HEMISPHERIC ASYMMETRY OF HIPPOCAMPUS PERFUSION AND ITS RESPONSE TO PHYSOSTIGMINE CHALLENGE IN A NATIONALLY REPRESENTATIVE SAMPLE OF GULF WAR VETERANS

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Introduction: A recent ASL study of a representative national sample of U.S. Gulf War veterans has corroborated a chronic hippocampal perfusion dysfunction in ill Gulf War veterans (1) first observed to persist and perhaps worsen in the 20 years since the war in a Seabees battalion (2-4). Hemispheric asymmetries in hippocampus perfusion that differed among healthy control and the three ill syndrome groups were observed in veterans from the Seabees battalion with infusion of both saline placebo and the reversible cholinesterase inhibitor physostigmine (5). This suggests laterality of functional impairments and may imply distinct pathological mechanisms across syndrome groups. In this abstract, hemispheric asymmetry of hippocampus perfusion in a nationally representative sample of Gulf War veterans is reported and compared previous results from a Seabees battalion.

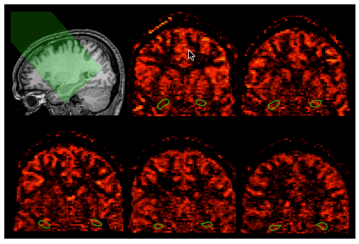

Figure 1 Oblique coronal imaging slab position (green shading) for ASL perfusion imaging (top left) and 5 slices alternately selected from 11 perfusion-weighted ASL images, with hippocampus regions of interest outlined in green, of one healthy control veteran from the saline infusion session.

Materials and Methods: National sample subjects for a nested case-control study were selected from 8,020 Gulf War-era veterans statistically representative of all U.S. Armed Forces active during the 1991 Gulf War (6). They were classified into five groups: three ill syndromes (Syn 1, Syn 2, Syn 3) and two healthy controls (deployed and non-deployed NC). Subjects were screened and gave written informed consent according to a study protocol approved by the local Institutional Review Board. For each subject, a two-session perfusion study, double-blinded by group and single-blinded by infusate, was performed (1).

Hippocampus perfusion studies using OPTIMAL FAIR (7) were performed on a 3T Siemens TIM Trio whole-body MR scanner with a body coil for RF transmission and a Siemens 12-channel phased array receive-only head coil. Oblique coronal imaging slices with 2 x 2 x 3.5 mm^3 imaging resolution were used for perfusion imaging (1). The FIRST tool of FSL was used to segment hippocampus. Motion correction and co-registration were performed using SPM.

As for the study of the Seabees battalion (2), laterality of hippocampus perfusion was evaluated by calculating an asymmetry index (A.I.) with the formula:

$$A.I.(\%) = \frac{CBF_{right} - CBF_{left}}{(CBF_{right} + CBF_{left})/2} \times 100$$

The asymmetric perfusion response of the hippocampus to physostigmine challenge was evaluated by using the difference of asymmetry indices between saline and physostigmine sessions: A.I. physostigmine – A.I. saline. Two-tailed paired t tests used to test for significant ($p < 0.05$) differences did not show significant differences between deployed and non-deployed veteran control groups in either hemispheric asymmetries of hippocampus perfusion or A.I. changes across the two infusion sessions. Therefore, data from the two healthy control groups were pooled before comparison with data from the three ill syndrome groups.

Results and Discussion: Perfusion-weighted images from the saline session of one healthy veteran from the national sample are displayed in Figure 1. Asymmetry indices for hippocampus perfusion in the four groups during saline and physostigmine infusion sessions and asymmetry index differences between the two sessions are presented in Figure 2 for both the 2008 Seabees battalion study and the 2009 national sample study.

