largely removes eddy current distortion-induced artefacts in the GFA map in addition to removal of gross geometric and signal distortion [15].

2.3. fMRI paradigm, analysis, and output

A word categorization task involving semantic understanding based on that used in [11] was used to provide activation of language and semantic networks. Distortion-corrected images were subjected to single subject statistical analysis (FEAT/FSL (FMrib, Oxford)). Figure 2 shows the activations identified using (cluster level stats, 4 mm smoothing, z > 2.6, p < 0.05). A widespread activation pattern is observed with left hemisphere lateralization, as is expected from language-related function.

2.4. Probabilistic fibre tracking

We use the PICo method to generate maps of connection probability (or confidence) [3, 4, 17]. PICo utilizes a Monte Carlo streamline approach, sampling probability density functions (PDFs) of estimated fibre orientation(s) at each location encountered by a streamline on each iteration; 1000 iterations were taken for each voxel within each start region. The number of occasions, N(p, N), over N repetitions, at which each voxel p is crossed by a streamline is used to define a map of the probability (or confidence) ψ of connection to the start point:

\[
\psi(p) = \lim_{N \to \infty} \frac{\mu_{\psi}(N)}{N}
\]

Sampling each PDF at random on each iteration takes into account the voxel-by-voxel uncertainty in fibre orientation. The maps of connection confidence provided by Eq. 1 therefore represent the line integral of fibre orientation uncertainty between any voxel and the start voxel [1]. Due to the propagation of uncertainty, longer-range connections will generally demonstrate lower confidence of connection than those at shorter range.

PDFs are generated using fibre orientation estimates obtained via the q-ball algorithm [7]. The effect of noise on orientation estimates in the case of single, two, or three fibre populations is modeled using MR measurements synthesized from test functions derived from a mixture of tensors [18, 19]. PDFs are parameterized using the methods presented in [17, 19], which use a calibration procedure to relate the curvature of the q-ball function at its peaks to the uncertainty in fibre direction at a given signal to noise ratio.

2.5. Inter-nodal tracking & anatomical connectivity matrices

Maps of ψ are generated for each voxel within each of the 17 fMRI-defined tracking start regions. Tracking is therefore initiated primarily in cortical grey matter, although some overlap with white matter occurs in most regions. The probability (or confidence) of connection from each area to each of the other 16 areas is quantified using a method similar to that presented in [20], generating 272 non-trivial node-to-node measurements. An anatomical connectivity matrix [9] may then be constructed from these measurements, which is then forced to be symmetric according to \((n,m) = ((n,m)+(m,n))/2\). The top quartile of inter-nodal connection probability values are taken to represent the highest confidence set of observed connections.

3. RESULTS

Figure 3 shows an example of the output of the probabilistic multi-fibre tractography using q-ball from an fMRI-derived functional region in the right inferior temporal gyrus / right fusiform gyrus (R IFG / FG). Relatively high levels of connection probability are apparent within the temporal lobe, to the parietal and occipital lobes, and to prefrontal regions from the start region.
task used in this work. The second key feature is the incorporation of a reversed $k$ space traversal scheme that successfully removes geometrical distortions. Application of this method to fMRI has, to the best of our knowledge, not previously been attempted, as it is inappropriate for application to GE-EPI due to intravoxel magnetization dephasing-induced signal loss. SE-EPI does not suffer from this limitation. The possibility for distortion correction, the improved precision of functional localization, and the good sensitivity of the method leads us to propose, at least at magnetic field strengths of 3 T and higher, that SE-EPI has some notable benefits for functional imaging.

We believe that this is the first application of recently-developed probabilistic complex fibre architecture tractography using q-ball [19]. The results of the fibre tracking indicate that it is possible to initiate tracking from fMRI-derived regions, as has been shown previously [8]. However, unlike previous studies, we have not attempted to derive ‘optimum’ seed points or regions from the fMRI information but have chosen to use the thresholded clusters in their ‘raw’ state. This is likely to lead to some difficulties in the tractography process – for example, the size of the fMRI loci will in general influence the pattern of anatomical connectivity derived from them. While this will in some cases be a desirable feature, in regions where artefactual locus extent is present this will introduce error, especially if an activation area extends across sulci (Fig. 2). Increased network information precision may be acquired with the use of prior functional neuroanatomical knowledge to indicate the ‘real’ site of activation in such situations. However, this would be at the expense of objectivity. Similarly, errors (false positives and false negatives) clearly remain in the tractography process. For example, we do not see the arcuate fasciculus connecting Wernicke’s area and Broca’s area in Fig. 5, as this connection did not fall within the top quartile of connections identified in Fig. 4 (although it does fall in the $2^{nd} - 3^{rd}$ quartile interval). This is likely to be due in part to the arbitrary setting of the ‘of interest’ threshold in the connectivity matrix. Probability of connection necessarily falls off with distance when using current probabilistic tracking methods due to the propagation of uncertainty from voxel to voxel (Fig. 3). The arcuate fasciculus, being a long range association bundle, may suffer from this effect more than short range connections. New developments designed to define probabilistic tractography connection significance and to ameliorate distance-related effects are likely to reduce this problem [21].
A second source of error is the localization of function to grey matter. To identify inter-nodal anatomical connections the tracking process must first exit a 'source' grey matter region and subsequently enter the 'target' region. The second of these processes in particular is affected by the low grey matter diffusion anisotropy, which leads to low connection probability. It is likely that processing of the fMRI loci to extend them into neighbouring grey white matter will improve the reliability of this step, although this may require some expert neuroanatomical input.

We anticipate that the definition of the anatomical substrates to functional networks based on the methodology presented here will provide otherwise unavailable information for modeling inter-regional functional interactions. This will be valuable in understanding normal brain function, for interpreting the functional effects of lesions, and for understanding some of the mechanisms underlying brain plasticity and recovery after injury.

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6. REFERENCES


