

## Quality Assessment and Consistency of Serial Multi-Center Resting-State fMRI in Alzheimers Disease

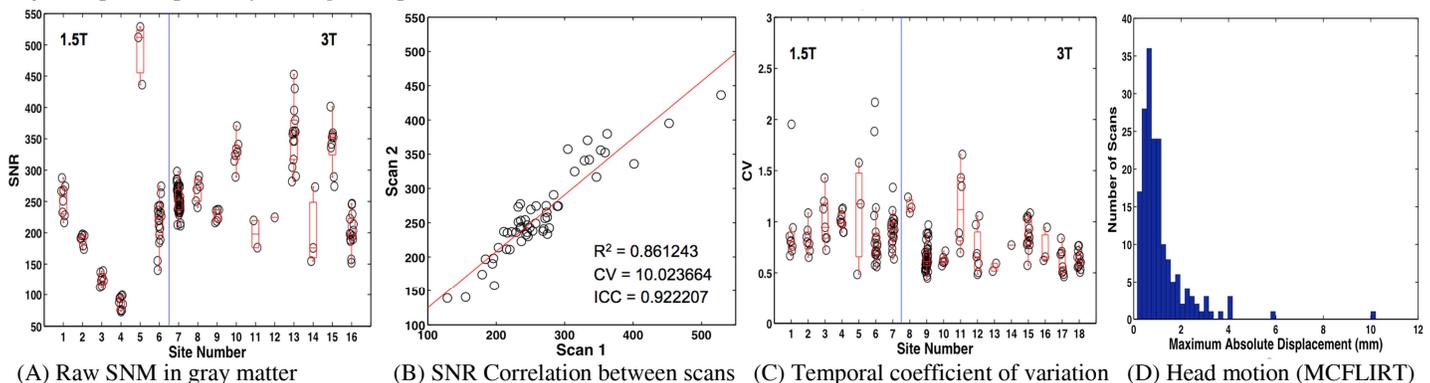
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**Introduction:** Several single site resting-state fMRI studies (RS-fMRI) have shown that brain functional connectivity metrics are altered in Alzheimer Disease (AD) patients. Exploratory RS-fMRI was included in two global Phase II studies of a novel AD drug. We report here fMRI data quality control procedures and observed quality metrics from screening and very early on-treatment scans.

**Materials & Methods:** Data Acquisition: A total of 180 scans were acquired from 103 patients across 20 sites in N. America and Europe. Selected sites were a subset of the clinical trial sites who self-reported previous experience using fMRI. Seven sites used 1.5T and the remaining 11 sites used 3T magnets from three major manufacturers, Philips, Siemens, and GE. For 48 patients, two or three RS-fMRI datasets were acquired at 7-week time intervals. Due to the relatively short inter-scan interval, we made the assumption that consecutive intra-subject scans were equivalent to “test-retest” data sets (i.e. minimal effect of disease progression or therapy). There were 68 such consecutive pairs of RS-fMRI datasets. The RS-fMRI acquisition consisted of a 2D, single-shot, GRE-EPI sequence and was accompanied by an anatomic 3D, high-resolution T1-wt, spoiled gradient-recalled echo sequence. A standard imaging protocol was provided to all sites. Sites were allowed to use a locally established fMRI scan protocol with the exception of the following required parameters: TR=3000 ms, 140 time points (i.e. 7min. scan), Right-Left frequency encode, 64x64 matrix 224x224 mm FOV, slice thickness 4.5 mm, ~160 mm SI coverage, TE =30/50 ms with flip angle 90°/80° at 1.5T/3T, local fat saturation method, high order shimming if available, acceleration discouraged. Subjects were asked to rest eyes closed. All images were analyzed centrally. Pre-processing: An automated processing and quality control pipeline was set up FSL and in-house developed MatLab and Perl functions. EPI data were brain-extracted, motion-corrected, spatially (5 mm FWHM kernel) and temporally (100s high pass cutoff) filtered and signal intensity normalized. EPI datasets were registered to the brain extracted anatomical T1 scans, and subsequently registered to MNI152 standard space using both linear and non-linear registration algorithms. The following nuisance variables were regressed out of the EPI data by general linear model fitting: mean of predefined CSF and WM seed, global brain signal, 6 motion correction parameters. To estimate raw SNR, signal was average from a gray matter mask in the center 10 slices and noise was defined as the standard deviation of background voxels in the corners of the most superior slice. Coefficient of variation (CV) as defined as the average of voxelwise temporal standard deviation / mean in gray matter voxels; CV was measured after each pre-processing step. Head motion was assessed using the output of FSL’s MCFLIRT tool.

**Results:** Protocol compliance: deviations from the prescribed imaging protocol were observed at 10 sites however the majority were minor (e.g. small TE or TR changes) and occurred consistently in all scans from the site. Analyzable data was obtained from ~95% of scans received. Significant variation in raw gray matter SNR was observed across sites (A) but was highly consistent between ‘test-retest’ pairs of scans from any specific site (B). Some low SNR sites used volume head coils, while some very high SNR sites had applied some filtering to the DICOM images. Median SNR at 1.5T sites was 200, and at 3T sites was 255. Gray matter CV showed much less inter-site variation than SNR (C). As a function of pre-processing step; after registration, median CV was 1.0, decreasing to 0.75 after regressing out nuisance variables, decreasing to 0.25 after temporal/spatial filtering. Linear vs. non-linear registration made no difference to median CV. The correlation of CV between test-retest pairs was moderate ( $R^2=0.29$ , ICC = 0.55). Median (pre-filtered) CV at 1.5T sites was 0.87, and at 3T sites was 0.67. Subject head motion was consistently well controlled across sites (D); maximum displacement was < 1 voxel in all but 2 scans. Subject feedback was obtained after 40% of scans; in 15% of these scans the subject reported possibly falling asleep.



**Conclusions:** We successfully implemented a simple RS-fMRI protocol as part of a multi-site AD trial. Subject tolerance and protocol compliance was good. In spite of heterogeneous scanning equipment and variable raw SNR across sites, the pre-processing pipeline resulted in consistent CV data, with few scans that could not be used for subsequent functional connectivity analysis. Time will tell whether functional connectivity metrics are sensitive to Alzheimers disease progression and/or therapy, however the multi-center RS-fMRI approach described here may be a valuable tool to facilitate drug development in many other disease areas.