Comparing Corticocortical Interconnection Information from Tracer Studies and Probabilistic Tractography in the Postmortem Macaque Brain

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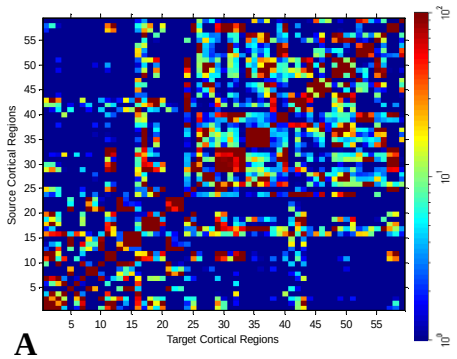
Introduction In an attempt to validate the corticocortical connection information we can gain from diffusion weighted MR data, we have implemented probabilistic tractography in data acquired in a macaque model and compared this with connection information already known from invasive tracer studies in the same model. The nature of the information gained from probabilistic tractography is different to that gained from invasive studies, and thus our comparison is on a binary level of whether corticocortical connections were found with either technique or not. Although probabilistic tractography experiments can yield connection strengths between all cortical areas, there are only sparse corticocortical connection strengths available from published invasive studies.

Methods MR diffusion-weighted data were acquired in a formalin-fixed post-mortem brain of a rhesus macaque (*Macaca mulatta*) on a 4.7T Bruker BIOSPEC vertical bore scanner. A 2D spin echo sequence was implemented with TE = 78ms, TR = 9s, G_{max} = 47mT/m, 104 × 94 imaging matrix, 58 contiguous slices, isotropic voxel resolution 0.8 mm, 61 non-collinear diffusion sensitisation directions at b = 4,000s/mm^2 (Δ = 39ms, δ = 31ms), 7 at b = 0, NA = 4. The total imaging time was ~ 64 hours. To improve the signal-to-noise in the diffusion-sensitised images, for the purposes of tractography, we applied 5 iterations of 2D anisotropic diffusion smoothing[1] (rsb.info.nih.gov/ij/plugins/anisotropic-diffusion-2d.html) using ImageJ (rsb.info.nih.gov/ij/index.html). Software was developed in-house in MATLAB (www.mathworks.com/products/matlab/) to implement q-ball[2] analysis on our data, and to implement model-based residual bootstrapping[3,4] to generate a diffusion probability density function (PDF) for probabilistic tractography. The Probabilistic Index of Connectivity (PICo)[5,6] software, incorporating multi-fibre information, was employed to implement probabilistic tractography. *Model-based Residual Bootstrapping:* The dataset was first processed with q-ball[2] to generate diffusion orientation distribution functions (ODF)[2] whose peaks relate to the principle underlying fibre orientations (one or more). Using the number of fibres extracted in each voxel from the ODFs we fitted one, two or three diffusion tensors to the original diffusion-weighted signal acquired[7], or assumed isotropic diffusion if the number of fibres extracted using q-ball was greater than three. The predicted signal was then recovered using the fitted diffusion tensors[7]. Residuals were calculated between the predicted diffusion-weighted signal from the multi-tensor fitting and the original acquired diffusion-weighted signal. Over 32 iterations, a new image set was created by randomly shuffling the residuals, for any given voxel, amongst all the diffusion-encoding directions and then adding them on to the predicted diffusion-weighted signals. The image set created by each bootstrap sampling was then processed with q-ball to extract the estimates of underlying fibre orientations, as described above. The PDF for probabilistic tractography was created from the 32 samples of fibre orientation generated for every voxel in the dataset. *Cortical Parcellation:* We took the cortical partitioning scheme of [8] (LVE00a) available as part of the Caret[9] 5.5 software (brainmap.wustl.edu/caret) for the F99UA1 rhesus macaque brain atlas. In order to use this cortical partitioning scheme in our dataset we applied non-linear warping to the anatomical MRI brain volume of F99UA1 to spatially match the brain volume of our dataset as close as possible using the Normalize tool in SPM5 (www.fil.ion.ucl.ac.uk/spm/software/spm5/). The transformation parameter file from this non-linear warping was then applied to the LVE00a[8] cortical partitioning template. *Tractography:* Each of the 59 cortical regions in the spatially matched LVE00a template was used as a seed region for probabilistic tractography using PICo in our dataset with 1000 Monte Carlo streamlines[6,7]. A corticocortical interconnection matrix was created by measuring how many of 1000 streamlines from a specified cortical region passed through all of the other cortical regions. This gave us a matrix of "strengths" of corticocortical interconnection (SCI) on a scale of 0-100%. We applied a threshold to exclude any interconnections below 1% (probability of connection < 0.01). *Tracer Studies:* The CoCoMac[10] database (cocomac.org/home.asp) provides details of interconnection between thousands of sites in the macaque brain gained from invasive tracer studies described in the literature. We obtained the interconnections found between the regions in the LVE00a[8] cortical partitioning scheme from CoCoMac as a connectivity table, where the SCI is on a categorical scale of 0-3 (0 = no connection reported, through to 3 = strong connection reported). However, unlike the interconnection results from tractography, information from tracer studies is unidirectional and sparse, as the full set of possible interconnections is unavailable for the LVE00a map.

