Systematic evaluation of region-wise iVASO reproducibility at multiple blood water nulling times

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TARGET AUDIENCE: Basic scientists interested in non-invasive mapping of brain hemodynamics.

INTRODUCTION: Cerebral blood volume (CBV) is an important physiological measure of vascular tone. Elevations in CBV have been suggested as a preclinical biomarker in Schizophrenia, Alzheimer's disease, Parkinson's disease, as well as a marker of autoregulatory capacity in cerebrovascular disease. Importantly, functional imaging based on CBV has potential for more quantitative assessment of brain activity relative to more common BOLD imaging. Most CBV measurements employ exogenous contrast agents, limiting their use in longitudinal monitoring or in functional experiments that require repeated measurements with high temporal resolution. Furthermore, autoregulatory mechanisms and functional hyperemia are related to relaxation of smooth muscle surrounding arterioles, making arterial CBV (aCBV) a valuable parameter to measure[1]. Inflow-VASO (iVASO) measures aCBV using arterial blood water as an endogenous contrast. iVASO acquisition consists of subtraction of a "control" image with steady-state tissue and blood signal from a "null" image that contains only tissue and venous signal[2-3]. iVASO is a relatively new technique, and its reproducibility, characteristics in the temporal lobe, and the range of optimal blood water nulling times have not been rigorously evaluated. The overall goal of this work was to assess intra- and inter-scan iVASO reproducibility using intra-class correlation (ICC) analysis, performance in cortical and subcortical regions, along with the range of optimal blood water nulling times.

METHODS: Ten healthy control volunteers (age = 22.0±2.3 years) provided written informed consent and were scanned at 3T (Philips). Reproducibility was assessed within the same scan session and between two scan sessions, performed 12±11 days apart in the cortex and the hippocampus. ***Experiment:*** T1-weighted MPRAGE (1 mm isotropic): Images were centered and aligned parallel to the sagittal sinus to minimize effects of head tilt. The 3D volume was then resliced to obtain a cortical slice parallel to the AC-PC line and another slice containing both hippocampi. Orientation information was noted for the inter-scan session. iVASO: TE=15 ms, TR = 500, 1000, 1492, 2000, 5000 ms corresponding to a TI = 429, 725, 914, 1034, 1191 ms, respectively, spatial resolution = 2.5×2.5×4 mm^3. 60 dynamics were acquired with alternating control and null images (30 each). The inversion slab for non-selective inversion included the imaging slice and was similar to Sequence IIa described in Hua et al[2]. ***Analysis:*** iVASO images were motion corrected in AFNI to the first image. aCBV was calculated[3] using the following equation with the assumption of perfect efficiency of the adiabatic pulses to invert and subsequently null blood water:

$$aCBV = \frac{\Delta S}{AM_b^0 C_b \left(\frac{TI}{\tau}\right) E1E2}$$

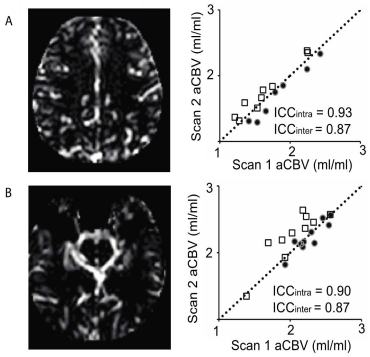

Figure 1: *aCBV maps with correlation plots for the cortex (A) and hippocampi (B). Plots showing intra- (filled) and inter- (open) scan reproducibility of aCBV measurement at TI = 914 ms. The dotted line represents a correlation of 1.*

ΔS is the difference between the control and null image, $M^0{}_b$ is the steady-state magnetization of blood water, C_b is the blood water density (0.87ml/ml)[4], A is a constant, $E1 = 1 - e^{(-TR/T1)}$, and $E2 = e^{(-TE/T2b^*)}$ where $T2_b^*$ is the $T2^*$ of blood water. $AM^0{}_b$ was calculated from the control image for each TR/TI combination using a sagittal sinus ROI and a correction for differences between arterial and venous $R2^*$ as outlined by Petersen et al[5]. Hippocampal ROIs were manually segmented while the gray matter cortex was segmented using FSL-FAST[6]. For each TI, intra-class correlation coefficients (ICCs) with the 95% confidence intervals were calculated for both regions.

RESULTS: The average cortical aCBV values were 1.58±0.46, 1.86±0.35, 1.87±0.32, 1.89±0.35, and 1.80±0.40 ml/ml at TI = 429, 725, 914, 1034, 1191 ms, respectively. The corresponding aCBV values averaged across the hippocampi were 2.21±0.42, 2.26±0.25, 2.28±0.24, 2.32±0.27, 2.20±0.27 ml/ml. Cortical aCBV was significantly lower than hippocampal aCBV ($p<0.05$) at each TI. The *intra*-scan ICC values ranged from 0.90-0.93 for the hippocampi for TI≤914 ms (no significant correlation was detected at longer TIs) and 0.93-0.97 for the cortical gray matter across all TIs. For each TI, the *inter*-scan ICC values ranged from 0.62-0.87 for the cortex and 0.50-0.87 for the hippocampi. Inter- and intra-scan ICCs were higher for intermediate values of TI (914 and 1034 ms) in the cortex and higher for shorter TIs (914 and 1034 ms) in the hippocampus. **Figures 1A** and **1B** show aCBV maps and correlation plots for cortex and hippocampus, respectively, at TI = 914 ms. With a similar sample size (n=10), aCBV differences of 0.49 and 0.68 can be detected at $p<0.05$ between populations in the cortex and the hippocampus respectively. Our ICC values fall in the same range as other MR-based CBV measurements. Contrast-based MR approaches have an ICC range of 0.73-0.84 while pseudo-continuous arterial spin labeling approaches, which are similar to iVASO, have an ICC of 0.07-0.78[7,8]. High hippocampal aCBV values compared to cortex aCBV values are likely due to higher baseline hippocampal activity and cortical partial volume effects. Single slice acquisition is a limitation of this study, and fast acquisition sequences such as 3D GRadient And Spin Echo[9] will allow for whole brain coverage to interrogate regional dysfunction hypotheses in neuropsychiatric disorders.

CONCLUSION: We have shown that iVASO produced reproducible measurements in the cortex as well as the hippocampus. Hippocampal aCBV values had high reproducibility at TI<1000 ms, while cortical aCBV measures high reproducibility with TI>900 ms..

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