Test-Retest Reproducibility Assessment of CBF Measurements with 3D GRASE ASL at 1.5 T in Aged Population with Alzheimer's Disease

A. Coimbra[1], D. Feng[2], S. Apreleva[2], P. Hu[3], S. Ramana[4], A. Bernstein[5], M. Guenther[6], W. Cho[7], M. Forman[8], A. Verma[9], G. Herman[10], R. Baumgartner[2], and D. Feinberg[4]

[1]Imaging, Merck & Co, Inc, West Point, PA, United States, [2]Biometrics, Merck & Co, Inc, Rahway, NJ, United States, [3]BARDS, Merck & Co, Inc, Upper Gwynedd, PA, United States, [4]Advanced MRI Technologies, Sebastopol, CA, United States, [5]Redwood Regional Medical Group, Santa Rosa, CA, United States, [6]Fraunhofer MEVIS-Institute for Medical Image Computing, Bremen, Germany, [7]Experimental Medicine, Merck & Co, Inc, Upper Gwynedd, PA, United States, [8]Clinical Pharmacology, Merck & Co, Inc, Upper Gwynedd, PA, United States, [9]Translational Neurology, Biogen Idec, Cambridge, MA, United States, [10]Clinical Research, Merck & Co, Inc, Rahway, NJ, United States

Introduction

Arterial Spin Labeling (ASL) is showing great promise as a tool for non-invasive measurement of cerebral blood flow (CBF). It is therefore important to understand and assess the test-retest reproducibility of the measured CBF, in particular when it is used in biomarker applications (disease progression, treatment effect estimation). In this contribution we assessed the test-retest reproducibility of 3D GRASE ASL technique at 1.5 T and in populations of AD patients and age matched control. Assessment of measurement reproducibility was done using graphical methods as well as quantitative metrics such as Intraclass Correlation Coefficient (ICC) and within subject coefficient of variability (WSCV).

Materials and Methods

3D GRASE ASL pulse sequence was used which accomplishes 3D brain coverage within 24 seconds (Ref 1). Sequentially scanning of flow-sensitive images with varying pulse sequence inversion time (TI) allows for calculation of absolute CBF and other flow dynamics, including arterial transit time (ATT) for specific brain regions. In this work we focus on CBF measurements. 40 untreated subjects were examined in 2 visits (V1 and V2), approximately 1 week apart. The ASL images obtained were transformed to MNI standard space. Regions-of-Interest were defined by Tzurio-Mazoyer anatomical atlas (AAL). For each subject, mean values of the CBF across predefined anatomical ROI were calculated for each visit. Subjects used in this investigation belonged to two groups, Alzheimer's disease (AD, N=20) patients (N=20) and age matched normal controls. Due to blinding of the groups to the current analysis, the data from both groups were pooled providing for larger dynamic range of CBF measurements as compared to analyzing data from the population of normal healthy volunteers. Scatter-plots of the data with 45 degree line were constructed (higher reproducibility yields less scatter from the 45 degree line). In addition, Bland Altman plots with corresponding limits of agreement were also displayed. ICCs with WSCV were computed following methods described in Refs 2, 3.

Results

Figure 1 (a) displays the graphical plots for an example region of interest (ROI), namely the Right Frontal Superior Orbital (rFSO). Note good agreement between the measurements corresponding to V1 and V2. Figure 1 (b) shows the Bland-Altman plot corresponding to the rFSO ROI. Note that most of the points shown are within the limits of agreement (green area). The ICC and WSCV for the rFSO ROI were 0.69 (0.47, 0.83, 95% C.I.) and 0.22 respectively, demonstrating good reproducibility. In comparison to previously reported reproducibility for ASL-measured CBF values in healthy individuals, the current results show similar ICC's, but larger WSCV.

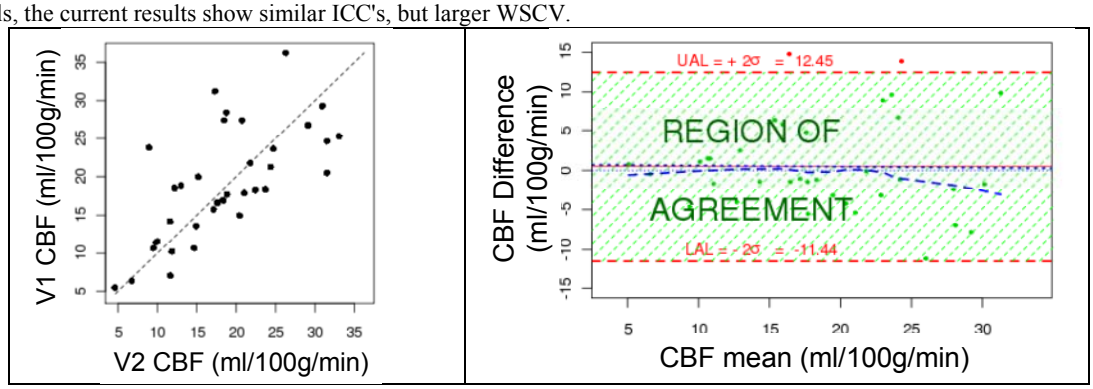

Figure 1 Right Frontal Superior Orbital ROI: (a) Scatter plot with 45 degree line with visit 1 vs. visit 2, (b) Bland-Altman plot with the limits of agreement in red

Similar results to the rFSO-ROI were obtained from the other ROIs. Specifically, out of 106 ROIs analyzed, 42 ROIs had ICC>0.7 (very good reproducibility), ICC for 49 ROIs ranged between 0.5 and 0.7 (moderate reproducibility) and 15 ROIs had ICC less than 0.5 (poor reproducibility). Typically, ROIs with high ICCs exhibited low WSCV, where the WSCV ranged from 14% to 40%. Other relevant regions for AD include Posterior Cingulum, with ICC=0.73 (0.54, 0.86, C.I.) and 0.55 (0.27, 0.74, C.I.), and WSCV=26.5 and 35.4% (for right and left hemispheres respectively); Inferior Parietal Lobe ICC=0.36 (0.03, 0.61) and 0.42 (0.11, 0.66), and WSCV=41.9 and 36.7% and Middle Frontal Orbital Lobe ICC=0.70 (0.49, 0.84) and 0.73 (0.53, 0.85), and WSCV=20.9 and 19.1%.

Conclusion

Our findings suggest that the test-retest reproducibility of 3D GRASE ASL varies between ROIs, and overall moderate to very good reproducibility can be achieved with 3D GRASE ASL technique at 1.5 T in an aged subject population with AD. Further improvement in reproducibility might be achieved with computational segmentation algorithms for circumscribing ROIs at cortical-CSF and Cortical-white matter boundaries. Assessment of reproducibility is an important first step to inform design (e.g. parallel versus cross-over) of future studies of disease progression and treatment effect.

References: 1. Guenther M, Oshio K, Feinberg D, MRM 54, 2005, 491-498; 2. Quan H, Shih WJ, Biometrics, 52(4),1996, 1195-203. 3. Shrout PE, Fleiss JL, Psychol. Bull, 1979, 420-8.