

Quantitative Validation of MR Tractography using the CoCoMac database

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Introduction

From the beginning of the development of MRI tractography, validation of the reconstructed tracts has been a major difficulty, since gold standards against which the method can be tested are difficult to obtain. Several strategies were used in order to try to characterize the performance of tractography. Numerical or physical phantoms [1], gross comparison of major tracts between tractography and macroscopic dissection were used. Recently Schmahmann et al. [3] compared about 10 association tracts computed from fixed macaque brain tissue which was scanned with DSI with a collection of autoradiography tracing studies of the same species and they found a good agreement between both methodologies. If all these validation studies have been immensely valuable to get some confidence in MR tractography none of them is quantitative. In other words, there is an absolute necessity to characterize sensitivity and specificity of a MR tractography experiment. This is precisely the aim of this study that compares a MR tractographic experiment performed in a fixed macaque brain with a set of 313 connections identified by diverse histologic tracing studies and stored in the CoCoMac database.

Material and Methods

Histologic Tracing : The macaque neocortex is parcellated according to the original Felleman and Van Essen paper [3] and includes visual, somatosensory and motor cortical regions. The connections between these regions were manually collated in the CoCoMac database from published tracing [4]. Subsequently, all relevant data were translated algorithmically to the Felleman and Van Essen cortical map using coordinate-independent mapping. After resolution of redundant and inconsistent results a binary connection matrix with 47 nodes (vertices) and 505 edges (connections) was generated. Then the matrix is made symmetric as for MR tractography orientation of the projections is not possible to determine. The result is a 47 by 47 connection matrix where 313 effective histologically traced connections are coded in red, 469 documented absent connections in blue and unknown fields in green.

MR Tractography: We used one hemisphere of an adult male fascicularis monkeys. After euthanasia, the brain was fixed with formalin for at least 4 weeks. Then the brains were soaked for at least 28 days in a buffer solution containing gadolinium (Gd-DTPA) and scanned on a 4.7 T Bruker Biospec system. The pulse sequence was a 3D diffusion weighted spin-echo EPI sequence, TR/TE 450/63 ms, with an imaging matrix of 128 x 256 x 128 pixels with isotropic spatial resolution of 300x300x400 μm^3 . Diffusion spectrum encoding was performed as previously described in [5]. It consisted of 515 diffusion weighted measurements, corresponding to a cubic lattice in Q-space contained within the interior of a ball of maximum radius $b_{\text{max}} = 4 \times 10^4 \text{ cm}^2/\text{s}$, with $\Delta = 12 \text{ ms}$, $\Delta = 31 \text{ ms}$. Total acquisition time was 25 h. Diffusion spectra were reconstructed for each voxel by 3D Fourier transform of the modulus of the acquired data. Whole (hemi)-brain DSI streamline tractography was performed. The hemispheric cortex was partitioned into 1000 ROIs of equal size as described in [6]. A 1000 by 1000 connection matrix was then built by capturing the fibers ending in each pair of ROIs and the connection density was calculated. Then manually these small ROIs were grouped to match the Van Essen cortical partition as depicted in Fig 1. The mean connection density between these cortical regions was calculated and reported in a 47 by 47 regional connection matrix (Fig 3).

Results

Considering the binary gold standard matrix (Fig 2) and comparing it with the weighted DSI connection matrix (Fig 3), we readily see similarities. Blue pixels in Fig 2, which means absent connections correspond to blue areas in Fig 3 which mean absent or weak connections. On the other hand red pixels in Fig 2 correspond to red or yellow pixels in Fig 3, demonstrating significant agreement. In order to quantify the performance of MR tractography we compute sensitivity and specificity for different thresholds on the connection density of Fig 3. The result is plotted as a Receiver Operating Characteristic (ROC) curve. We see for example that for a sensitivity of 60% the specificity is about 70% or for a specificity of 90% the sensitivity drops to 40%. There also seems to be an asymptote at 70% sensitivity.

Discussion

This is the first report on a systematic quantitative assessment of the performance of MR tractography compared against an effective gold standard, namely a collection of more than 300 published histological tracer studies. Furthermore the false detection rate can also be estimated since the histological tracing studies on which we base our analysis documents effective absent connections between well defined areas, this for over 400 pairs of regions. This analysis clearly states 1) that MR tractography is a valuable tool to map connections in the brain with acceptable performance (i.e. sensitivity and specificity). 2) However the agreement is by far not perfect, in particular it seems that about 30% of the connections cannot be identified, whatever the threshold on the connection density. What characteristics do these lost connections have? Are they weak, short or of strange trajectory? Further analysis of our data will be needed. But it is clearly expected that due to limited resolution very sparse connection cannot be identified by MRI. 3) There is significant room for acquisition and algorithm improvement for MR tractography. The ROC curve is going to be the ultimate performance assessment tool. 4) The DSI data used in this study have been acquired postmortem with very high SNR. Further studies will be needed in order to evaluate the effective performance in a clinical setting or with other diffusion MRI schemes like DTI.

References [1] Lin et al. Neuroimage 19:482-95 (2003) [2] Schmahmann JD et al. Brain 130 :630-54 (2007) [3] Felleman, DJ & Van Essen, DC.) Cereb Cortex 1 :1-47 (1991) [4] Kötter R (2004) Neuroinformatics 2:127-44 [5] Wedeen VJ et al (2005) Magn Reson Med 54: 1377-86. [6] Hagmann P et al (2007) PLoS ONE 2: e597

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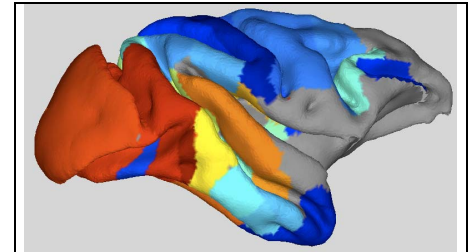


Fig 1: Partition of macaque cortex into 47 anatomical ROIs as defined by [4].

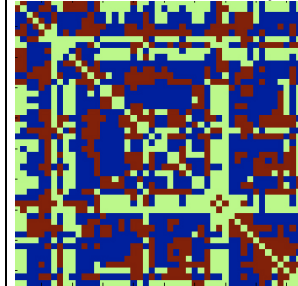


Fig 2: Connection matrix derived from the CoCoMac database collecting histologic tracing studies in the macaque brain. The 47 matrix entries correspond to the 47 ROIs of Fig 1. Pixel value: Red=connected, Blue = not connected, Green = unknown.

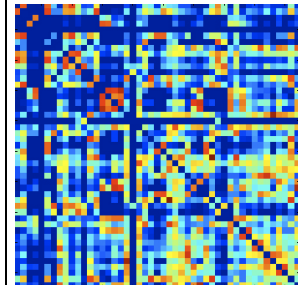


Fig 3: Connection matrix derived from post-mortem MR Tractography in a macaque brain. The 47 matrix entries correspond to the 47 ROIs of Fig 1. Pixel value: connection density.

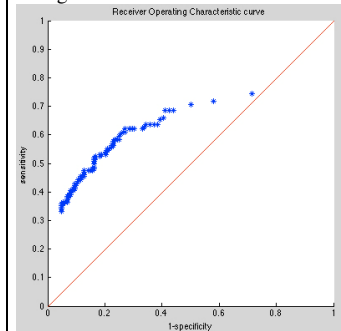


Fig 4: ROC curve by comparing various thresholdings of Fig 3 with Fig 2.