We compared our SCI results from tractography with those from tracer studies graphically as color-rendered plots, but only where information is available from both. We performed the Kruskal-Wallis (KW) non-parametric test to compare SCIs from tractography grouped according to the corresponding (categorical) SCIs from tracer studies.



Results The source and target cortical regions numbered 1 to 59 on the matrices in Figs. A & B correspond to the subset of cortical areas in the left hemisphere labelled as follows in the LVE00a scheme: 1, 2, 4, 23, 45, 24d, 3a, 46p, 46v, 4C, 5D, 5V, 6Ds, 6Val, 6Vam, 6Vb, 7a, 7b, 7op, 7t, 8Ac, 8Am, 8As, A1, AIP, DP, FST, IPa, LIPd, LIPv, LOP, MDP, MIP, MSTda, MSTdp, MSTm, MT, Pi, PIP, PO, PrCO, Ri, S2, TAa, TE1-3, TEa/m, TF, TPOc, TPOi, TPOr, Tpt, V1, V3, V3A, V4ta, V4tp, VIPl, VIPm, VP, respectively. A value of -1 has been used in Fig. B to fill in empty cells where there is no interconnection information from tracer studies in the CoCoMac LVE00a database. The KW test showed that the tractography SCI values are significantly different between the categories of SCI from the LVE00a invasive data ($p < 0.001$). This is shown by the box plot in Fig. C. The probabilistic tractography SCI corresponding to a tracer SCI of 0 (with a median tractography SCI of 0%) is significantly lower than those corresponding to a tracer SCI of 3 ($p < 0.001$). If we combine the probabilistic tractography SCIs that correspond to tracer SCIs of 1, 2 and 3 and compare against those corresponding to a tracer SCI of 0, then the combined group of all non-zero invasive tracer SCIs has significantly higher tractography SCIs than the group for which invasive tracer SCI = 0 ($p < 0.001$).

Conclusions Our results using the LVE00a parcellation scheme indicate that probabilistic tractography is able to give comparable information on corticocortical interconnections to invasive tracer studies,. It is also clear from Fig. C that a number of false positive connections may exist in the tractography results, although the exact number is unclear due to the unidirectional nature of the invasive tracking. Further work will investigate the level of agreement between probabilistic tractography and invasive tracers using additional cortical partitioning schemes to build up a comprehensive assessment of tractography validity.

References 1. Tschumperlé & Deriche, *IEEE Trans Pattern Anal Mach Intell*, **27**:506, 2005. 2. Tuch, *Magn Reson Med*, **52**:1358, 2004. 3. Haroon & Parker, *ISMRM*, 903, 2007. 4. Berman, *et al*, *ISMRM*, 1471, 2007. 5. Parker & Alexander, *Lect Notes Comput Sci*, **2732**:684, 2003. 6. Parker & Alexander,*Phil Trans R Soc Series B*, **360**:893, 2005. 7. Alexander, *et al*, *Magn Reson Med*, **48**:331, 2002. 8. Lewis & Van Essen, *J Comp Neurol*, **428**: 79, 2000. 9. Van Essen, *et al*, *J Am Med Inform Assoc*, **8**: 443, 2001. 10. Stephan, *et al*, *Phil Trans R Soc Lond B Biol Sci*, **356**:1159, 2001.

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