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Impaired response inhibition in ill Gulf War veterans

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ABSTRACT

Poor performance on tasks requiring response inhibition has been observed among chronically ill veterans of the 1991 Persian Gulf War. Semantic difficulties have also been reported. We collected event-related potential (ERP) and behavioral data from 25 Gulf War veterans who complained of cognitive difficulties and from 23 matched controls, who were deployed but not symptomatic, while they performed a GO–NOGO task that required both a semantic decision and inhibitory processing. A significantly greater false-alarm rate among the ill veterans was accompanied in the ERP data by significantly reduced amplitude in the NOGO P3, consistent with previous ERP studies of other patient groups that have shown poor inhibitory response performance. This supports the contention that the ill veterans' deficit lies more in inhibiting than in detecting task-related differences in the stimuli.

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1. Introduction

Many veterans returning from the 1991 Persian Gulf War complained of symptoms such as confusion, nausea, memory problems, balance problems, and depression. There have been several studies (e.g., [1–4]) that have identified clusters of symptoms. One cluster is associated with reports of cognition problems: distractibility, memory and reasoning problems, fatigue, confusion, disorientation, word-finding difficulty, and emotional lability. In the Fukuda et al. analysis of still enlisted Gulf War veterans, these cognitive complaints loaded onto one factor, whereas in the Haley et al. study that included GW veterans who were no longer serving in the military, these cognitive symptoms presented as two separate factors: impaired cognition and confusion-ataxia. A second cluster is associated more with somatic complaints, such as joint and muscle pain. The mechanisms leading to this confluence of symptoms is still being assessed [5].

Neuropsychological assessments of affected veterans have revealed significantly poorer performance on continuous performance tests (CPT) such as the Neurobehavioral Evaluation System 2 (NES2; [6–8]) and Sustained Attention to Response Task (SART; [9,10]). On CPT tasks where participants are to withhold a response to the infrequent target stimuli and respond to the frequent nontarget stimuli over a considerable number of trials, subpar performance can be considered indicative of poor response inhibition [11–13]. Additionally, returning Desert Storm veterans' performance on Stroop tasks has indicated greater difficulty in suppressing interference of prepotent stimulus information [10,14,15], which can also be the result of an inhibition deficit [16]. It could be argued that inhibition dysfunction plays a role in many of the symptoms reported by ill Gulf War (GW) veterans who complain of neurocognitive problems. For example, inefficient inhibition of intruding thoughts can contribute to distractibility, confusion, and emotional lability.

GO–NOGO tasks, which are similar to CPT tasks but without the prolonged time period of testing and number of trials, have long been used to directly assess response inhibition. Analysis of GO–NOGO behavioral measures has yielded information about group differences [17–19], task demands [20,21], and cognitive development [22,23]. Event-related potential (ERP) studies have examined these effects by analyzing the N2–P3 complex, an anterior negative deflection around 200 ms closely followed by a frontocentral positive deflection at approximately 300 ms. Studies have shown that both the negative magnitude of the N2 and the positive magnitude of the P3 are greater in the NOGO condition than in the GO condition (e.g., [24,25]). Parsing these components to establish which aspect reflects NOGO stimulus differentiation and which aspect reflects inhibition of the response has been the focus of several studies [e.g., 26].

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The N2 component is found in ERP responses to tasks other than the GO–NOGO paradigm. Tasks requiring the inhibition of either motor or nonmotor responses [27] can elicit large N2s. The N2 is also considered to be represented in the mismatch negativity observed when a rare stimulus is presented among frequent stimuli and has been convincingly associated with the orienting of attention [28]. Other studies have found the N2 to be associated with cognitive control [29] and with conflict processing of sequentially presented stimuli [30]. A general description of the N2 would be that of a negative deflection marking the detection of task-related dissimilarities between stimuli. A body of work has accrued that argues that, in the GO–NOGO paradigm as well, the N2 is also a marker of conflict or difference detection ([26,31,32]; but see also [24,33]). An independent components analysis employed by Kropotov and Ponomarev [34] revealed three separate components within the NOGO N2 that mapped onto three separate processes of their paradigm: sensory comparison, conflict monitoring, and action suppression.

