

ASL HIPPOCAMPUS PERFUSION IMAGING OF GULF WAR VETERANS: PRELIMINARY RESULTS FOR NATIONAL SURVEY STUDIES

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Introduction: Perfusion studies using SPECT (1) and ASL (2) imaging methods have demonstrated significantly different baseline hippocampal perfusion and hippocampal perfusion responses to cholinergic challenge via physostigmine infusion in veterans with Gulf War Illness, consistent with the memory loss and movement disorders reported for ill Gulf War veterans (3,4), and corroborating the hippocampal dysfunction reported in MRS studies (5). The previous SPECT and ASL perfusion studies were performed with veterans selected from the 24th U.S. Naval Reserve Mobile Construction Battalion (CB), a sample not statistically representative of all Gulf War veterans. To verify these previous findings, subjects were recruited from a representative national survey of over 8,000 veterans for arterial spin labeling hippocampus perfusion studies similar to those of the previous CB veteran study. The preliminary results reported here are for the sickest of the three major Gulf War illness variants, Syndrome 2.

Materials and Methods: Subjects were selected from a cohort of 8,020 Gulf War veterans statistically representative of all active for the 1991 Gulf War, and classified by factor analysis (3) into veterans with Gulf War Syndromes 1, 2, 3, and deployed and non-deployed healthy controls. The preliminary results reported here are from Gulf War Syndrome 2 (Syn 2) (3,4) and healthy non-deployed veterans, as described in Table 1. All subjects were screened and gave written informed consent according to a study protocol approved by the local Institutional Review Board.

A two-session perfusion study, double-blinded by group and single-blinded by infusate, was performed during the afternoon for each subject. Saline was infused during the first session and physostigmine (~0.6 mg), a short-acting cholinesterase inhibitor, was infused during the second session, each at 130 mL/hour for 30 minutes prior to imaging. Glycopyrrolate (0.3 mg) was injected prior to physostigmine infusion to combat nausea; a placebo saline injection was given prior to the saline infusion in the first session. During the imaging, subjects were awake with eyes closed.

Studies were performed on a 3T Siemens TIM Trio whole-body MR scanner. The body coil was used for RF transmission; a Siemens 12-channel phased array head coil was used for signal reception. OPTIMAL FAIR (6) was used, with 3.5 mm thick oblique coronal slices. Two of the 20 slices were anterior to the hippocampus head. Imaging slices were reproducibly placed using Auto-Align, and 3D PACE (7), a real-time prospective motion correction technique, was used to help reduce motion artifacts.

Hippocampus perfusion imaging parameters were: TR/TE = 3000/14 ms, FOV = 128 x 128 mm², matrix size = 64 x 64, in-plane resolution = 2 x 2 mm², slice thickness/distance factor = 3.5 mm/20%, number of imaging slices = 20, left to right phase encoding with 30% oversampling, 6/8 partial Fourier, iPAT GRAPPA factor = 2, A-P slice acquisition order, advanced 3D shimming, selective/spatially-confined inversion slab = 148/328 mm, temporal bolus width (TI₁)/post-bolus delay (TI₂) = 600/1000 ms, inferior saturation pulse number/size/ repetition interval = 40/20 mm/25 ms, and 150 labeling and control image pairs. Proton density images (M₀) were acquired using the same EPI imaging parameters but 8 s TR.

The hippocampus was segmented using the FIRST tool of FSL software. Hippocampus ROIs and corresponding anatomic images were co-registered to ASL time series. Image pre-processing was performed with SPM. CBF quantification used a single blood compartment model (8). Hippocampus CBF percentage changes were calculated as $\Delta\text{CBF}(\%) = (\text{CBF}(\text{physostigmine}) - \text{CBF}(\text{saline})) / \text{CBF}(\text{saline}) \times 100$. Two tailed t tests were performed to detect significant differences ($p < 0.05$) of measured perfusion across two sessions (paired t tests) and between groups (unpaired t tests) in left, right and bilateral regions of the hippocampus.

