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Electrophysiological correlates of semantic memory retrieval in Gulf War Syndrome 2 patients

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ABSTRACT

Gulf War veterans meeting criteria for Haley Syndrome 2 of Gulf War illness endorse a particular constellation of symptoms that include difficulty with processing information, word-finding, and confusion. To explore the neural basis of their word-finding difficulty, we assessed event-related potentials (ERPs) associated with semantic memory retrieval in 22 veterans classified as Syndrome 2 and 28 veterans who served as controls. We recorded EEGs while subjects judged whether pairs of words that represented object features combined to elicit a retrieval of an object memory or no retrieval. Syndrome 2 subjects' responses were significantly slower, and those participants were less accurate than controls on the retrieval trials, but they performed similarly on the nonretrieval trials. Analysis of the ERPs revealed a difference between retrievals and nonretrievals that has previously been detected around 750 ms at the left temporal region was present in both the Syndrome 2 patients and controls. However, the Syndrome 2 patients also showed an ERP difference between retrievals and nonretrievals at the midline parietal region that had a scalp voltage polarity opposite from that recorded at the left temporal area. We hypothesize that the similarities between task performance and ERP patterns in Syndrome 2 veterans and in patients with amnestic mild cognitive impairment reflect disordered thalamic cholinergic neural activity, possibly in the dorsomedial nucleus.

1. Introduction

It has been suggested that approximately 25–30% of those deployed in the 1991 Persian Gulf War have developed persistent cognitive deficits [1]. A common symptom reported in these individuals is difficulty with finding words [2–5]. The prominence of this dysfunction is such that it has been captured in symptom-derived definitions classifying patients with Gulf War-related Illnesses. Haley and colleagues developed a classification for those suffering symptoms following being deployed in the Persian Gulf [6–8]. Haley Syndrome 2 patients exhibit confusion that is characterized by difficulty with processing information, word finding, emotional lability, confusion, and balance problems [6].

We previously used functional MRI (fMRI) to study a group of US Naval Construction Forces personnel ("Seabees") as they performed a semantic memory retrieval task in order to localize the brain regions associated with performance of that task [4]. In that study, subjects were presented with two words that represent features of objects and were asked to indicate whether the words together resulted in retrieval of a specific object from memory. Neural correlates of normal subjects performing this task have been studied using behavioral [9], fMRI [10–12], event related potential (ERP) [13], and electroencephalographic time-frequency analysis [14,15] techniques. The task has also been used to probe dysfunction in patients with mild cognitive impairment and/or Alzheimer's Disease [9,16,17], schizophrenia [18], stroke [19,20], and concussion and aging [21]. In a study of normal controls performing the task during fMRI, significant BOLD signal changes were detected for the correct retrievals in bilateral medial Brodmann Area 6 (pre-SMA region), dorsomedial and pulvinar thalamic nuclei, caudate nuclei, and bilateral temporo-occipital regions [10,11,21]. There is also a an ERP difference between retrievals and nonretrievals at approximately 750 ms with a maximum at the left fronto-temporal region that has been proposed to signify co-activation of common feature representations of the object being retrieved [13].

In our previous Seabee study [4], subjects with Haley Syndrome 2 made significantly more errors than did study subjects in the other groups (i.e., controls, Syndromes 1 and 3), consistent with their subjective complaints of word finding and memory difficulties. In addition, the Syndrome 2 patients had patterns of signal changes in the caudate and

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thalamus that were noticeably different from the other Haley Syndromes and normal controls during correctly performed trials. In these regions, we found increased BOLD signal changes with longer reaction times on the task, in contrast with the subjects in the other groups including the controls, who showed the opposite pattern. This atypical BOLD–reaction-time correlation in correctly performed trials was proposed to represent an increased effort in an attempt to maintain performance in the setting of dysfunctional underlying neural resources. We also administered word generation tasks to the same groups while we recorded fMRI [5]. The task required the subject to recall the names of as many members of a category of objects or of words that begin with a specific letter as he or she could. Syndrome 2 patients performed significantly worse behaviorally on letter and category fluency compared to Syndrome 1 subjects and controls. The Syndrome 2 subjects also showed reduced BOLD signal in the thalamus and putamen compared to controls, consistent with the proposal that the thalamus is involved in word generation when semantic input is used for word finding [22]. ERP studies were not obtained in conjunction with either of these two Seabees' studies.

We undertook the current study to determine whether the findings in the initially characterized Seabee sample are also detectable in Haley Syndrome 2 patients more generally, and whether the ERP correlates of semantic memory retrieval that we found in normal controls are also present in patients with Haley Syndrome 2.