Evidence has accrued associating the variance of the P3 aspect of the N2–P3 complex with response inhibition [26,31,35–37]. An absent or attenuated P3 response for NOGO items, even in conjunction with a normal N2 response, has been linked to inhibitory difficulties in some populations. For example, studies comparing GO–NOGO performance of children with ADHD to controls [38] and comparing young children to adults [39] have shown that young children and ADHD children, who show significantly more impulsivity and false alarms in their behavioral performance, also produced reduced or absent NOGO P3s, yet their N2s were not significantly different from controls'. A study of patients with Huntington disease also revealed an attenuated NOGO P3 and higher false positives, but N2s that were not significantly different from controls' [40].

To assess the nature of the poor CPT performance of symptomatic GW veterans, and to gain a better understanding of their semantic processing difficulties, we collected electroencephalographic (EEG) and behavioral data from veterans who met requirements for Gulf War Syndromes 1 and 2 [3] and from age- and education-matched GW veteran controls who were deployed but did not report cognitive complaints, while they performed a semantic inhibition task. This task required a semantic categorization assessment of each stimulus before choosing to respond or to withhold a response. This task has been shown to elicit the expected N2–P3 response in normal young adults [25]. We analyzed the behavioral and ERP data from this task to inform the issue of whether semantic target detection, response inhibition, or both were contributing to a poor response inhibition performance in GW veterans.

2. Method

2.1. Participants

The subjects were 48 GW veterans who had been deployed to the 1991 Persian Gulf War. Twenty-five presented with major cognitive complaints and composed the patient group. The 23 age–sex–education-matched Persian Gulf War veterans who served as controls consisted of those who remained well or who presented predominantly with peripheral pain symptoms. All participants had served in the same construction battalion of the United States Naval Reserve during the 1991 Persian Gulf War and had participated in prior studies of Gulf War syndrome [3,41]. For the study, the subjects were housed and monitored at The University of Texas Southwestern Medical Center's Clinical and Translational Research Center in 2008 and 2009 and underwent a week-long multi-modal neuroimaging and biomarker study. All subjects were male. The cognitive syndromes group ranged in age from 40 to 73 years ($M = 58.4$), and the control group, from 47 to 76 years ($M = 58.8$). All subjects gave written informed consent according to a protocol approved by the university's institutional review board.

2.2. Stimuli

The stimuli used were 200 black line drawings on a white background chosen from the collection of stimuli published by Snodgrass and Vanderwart [42] or drawn with similar line thickness and drawing style by an artist hired to produce stimuli for this study. All of the drawings were fitted to a 600×600-pixel square. The stimuli consisted of 160 drawings of objects, meant to elicit a GO response. Objects comprised food, cars, clothes, kitchen items, body parts, and tools. Stimuli for the NOGO response consisted of drawings of 40 animals, from the very typical (cat, dog) to less typical (worm, lobster). To control for effects of order, each participant was shown one of six randomizations of the 200 stimuli. Each stimulus was presented for 300 ms followed by a 1700-ms fixation point. The task was completed in approximately 8 min.

2.3. Procedure

Sixty-four silver/silver-chloride electrodes mounted within an elastic cap on the participant's head recorded the ongoing EEG activity. Blinks and eye movement were monitored via four electrodes, one mounted above the left eyebrow and one mounted below the left eye to monitor vertical eye movement, and one mounted at each temple to monitor horizontal eye movement. The reference electrode was located near the vertex, but the amplitude of each electrode was re-referenced off-line to the average of all electrode sites at each time point. The APZ electrode served as the ground electrode. Impedance for each electrode did not exceed 10 kΩ as measured before the test session.

After the participants were fitted with the electrode cap and prior to the experiment, they were shown and read the written instructions and were allowed to have their questions answered. During the task, participants were seated in a soundproof booth. The 48-cm monitor on which the drawing stimuli were presented was 1 m in front of the participant. The drawings subtended approximately 18° of visual angle. When the task began, the first slide seen by the participants was an instruction slide reiterating the instructions. The participants were instructed to press the button on the response pad with the index finger of their right hand for all of the 160 stimuli that were not animals and to refrain from responding to animal stimuli. The button interfaced with the Stim^2 (Compumedics Neuroscan) software, which recorded the accuracy of the responses and their reaction times. A time-locked mark of each stimulus onset and response was recorded on the continuous EEG.

