ASYMMETRIC CHARACTERISTICS OF HIPPOCAMPUS PERFUSION AND ITS RESPONSE TO PHYSOSTIGMINE

CHALLENGE IN GULF WAR VETERANS

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Introduction
As indicated by previous perfusion studies (1-2), abnormalities consistent with clinical symptoms, e.g., movement disorders and memory loss (3-4), exist in the hippocampus of veterans with Gulf War Illness. To test for hemispheric laterality in these abnormalities, the asymmetric characteristics of hippocampus perfusion were explored for veterans with Gulf War Syndromes 1, 2 and 3 (3) and healthy veterans as controls (2).

Materials and Methods
The ASL perfusion study, double-blinded to group and single-blinded to infusate, used two imaging sessions two days apart: the first session with saline infusion and the second session with infusion of physostigmine, a short-acting cholinesterase inhibitor. A mean dose of ~0.6 mg physostigmine was infused at 130 mL/hour prior to imaging, during the 30 minutes after the IV administration of 0.3 mg of glycopyrrolate to blunt nausea. Subjects were awake with eyes closed during the imaging session.

Veterans with Gulf War Syndromes 1 (Syn 1), 2 (Syn 2), 3 (Syn 3), and healthy controls (NC) were selected from the 24th U.S. Naval Reserve Mobile Construction Battalion (Table 1). Subjects were screened and gave written informed consent according to a study protocol approved by the local Institutional Review Board.

Studies 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 5 mm³ imaging resolution were used for perfusion imaging with OPTIMAL FAIR (5). The FIRST tool of FSL was used to segment hippocampus. Motion correction and co-registration were performed using SPM.

The asymmetry of hippocampus perfusion was evaluated by calculating an asymmetry index (A.I.) with the following formula:

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

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 were used to test for significant (p < 0.05) differences.

Results and Discussion
One healthy veteran’s perfusion-weighted (from saline session), proton density and co-registered anatomic images are displayed in Figure 1. The veteran groups had different asymmetries of hippocampal CBF and asymmetry changes with physostigmine (Figure 2 and Table 2). No significant laterality in hippocampus CBF was observed in the control group for saline, physostigmine, or the difference of the two conditions. However, veterans of both Syndromes 2 and 3 had significantly lower baseline (saline) perfusion in the right hippocampus than in the left hippocampus. With physostigmine infusion, hippocampal CBF became more lateralized to the left in Syndrome 1 and less lateralized in Syndrome 3, with no change in Syndrome 2.

The observed hemispheric asymmetries in hippocampus perfusion in the veterans ill with Syndromes 2 and 3 suggest laterality of functional impairments. The differences of asymmetric characteristics across syndrome groups may imply distinct pathological mechanisms.

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