2. Method

2.1. Participants

All the participants had been in the military during the 1991 Persian Gulf War. The exacting measures taken to identify, contact, and recruit a representative sample of veterans are have been described fully in previous reports [8,23] and supplementary materials [23]. For this report, data from 3 of the 31 veterans in the control groups and from 2 of the 24 veterans in the Syndrome 2 group were excluded from the analysis due to there being too few artifact-free epochs to create reliable ERP averages. Thus, we analyzed data from 50 participants (11 female). Twenty-two (6 female) of these met the Haley et al. [6,7] criteria for Syndrome 2 of GW Illness. Syndrome 2 is associated with more debilitating neurocognitive issues—confusion, word-finding and reasoning difficulties, emotional lability—and balance problems such as frequent stumbling and vertigo. The remaining 28 (5 female) veterans who did not meet the criteria for any of the six GW Illness Syndromes [6,8,23] served as controls. Chi square analysis indicated an expected distribution of male and female across the two groups studied here, $\chi^2 = 0.636$, $p = 0.425$. Additional medical information within each group is listed in Table 1. The subjects were housed and monitored at The University of Texas Southwestern Medical Center's Clinical and Translational Research Center in 2009 and 2010, and underwent a week-long multi-modal neuropsychological, neuroimaging, and biomarker study. All subjects gave written informed consent according to a protocol approved by the university's institutional review board.

Table 1
Demographic and comorbidity data.

N	Control 28	Syndrome 2 22
Age *M* (*SD*)	49.39 (7.65)	49.41 (7.43)
Age range	38–65	37–65
Number of females (%)	5 (18%)	6 (27%)
PTSD[a]	0	9 (41%)
Anxiety[a]	1 (4%)	16 (73%)
Depression NOS active[a]	0	16 (73%)
Major depressive disorder	0	1 (5%)
Alcohol abuse or dependence[a]	3 (11%)	10 (45%)
Drug abuse	4 (14%)	4 (18%)
Smoking[a]	0	5 (23%)
Hypertension	5 (18%)	8 (36%)
Cholesterol-reducing medication	3 (11%)	7 (32%)
Diabetes	1 (4%)	1 (5%)

[a] Indicates a significant difference between the groups.

2.2. Task and stimuli

Participants performed a task based on the Semantic Object Retrieval Test (SORT) [9,16]. We presented one hundred pairs of printed words that represent features of common objects, with one word above the other in black letters on a white screen. Fifty of the trials were made up of word pairs that have been shown to elicit retrieval of a specific object (e.g., “desert” paired with “hump” elicits the object “camel”) [11]; the remaining 50 word pairs were nonretrieval trials (e.g., “sleeve” paired with “jungle”). Each word pair was presented on a computer monitor positioned approximately 1 m in front of the participant for 3000 ms, and was followed by a 3000-ms fixation point. Participants were instructed to press the response pad button under their index finger when the word pair called to mind a specific object, rather than merely an association between the words. When the word pair did not call to mind a specific object, they were to press the response pad button under their middle finger. Six versions of the word pair presentation order were randomized across subjects.

2.3. Procedure

After the participants were fitted with the electrode cap, they were shown the instructions as they were read aloud to them. Participants were allowed to ask questions to assure that they understood the task. At the beginning of each task, the first image repeated the instructions.

2.4. EEG acquisition

We recorded EEG using a 128-electrode array mounted within an elastic cap. We positioned electrodes at the superior and inferior orbital margins to monitor blinks and vertical eye movements. The reference electrode was located near the vertex, and the APZ electrode served as the ground electrode. Before we started recording EEG data, we assured that the impedance for each electrode was below 10 kΩ.

We used Stim^2 (Compumedics Neuroscan, Charlotte, NC, USA) software to record the accuracy and reaction time of the responses and to mark each stimulus onset and response in the electronic EEG record. The EEG was recorded using a Neuroscan Synamps2 (Compumedics Neuroscan) amplifier at a 500-Hz sampling rate. The continuous EEG data were high-pass filtered at 0.15 Hz and re-referenced to the global mean amplitude. Blink artifacts were filtered from the continuous EEG file by using a spatial filter process included in the Scan 4.5 Edit (Compumedics Neuroscan, Charlotte, NC, USA) software. Data from 200 ms before the onset to 1800 ms after the onset of each stimulus were included in each epoch. From each subject's task data, retrieval and nonretrieval conditions were averaged. Each average consisted of epochs that had been baseline-corrected based on the 200-ms prestimulus data.

2.5. Data analysis

Only the ERP averages that comprised 20 or more artifact-free sweeps were used in the analysis. In order to reduce the dimensionality of the ERP data, 25 regions based on equivalent scalp areas were designated. Average amplitude for each 100-ms time window from stimulus onset to 1200 ms post-stimulus for each electrode within a region was calculated. This yielded 25 (space) × 16 (time) data points for each participant. A principal components analysis (PCA) was performed on this matrix, followed by Varimax rotation. Four orthogonal spatial factors