Ongoing EEG activity was recorded using a Neuroscan Synamps2 amplifier at a 1000-Hz sampling rate. Data from the continuous EEG were high-pass filtered at .15 Hz with a 12 dB/octave slope on all channels and were re-referenced to the global mean amplitude. Blink artifacts were filtered from the continuous EEG file by using a spatial filter process in the Scan 4.4 Edit (Compumedics Neuroscan) software. From each participant's EEG file, epochs for two conditions were averaged: GO and NOGO. Only correct responses were used in each average. Each epoch consisted of 200 ms before the onset of the stimulus to 1200 ms after onset. Each average comprised epochs that had been baseline-corrected based on the 200-ms prestimulus data, and low-pass filtered at 20 Hz using a filter slope of −48 dB per octave.

3. Results

Visual inspection of the grand average ERPs from the control group compared to those of the patient group revealed an observable anterior N2–P3 complex in both groups and in both conditions. Cursory inspection revealed that the NOGO P3 component (Fig. 1, bottom panel) of the patient group was blunted relative to that of the control group, yet the N2 components (Fig. 1, top panel) from the patient group did not show such a notable difference from that of the

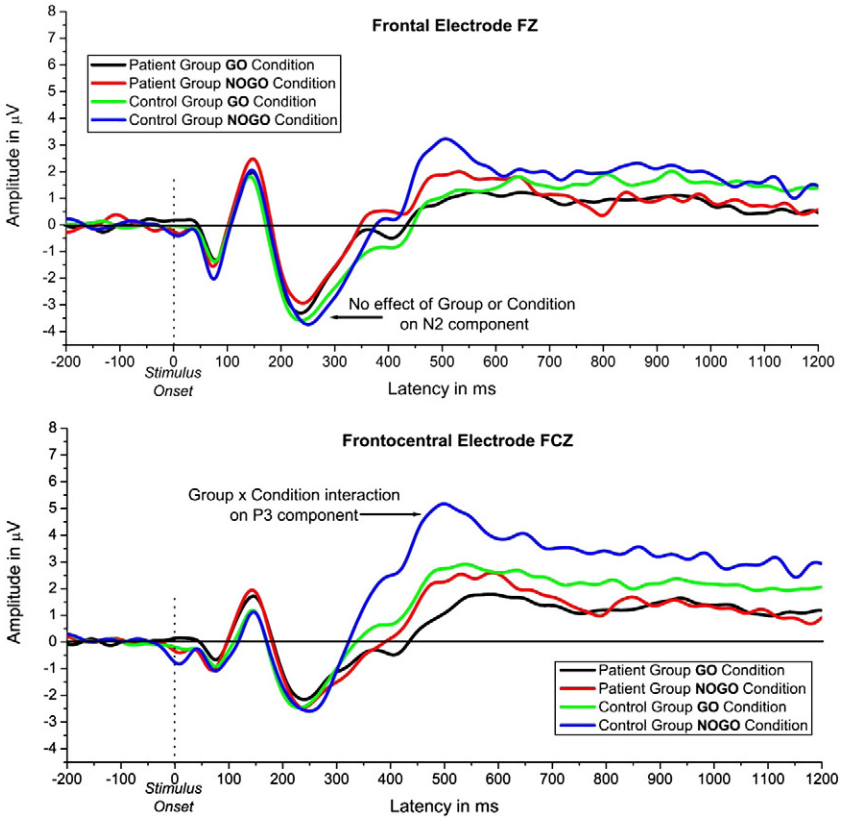

Fig. 1. The amplitude of the N2 component at frontal electrode FZ, whose maxima were at frontal midline electode FZ (top panel), showed no effect condition ($p = .4021$), a trend toward an effect of group ($p = .0727$), and no group x condition interaction ($p = .1578$). The amplitude of the P3 component, whose maxima were at frontocentral midline electrode FCZ (bottom panel), showed a main effect of condition ($p < .0001$) and an effect of group ($p = .0142$) that was driven by an interaction ($p = .0137$) wherein the difference between the GO and NOGO P3 amplitudes from the control group was greater than the difference between the GO and NOGO P3 amplitudes from the patient group.

control group. Fig. 1 also illustrates that there was less difference between the GO and NOGO P3 amplitudes of the patient group than between the GO and NOGO P3 amplitudes of the control group.

