

HIPPOCAMPUS PERFUSION STUDIES OF GULF WAR VETERANS USING OPTIMAL FAIR

X. Li¹, S. N. Sarkar², D. E. Purdy³, Q. Lin^{4,5}, D. M. Buhner⁵, R. W. Haley⁵, and R. W. Briggs^{1,5}

¹Radiology, UT Southwestern, Dallas, TX, United States, ²Radiology, Beth Israel Deaconess Medical Center, Boston, MA, United States, ³Siemens Healthcare, Malvern, PA, United States, ⁴Clinical Sciences, UT Southwestern Medical Center, Dallas, TX, United States, ⁵Internal Medicine, UT Southwestern Medical Center, Dallas, TX, United States

Introduction

Veterans with Gulf War Illness suffer movement disorders and memory loss indicative of hippocampus damage (1). Abnormal hippocampus resting state CBF and CBF regulation upon physostigmine challenge have been reported from a SPECT study in veterans with Gulf War Illness (2). To verify the previous findings and facilitate further investigation of the pathological characteristics of Gulf War Illness, hippocampus perfusion studies using OPTIMAL FAIR were performed for veterans with Gulf War Syndromes 1, 2 and 3 (3,4) and healthy veterans as controls.

Materials and Methods

This was a semi-blind study with two imaging sessions with one day gap in between: the first session with saline infusion and the second session with physostigmine infusion. The infusion, with a mean dose of ~0.6 mg, was administered during the 30 minutes prior to imaging. During the imaging, subjects were awake with eyes closed. Before the IV infusion of physostigmine, a very low dose of glycopyrrolate (0.3 mg) was administered IV to reduce peripheral side effects. Nearly all the MRI scans on veterans were performed in the early afternoon.

Veterans, from the U.S. Naval construction battalion, were classified into one of three Gulf War illness syndromes or a healthy control group based on factor analysis of symptoms (3,4). The mean ages of veterans of Gulf War Syndrome complexes 1 (Syn 1, N = 12), 2 (Syn 2, N = 14) and 3 (Syn 3, N = 12), and healthy controls (NC, N = 14) were 51 ± 6, 63 ± 7, 57 ± 6, and 60 ± 6 years, respectively. All subjects were screened and gave written informed consent according to a study protocol approved by the local Institutional Review Board.

All 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. Between day 1 and 2 for each subject the imaging slices were reproducibly placed using Auto-Align, Siemens' online co-registration and study planning tool. The oblique coronal ASL imaging slices were positioned to cover the hippocampus with the inferior edge of the imaging slab parallel to the longitudinal anterior-posterior axis of the hippocampus and covering the gyrus of the temporal lobe (Fig. 1). Due to subject-dependent variation in brain anatomy, manual translational adjustment was manually performed to ensure consistent slice position relative to selected anatomic landmarks across subjects by using MPRAGE T1-weighted high-resolution images for more accurate reference.

MRI parameters used for hippocampus perfusion were: TR/TE = 3000/14 ms, FOV = 128 x 128 mm, matrix size = 64 x 64, slice thickness/gap = 5.0/1.0 mm, number of imaging slices = 10, left to right phase encoding with 30% phase oversampling, 6/8 partial Fourier, iPAT GRAPPA factor = 2, A-P slice acquisition order, 148 mm selective inversion slab, 328 mm spatially-confined inversion slab, inferior saturation pulse number/size/ repetition interval = 48/20 mm/25 ms, temporal bolus width (TI₁) = 600 ms, post-bolus delay = 1200 ms, and 100 labeling and control image pairs. Two M₀ images were acquired using the same sequence, with TR = 8 s.

Hippocampus ROIs were obtained using the FIRST tool of FSL; anatomic images were co-registered to ASL time series images. Image pre-processing was performed with SPM. CBF quantification used a single blood compartment model (5). Hippocampus CBF percentage changes were calculated as $\Delta\text{CBF}(\%) = (\text{CBF}(\text{physostigmine}) - \text{CBF}(\text{saline}))/\text{CBF}(\text{saline}) \times 100$. In the analysis of hippocampus perfusion percentage changes due to physostigmine challenge, a one-way ANOVA was performed separately for left, right and bilateral hippocampus combined to find if there were significant differences across four groups (last row in Table 1). In addition, pairwise contrasts between the four groups were tested in each ANOVA, and Bonferroni correction was used to maintain a familywise error rate (FWE) at 0.05.

