TRANSLATING FMRI AND DTI BIOMARKERS FROM ACADEMIC STUDIES TO GLOBAL CLINICAL TRIALS IN ALZHEIMER'S DISEASE

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Introduction

Recent failures in phase III trials have demonstrated that the development of new treatments for Alzheimer's Disease (AD) could be facilitated by obtaining stronger evidence of efficacy in earlier phase clinical studies. Established structural MRI biomarkers (eg: hippocampal atrophy) require ~100 subjects per arm over 12 months for realistic powering in prodromal populations [1]. There is a pressing need for faster read-outs. Both Diffusion Tensor Imaging (DTI) and resting state functional Magnetic Resonance Imaging (rs-fMRI) measures correlate with AD disease stage and clinical scales [2,3]. Multi-centre studies are essential for rapid enrolment in therapeutic trials. In such a setting, it is essential to be able to collect high-quality data across different scanner vendors and over time in a standardized way. The second phase of the Alzheimer's Disease Neuroimaging Initiative (ADNI-2) has introduced DTI and rs-fMRI sequences at 3T, but only on a single vendor basis (DTI on GE systems and rs-fMRI on Philips systems). Our objective was to implement the ADNI-2 DTI sequence on Philips and Siemens scanners and the ADNI-2 rs-fMRI sequence on Siemens scanners in a consistent way and evaluate their equivalence and reproducibility prior to their use in a multi-centre study of a new therapeutic agent at sites with a mixture of Siemens and Philips 3T scanners.

Methods

Two healthy volunteers aged 24 and 29 were recruited and the DTI and rs-fMRI ADNI-2 sequences were acquired twice (with re-positioning) on each subject on the following MRI 3T scanners: Siemens Trio Tim VB15, Philips Achieva 3.2 and GE Signa HDx (DTI only). This procedure was repeated twice on the same volunteers on the Philips and Siemens scanners. The DTI sequence parameters were (GE/Siemens/Philips): TE =59/88/77 ms, TR =12200/7000/6086 ms, in-plane resolution = 2.7 x 2.7 mm, slice number = 59, slice thickness = 2.7 mm no gap, gradient number = 5 repeats of b=0 and 41 directions with b=1000 s/mm^2. The rs-fMRI parameters were: TE = 30 ms, TR = 3000 ms, in-plane resolution = 3.3 x 3.3 mm, slice number = 48, slice thickness = 3.3 mm (no gap), phase encode direction = AP, number of dynamics = 140. Images from both sequence types were assessed visually for the presence of gross artefacts. The DTI images were processed and analysed using BrainVISA/Connectomist-2.0 [4]: outlier detection and correction, eddy current and motion correction and DTI model processing. The data were assessed quantitatively by measures of mean FA within ROIs in the splenium and genu of the corpus callosum, manually-delineated on the FA maps. The rs-fMRI images were processed using Statistical Parametric Mapping (SPM8): motion correction, spatial smoothing (FWHM=5mm), spatial normalization to SPM8 EPI template and physiological noise correction using CORSICA [5]. The data were assessed quantitatively by measures of mean correlation between sets of predefined nodes in the Default Mode (DMN) and Sensorimotor (SMN) networks.

Results

The reproducibility and consistency of both sequences was within the range of previously published test-retest values. The scan-rescan variability of the genu and splenium FA values was under 2% and that of the rs-fMRI correlation in the DMN and SMN was 6% and 4% respectively (Figure (a)). The variability across scanners of the DTI FA values was under 3.5% for both splenium and genu ROIs (Figure (b)). The variability across scanners in rs-fMRI correlation was under 10% for the DMN and 3% for the SMN.
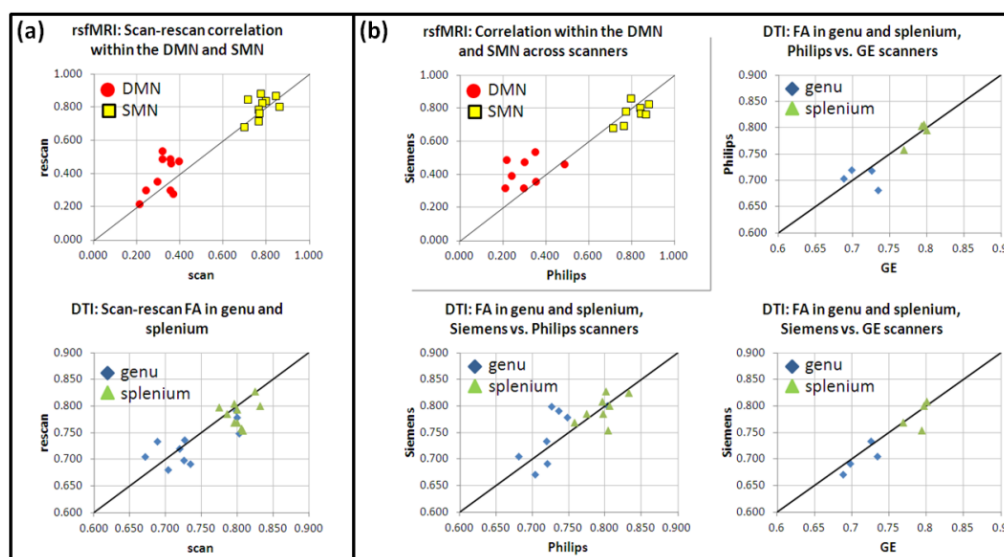
Figure: (a) Scan-rescan performance of rs-fMRI and DTI summary measures. (b) Relationship between rs-fMRI and DTI summary measures acquired on the different scanner types.

Conclusions

We have demonstrated a stable deployment of ADNI-style fMRI and DTI sequences in a multi-vendor environment, with between-scanner variability that is comparable to test-re-test variability on a single scanner [6,7]. The higher variability of rs-fMRI measures was expected from previous studies. This exercise is critical to ensure that DTI and rs-fMRI data acquired in multi-centre, multi-vendor studies will yield comparable numeric endpoints.

References

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