To assess whether these differences were significant, analyses of variance were computed on N2 and P3 amplitudes from the NOGO and GO conditions. Group (patients, controls) was the between-subjects factor and condition (GO, NOGO) was the within-subjects factor. The N2 peak amplitude chosen from each participant's GO and NOGO ERP average was defined as the most negative point between 175 and 300 ms at frontal midline electrode FZ. The P3 peak amplitude was defined as the most positive point between 280 and 600 ms at frontocentral midline electrode FCZ.

N2 amplitude showed a trend toward a main effect of group ($F(1, 46) = 3.373$, $p = .0727$), but there was neither a main effect of condition ($F(1, 46) = .715$, $p = .4021$) nor an interaction between group and condition ($F(1, 46) = 2.062$, $p = .1578$). Not more than 7% of the variance was accounted for by either group, condition, or their interaction. In contrast, P3 amplitude showed an effect of group ($F(1, 46) = 6.501$, $p = .0142$, $\eta^2 = .095$), where the mean amplitude of the control group was greater than that of the patient group, and a main effect of condition ($F(1, 46) = 38.631$, $p < .0001$, $\eta^2 = .099$), where the mean amplitude in the NOGO condition was greater than that of the GO condition. As shown in Fig. 1, these findings were in the context of the significant interaction between group and condition ($F(1, 46) = 6.569$, $p = .0137$, $\eta^2 = .017$) on P3 amplitude, which suggests that the aforementioned effects were driven by the increased NOGO amplitude in only the control group's averages.

The NOGO condition showed the greatest behavioral difference as well. The false-alarm rate of the patient group ($M = 30\%$) was significantly higher than that of the control group ($M = 18\%$; $t(46) = -2.584$, $p = .013$). The number of false alarms was not related to the familiarity of the stimuli ($r(38) = -.052$, $p = .77$). The hit rates of the patient group were significantly lower (91%) than that of the controls (96%, $t(46) = 2.205$, $p = .0325$).

4. Discussion

The Gulf War veterans with cognitive complaints demonstrated inhibition difficulty, which was confirmed by their significantly greater false-alarm rate in the semantic categorization GO–NOGO task. This is consistent with other GW veteran studies that have revealed poor performances on similar tasks, such as CPT [NES2; 7,8,43] and Stroop tasks [10,14,15]. The inhibition difficulty noted here in the subjects' performance was accompanied by ERPs whose NOGO P3 was significantly reduced in amplitude, whereas the NOGO N2 amplitudes were neither significantly different from those of the control group nor different from the GO N2 amplitudes. This is consistent with previous studies in other patient populations that have found compromised inhibitory response performance to be marked by blunted or absent NOGO P3 in the N2–P3 complex [44,45,53–55].

Additionally, given the trends in the studies that have sought to differentiate what cognitive processes each ERP aspect reflects [e.g., 26,31,32,34], the lack of difference between the groups in the N2 aspect of this complex is consistent with the contention that the cognitive deficit lies more in inhibition ability than in recognition of task-related differences in the stimuli. In a study of response inhibition among patients with Huntington Disease, patients with Parkinson Disease, a sample of young healthy controls, and a sample of older controls, Beste et al. [44] found that the Parkinson patients' and the older controls' GO and NOGO N2 components were not different from each other, yet their P3 components did show the

expected difference. Both of these groups showed false-alarm rates that were significantly *less* than those of the younger controls and Huntington patients, who exhibited a significant difference between the GO and NOGO N2. Thus, the N2 difference was not indicative of compromised response inhibition. The ages of the older controls in the Beste et al. study (ages 41–75, $M = 60.4$) were similar to the ages of the GW veterans in the present study (ages 40–76, $M = 58.6$).