Results and Discussion: Figure 1 shows co-registered anatomic, proton density and perfusion-weighted images of one representative healthy veteran, from the saline infusion session. Physostigmine challenge decreased hippocampal perfusion in the healthy non-deployed veterans, but increased hippocampal perfusion in veterans ill with Syndrome 2 (Figure 2), which is similar to previous findings (2). These hippocampus perfusion responses to physostigmine infusion are significantly opposite between the Syn2 and non-deployed control veteran groups in left, right and bilateral hippocampus (Figure 3). These preliminary results from a representative sampling of Gulf War veterans confirm the abnormal hippocampus perfusion observed in Gulf War veterans ill with Syndrome 2 in the previous study of subjects in the CB cohort (2).

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Table 1 Demographic information for normal healthy non-deployed veterans and veterans with Gulf War Syndrome 2*

Veteran Group	Male		Female		Both Gender	
	Number	Age	Number	Age	Number	Age
NC	12	52 ± 7	3	54 ± 10	15	52 ± 8
Syn 2	15	53 ± 10	4	46 ± 8	19	52 ± 10

*No significant age differences were found between the two groups for either gender or both. Subject ages are expressed in mean ± STD years.

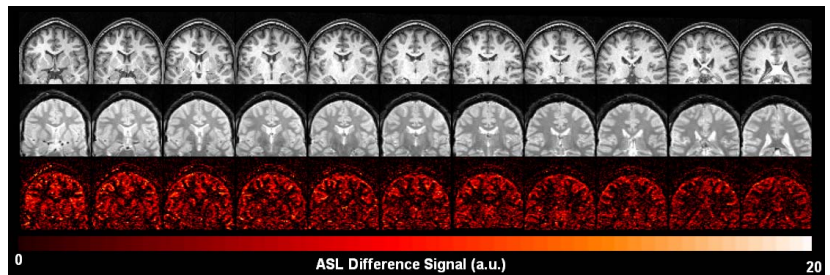


Fig. 1 Co-registered anatomic (top), proton density (middle) and perfusion-weighted (bottom) images of one healthy veteran from saline session. Eleven slices covering the hippocampus are displayed.

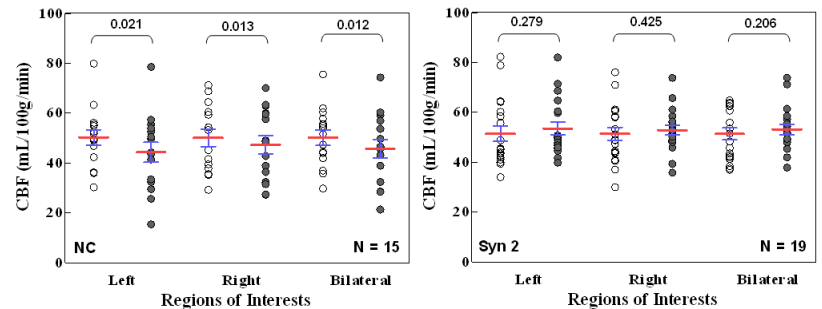


Fig. 2. CBF measurements in left, right and bilateral regions of the hippocampus. Open and filled circles represent CBF measurements from saline and physostigmine sessions respectively. Red lines represent group means, and blue error bars represent standard errors.

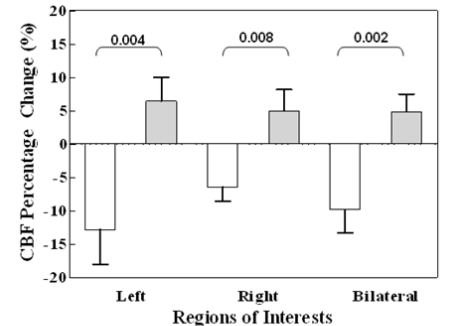


Fig. 3 Physostigmine-induced CBF percentage changes in control (white bars) and Syn2 (shaded bars) groups. Error bars represent standard errors.