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).

Table 1 Veterans for hippocampus perfusion studies

Veteran Group	Number of Subject	Age (years)	Syndrome Characteristics
NC	14	60 ± 6	N/A
Syn 1	11	51 ± 6	impaired cognition
Syn 2	14	63 ± 7	confusion and ataxia
Syn 3	11	57 ± 6	central pain

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 mm^3 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:

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

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

Table 2 Asymmetry index (A.I.) (MEAN ± SE, in %) of hippocampus perfusion and physostigmine-induced asymmetry changes*

Veteran Group	Saline Session A.I.	Saline Session P value	Physostigmine Session A.I.	Physostigmine Session P value	Across Session A.I. Change	Across Session P value
NC	-7.3 ± 4.3	0.117	-6.2 ± 5.4	0.242	1.1 ± 3.8	0.781
Syn 1	1.7 ± 4.3	0.658	-6.1 ± 4.7	0.339	-7.8 ± 3.0	**0.027**
Syn 2	-13.6 ± 3.7	**0.002**	-13.2 ± 6.8	0.087	0.4 ± 6.8	0.957
Syn 3	-13.5 ± 5.1	**0.023**	0.3 ± 4.7	0.886	13.8 ± 5.9	**0.041**

*P values are from two tailed paired t tests for comparing hippocampus perfusion measurements between the two hippocampi or asymmetry indices across two sessions for each group. A.I. change is calculated as: A.I. $_{physostigmine}$ – A.I. $_{saline}$.

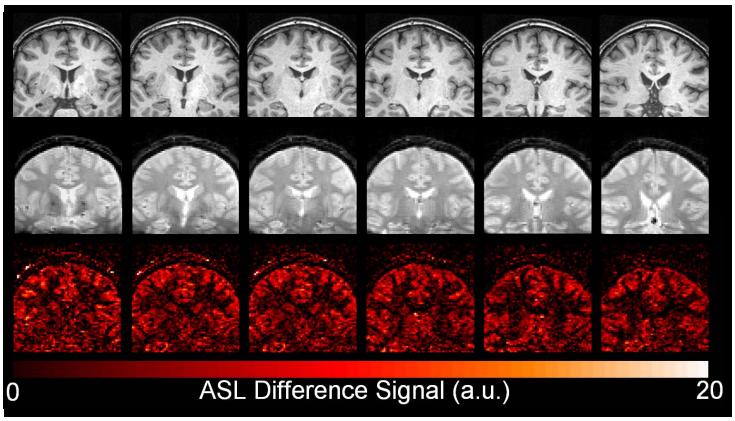

Fig. 1 One healthy veteran's co-registered anatomic (top row), proton density (middle row) and perfusion-weighted (bottom row) images from the saline session.

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 distinctive pathological mechanisms.

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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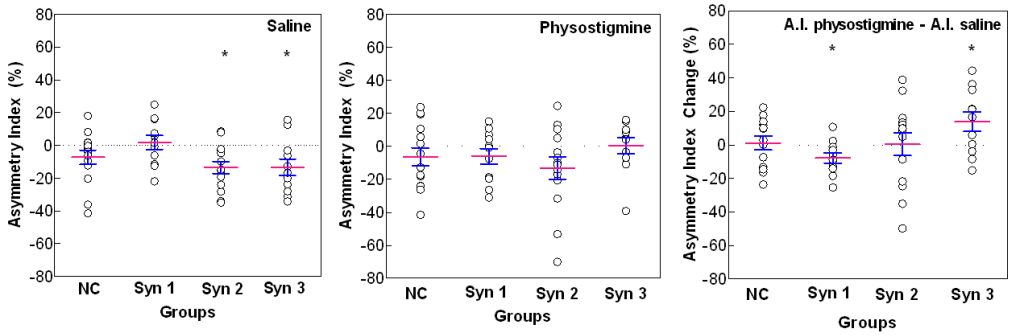

Fig. 2 Asymmetry for CBF measurements from saline (left) and physostigmine (middle) sessions, and asymmetry changes across sessions (right). Red lines represent group means, and blue error bars represent standard errors. Stars on the top of the figures indicate significant differences of CBF measurements between the two hippocampi or asymmetry changes across two sessions.