The P3 component in the GO–NOGO paradigm has been imputed to reflect the inhibitory aspect of withholding a response. The main generator of the NOGO P3 has been localized to the ventral frontal cortex [33], one of the areas that have been consistently implicated in fMRI studies of inhibition. Aron et al. [46] reported that while fMRI studies examining inhibitory circuits have reported signal changes in several areas of the frontal cortex, lesion studies have implicated the right inferior frontal region with the inhibitory process. Aron et al. [47] proposed a model wherein the stopping process of the NOGO is generated by inferior frontal cortex, which sends a signal to the subthalamic nucleus, whose projections elicit excitation in the pallidum, which then essentially intercepts the GO response by inhibiting thalamocortical input and reducing motor cortex activation. In an fMRI study, Fassbender et al. [48] used the Fixed and Random versions of the SART to compare an expected, planned withholding of a response (Fixed) to an unexpected, and thus presumably more urgently processed, withholding of a response (Random). Evidence suggesting separate circuitry for these conditions emerged. Whereas correctly executed planned inhibition in the Fixed task showed greater activation in the angular gyrus on the right and inferior and middle frontal gyrus and insula on the left, correct inhibition in the Random task showed greater activation in dorsolateral prefrontal cortex and putamen on the left, and in inferior parietal lobule and ventral prefrontal cortex on the right. Thus, damage to any of these structures might compromise inhibitory functions, depending on the inhibitory task.

Additionally, Forstmann et al. [49] proposed that individuals with more proficient selective response inhibition should show higher fractional anisotropy (FA) connectivity values in white matter tracts in the right inferior frontal area. Indeed, individuals who performed better on a modified Simon task showed higher FA values in the right anterior aspect of the inferior fronto-occipital fasciculus. These values correlated not only with inhibition ability but with the BOLD response in the right inferior frontal cortex during the response inhibition. Aron et al. [47] also emphasized the importance of the hyperdirect pathway, white matter tracts from inferior frontal cortex to the subthalamic nucleus of the basal ganglia, in stopping a prepotent GO response.

The above response inhibition circuitry models include three areas implicated in Gulf War Illness: basal ganglia, white matter, and frontal lobes. White et al. [50] found that patients with pathologies associated with structures believed to be targets of neurotoxins—basal ganglia and white matter—exhibited notably higher false positives on the NES2 continuous performance task. Haley and colleagues [41,51] and Meyerhoff et al. [52] have shown by using magnetic resonance spectroscopy that neuronal integrity, as reflected in *N*-acetylaspartate-to-creatine (NAA/Cr) ratio, was reduced in basal ganglia (in Haley Syndromes 1 and 2) and brainstem (in Haley Syndromes 2 and 3). Another study of GW veterans showed a dose-dependent correlation of DOD-modeled estimates of sarin exposure and reduction in white matter volume [5,53].

While ventral and inferior aspects of the frontal lobes are consistently implicated in studies of performance deficits in GW veterans, few studies to date have offered physiological corroboration of these implications. Several studies have found performance decrements in the Wisconsin Cart Sort [8], Continuous Performance Test [8,43,54], Stroop tasks [10,14,15], sustained attention [7], and Digit Span tasks [8,10,15,55], all of which are considered markers of frontal lobe dysfunction. These findings are supported by neuroimaging results suggesting decreased perfusion in the superior- and mid-frontal regions bilaterally in ill GW veterans [56]. The findings of the present study also suggest that frontal lobe regions may be dysfunctional, but, given previous research on response inhibition coupled with current physiological markers of Gulf War-related illnesses, we also entertain the likelihood that fronto-striatal pathways or basal ganglia structures may be largely responsible for the poor performance and ERP P3 marker.

Previous neuropsychological assessments of GW Veterans have suggested that there have been impairments in tasks of attention and vigilance—frontal lobe functions [7,10,14,15]. However, no previous studies have concluded that an underlying dysfunction in GW veterans is impaired inhibition, or that this accounts for many of the cognitive symptoms (such as those mentioned above as well as word-finding difficulties and emotional lability) or impairments in these veterans. The semantic category inhibition task employed here was targeted to assess the ability to inhibit object choices in memory, which has a direct bearing on performance of word-finding related tasks [57]. The lack of effective inhibition as demonstrated in both behavioral performance and in electrophysiological responses may be able to account for multiple other symptomatic complaints. For example, a lack of effective inhibition can represent a plausible etiology for the deficits in executive function [3,8,14,15,58,59], attention [8,59–62], and abstraction/problem solving [60,63]. Because it can account for such a wide array of symptoms, impairment in inhibition is compatible with the variety of complaints reported by GW veterans, although they may not specifically report 'a lack of inhibition.' Our data suggest that an underlying general dysregulation of inhibition, via disruption of the integrity of fronto-striatal circuits, contributes to a wide variety of cognitive dysfunction as well as symptomatic complaints in this population.

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