Results and Discussion

Physostigmine-induced percentage changes in hippocampus CBF for the four groups are displayed in Fig. 2, and group comparisons are presented in Table 1. Compared to healthy controls, veterans with Syndromes 2 and 3 have significantly different perfusion responses to physostigmine challenge in the left, right and bilateral regions of the hippocampus. Veterans with Syndrome 1 have significantly different perfusion changes from Syndromes 2 and 3 in the right hemisphere of the hippocampus. No significantly different hippocampus CBF percentage changes were found in left, right and bilateral regions of the hippocampus between matched healthy controls and veterans with Syndrome 1 or between veterans with Syndromes 2 and 3.

The different hippocampus perfusion responses to physostigmine challenge of veterans with Syndromes 2 and 3 from those of healthy controls and Syndrome 1 are similar to those found in the SPECT studies performed in 1997-1998, indicating that the physiological effects upon hippocampal blood flow still persist a decade later.

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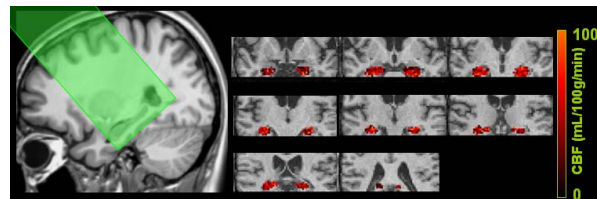


Fig. 1 Imaging slice position (left) and one subject's regional CBF maps overlaid on co-registered anatomic images (right).

Table 1 Statistical Analysis Results for Hippocampus CBF Percentage Changes upon Physostigmine Challenge†

Comparisons	P Values *		
	Left	Right	Bilateral
NC vs Syn 1	1.59 x 10 ⁻¹	9.43 x 10 ⁻¹	4.76 x 10 ⁻¹
NC vs Syn 2	6.63 x 10⁻⁵	3.09 x 10⁻³	9.17 x 10⁻⁵
NC vs Syn 3	1.49 x 10⁻³	3.45 x 10⁻⁴	1.40 x 10⁻⁴
Syn 1 vs Syn 2	1.01 x 10 ⁻²	6.37 x 10⁻³	1.85 x 10⁻³
Syn 1 vs Syn 3	7.23 x 10 ⁻²	8.10 x 10⁻⁴	2.18 x 10⁻³
Syn 2 vs Syn 3	4.65 x 10 ⁻¹	3.54 x 10 ⁻¹	8.95 x 10 ⁻¹
One-way ANOVA p value	3.06 x 10⁻⁴	2.83 x 10⁻⁴	4.24 x 10⁻⁵

† Left, right and bilateral represent the left, right, bilateral regions of the hippocampus, respectively.

* P values in bold are lower than Bonferroni corrected significance level of 0.00833 (0.05/6) with FWE=0.05.

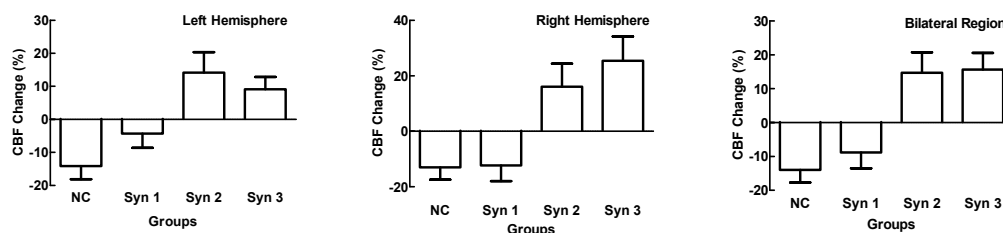


Fig. 2. Physostigmine-induced CBF percentage changes in left, right and bilateral regions of the hippocampus for four groups of subjects. Error bars represent standard errors.