For both Seabees and national sample cohorts, the control group had no significant laterality of hippocampus CBF for saline or physostigmine sessions or difference in laterality between physostigmine and saline conditions, the Syndrome 3 group had significantly lower baseline (saline) perfusion in the right hippocampus than in the left hippocampus, and with physostigmine compared to saline infusion, hippocampal CBF became significantly more lateralized to the left in Syndrome 1, with no change in Syndrome 2. In the Syndrome 2 saline sessions, Seabees had significantly lower CBF in right than in left hippocampus, while national sample subjects had similar CBF in both hemispheres. In the Syndrome 1 physostigmine sessions, the national sample had significantly lower CBF in right than in left hippocampus. For physostigmine compared to saline infusion, hippocampal CBF was less lateralized to the left in Syndrome 3 Seabees

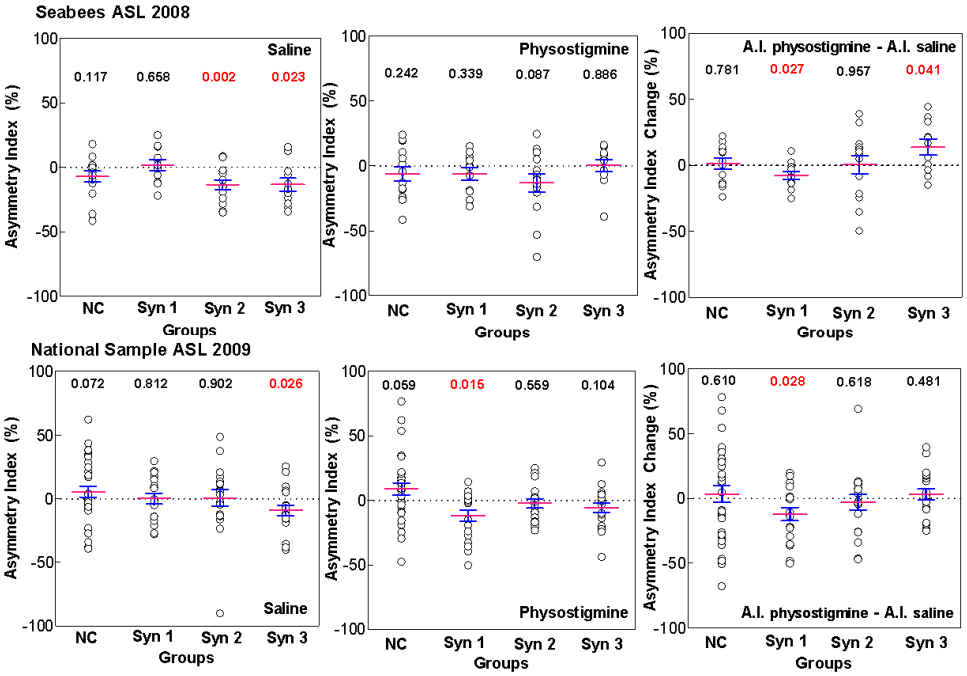

Figure 2 Hemispheric asymmetry for hippocampus CBF measurements from saline (left) and physostigmine (middle) sessions and laterality changes across sessions (right). Red lines represent group means, and blue error bars represent standard errors. P values are above the data points; red font indicates significant differences of CBF between the two hippocampi or of laterality differences between the two sessions.

Conclusions: Laterality patterns of hippocampus CBF in and between infusion sessions with saline placebo and short-acting cholinesterase inhibitor physostigmine were similar in Seabees and national sample cohorts of ill Gulf War veterans, with a few exceptions. Healthy control veterans consistently lacked laterality. This information may aid our understanding of pathological mechanisms of chronic brain damage from exposure of some veterans of the 1991 Persian Gulf War to neurotoxic cholinesterase inhibitors (e.g., organophosphate pesticides, pyridostigmine bromide, and low-level sarin nerve gas).

Acknowledgements: This study was supported by IDIQ contract VA549-P-0027, awarded and administered by the Department of Veterans Affairs Medical Center, Dallas, TX, by DoD grant DAMD 17-01-1-0741, and by NIH (NCRR) Grant Number UL1RR024982. The content does not necessarily reflect the position or the policy of the Federal government or the sponsoring agencies, and no official endorsement should be inferred.

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