Acquisition of Diffusion MRI data with High Spatial and Angular Resolution on Postmortem Monkey Brains Using 3D Segmented EPI

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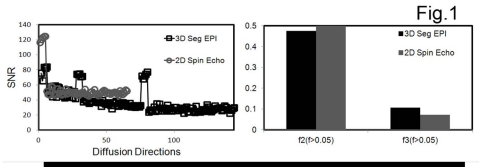
Audience: Scientists and clinicians interested in acquiring high-quality diffusion MRI data on postmortem animal brains for connectivity studies.

Background: Brain researchers need to collect diffusion MRI (dMRI) data on postmortem animal brains with high diffusion contrast, and high spatial and angular resolution, as such data provide overall superior quality for probing brain connectivity compared to the in-vivo counterparts [1, 2]. To date, postmortem monkey brains have been scanned with standard 2D or 3D spin-echo diffusion MRI sequences [1, 2]. However, because of its low sampling efficiency, this technique usually generates diffusion data with relatively low diffusion weighting (b-value <3000 s/mm^2) and angular resolution (diffusion directions < 60), which limits its application in brain connectivity studies. We have developed a pipeline incorporating sample preparation, sequence optimization and post processing that can acquire dMRI data on macaque monkey brains with high spatial resolution, angular resolution, and diffusion contrasts in less than 40 hours. Such a pipeline for collecting high-quality diffusion MRI data on postmortem macaque brains may assist in bridging the abundant connectivity information derived in monkey tracer studies and human connectomic studies via diffusion tractography.

Methods: *Sample preparation*: As the long readout in echo-planar imaging will cause distortion along the phase encoding direction, the brain sample needs to be prepared for susceptibility matching. 500ml water with 2% agarose solution and 0.36g Gd (III) oxide was stirred well in a beaker and heated to boil. Then a formalin-fixed postmortem macaque brain was immersed in the solution after the temperature of the solution was dropped below 60º. The brain sample immersed in the solution was then shaken on a shaker to remove the bubbles attached on the surface and then was cooled to the room temperature to allow the agarose gel to solidify. Last, the extra solidified agarose gel around the brain sample was removed with a blade to leave a ~ 10mm coating on the brain for susceptibility matching. *Data acquisitions: The ex-vivo experiment* was performed on a Bruker BioSpec 9.4 T system equipped with 200 mT/m actively shielded gradients. The brain were scanned with a transmit/receive r.f. volume coil (ID:72 mm) and the data were acquired with a 3D segmented spin-echo EPI diffusion sequence with the following parameters: TR/TE=300/34ms; FOV=70x90x70 mm3; resolution= 500µm isotropic; b=2000, 3000, 4000 s/mm^2; total diffusion directions = 128 (21, 43 and 64 on the first, second and third shells); segments = 10; partial Fourier factor = 1.3. Its total scan time for two repetitions was **34 hrs**. 3D RARE images with the identical spatial resolution, FOV and similar gray matter/white matter contrasts were also collected for correcting the residual geometric distortion presented in the data. The parameters for the RARE sequence were as follows: TR/TE=2500/13ms; RARE factor=8; flip angle=180; repetitions=7. The total scan time was 7. *Data processing*: RARE images were utilized as the reference for removing the geometric distortion in the dMRI data using "topup" as they were distortion free and had similar contrasts [3]. The first (f1), secondary (f2) and tertiary fiber (f3) compartments and their percentages over the total number of brain voxels were estimated using "bedpostx" in FSL. To demonstrate the overall high quality of the data, we compared our results with a set of postmortem macaque dMRI data collected previously on the same scanner using the standard 2D spin-echo dMRI sequence. The main parameters of the data were as follows: TE=22.25ms, 550 µm isotropic resolution, b=2000, diffusion directions of 60. Only data from the central part of the brain was acquired due to the long scan time required by the spin-echo diffusion sequences. The total scan time was **72 hrs.**

Results: The signal-to-noise-ratios (SNRs) of the acquired images using the 3D EPI-based diffusion sequence in the first 128 diffusion directions, as measured by the ratio between the mean signal intensity in an ROI of the brain white matter and the stand deviation of the background ROI, were plotted in Fig.1, upper left. The SNR of the data collected using standard spin-echo dMRI sequence (Fig.1, upper left, gray) was also plotted using the same method. It can be seen that with the b value of 2000, high SNR could be achieved using the 3D segmented EPI dMRI sequence. However, the data collected using the EPI-based approach acquired four times more data with equivalent or higher diffusion weighting in half the scan time by the standard spin-echo sequence. The superior quality of the data using our pipeline can be further demonstrated by the percentages of the f2 and f3 fibers that survived 5% of the total fiber compartments: The data acquired using the EPI-based diffusion sequence showed a comparable percentage of f2 and 40% more f3 compared to those by the standard spin-echo-based sequence (Fig.1 upper right), even though the former's spatial resolution was even higher (0.5mm vs. 0.55mm isotropic). After the susceptibility distortion correction, the corrected diffusion MRI data (Fig.2b) showed minimal distortion compared to the RARE (Fig.2a) image. When visualizing the f2 (blue) and f3 (pink) compartments in the data acquired using the two sequences, the data collected using the 3D EPI-based diffusion sequence (Fig.2c) showed higher proportions of f2 and f3 in the white matter areas, resembling those of the high-quality Human Connectome Project diffusion data, whereas the f2 and f3 obtained with the standard spin-echo sequence have more random and discrete distributions in both gray and white matter (Fig.2d).



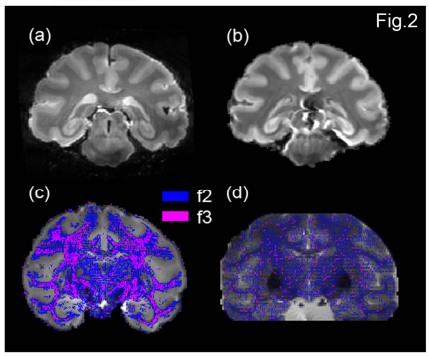


Fig.1: left: the SNR of the 3D segmented EPI (black) and the standard 3D spin-echo (gray) diffusion sequences; Right: the estimated secondary (f2) and tertiary (f3) fiber compartments survived 5% of the total fiber compartments.

Fig.2. The (a) RARE image and (b) distortion-corrected b0s; The spatial distributions of f2 and f3 in the data collected using the (c) 3D Segmented EPI and (d) 3D standard spin-echo sequences.

Conclusions: Our protocol for collecting high-quality diffusion MRI data from postmortem macaque brains using a 3D segmented EPI diffusion sequence yields significantly higher-quality data with less scan time than the standard spin-echo sequence. Using a customized coil with an inner diameter of 10cm, this pipeline has also been adapted to collect high-quality diffusion data on postmortem chimpanzee brains with high spatial resolution (1.1mm isotropic), angular resolution (D=128), diffusion contrast (b=2000, 3000, 4000) over a weekend scan (60 hrs).

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