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Central Executive Dysfunction and Deferred Prefrontal Processing in Veterans With Gulf War Illness

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Abstract

Gulf War Illness is associated with toxic exposure to cholinergic-disruptive chemicals. The cholinergic system has been shown to mediate the central executive of working memory. In the current work, we propose that impairment of the cholinergic system in Gulf War Illness patients (GWIPs) leads to behavioral and neural deficits of the central executive of working memory. A large sample of GWIPs and matched control participants underwent functional MRI during a varied-load working memory task. Compared with matched control participants, GWIPs showed a greater decline in performance as working memory demand increased. Functional imaging results suggested that GWIPs evinced separate processing strategies, deferring prefrontal cortex activity from encoding to retrieval for high-demand conditions. Greater activity during high-demand encoding predicted greater working memory performance. Behavioral data suggest that working memory executive strategies are impaired in GWIPs. Functional data further support this hypothesis and suggest that GWIPs use less effective strategies during high-demand working memory.

Keywords

neuropsychology, neuroimaging, war, memory, nervous system disorders

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Twenty-five percent of the 700,000 troops deployed to the Persian Gulf War during 1990–1991 returned with a chronic and often disabling constellation of symptoms (Research Advisory Committee on Gulf War Veterans' Illnesses, 2008). This unique symptom cluster, known as Gulf War Illness (GWI), is the most prevalent health issue affecting veterans of this campaign and features fatigue or sleep issues, widespread neuropathic pain, neurological/mood/cognitive changes (e.g., chronic headaches, cognitive difficulties, mood disturbances), gastrointestinal issues (e.g., chronic diarrhea, abdominal cramping), respiratory issues (e.g., wheezing, coughing), and unexplained rashes (Golomb, 2008; Research Advisory Committee on Gulf War Veterans' Illnesses, 2008). Similar chronic symptomatology is exhibited by populations with either chronic (Ecobichon, 1994) or acute (Yokoyama et al., 1998) cholinergic (Ch) toxicity. In accordance, strong associations have been found between GWI and exposure to Ch-disruptive chemicals, such as sarin nerve agents, organophosphate pesticides, and pyridostigmine bromide (Chao, Rothlind, Cardenas, Meyerhoff, & Weiner, 2010; Golomb, 2008; Haley et al., 2009; Haley et al., 2013; Haley & Tuite, 2013; Henderson et al., 2002; Li et al., 2011; Research Advisory Committee on Gulf War Veterans' Illnesses, 2008; Tuite & Haley, 2013). Although alternative etiologies of GWI have been proposed (e.g., vaccines, infectious disease, stress), the Ch-toxicity hypothesis has been found to be the most consistent with results from both human and animal studies (e.g., Chao et al., 2010;

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Golomb, 2008; Haley et al., 2009; Haley et al., 2013; Haley & Tuite, 2013; Henderson et al., 2002; Li et al., 2011; Research Advisory Committee on Gulf War Veterans' Illnesses, 2008; Tuite & Haley, 2013).

The etiology of GWI is thought to result from the delayed effects of toxic exposure to cholinesterase-inhibiting chemicals (Chao et al., 2010; Golomb, 2008; Haley et al., 2009; Haley et al., 2013; Henderson et al., 2002; Li et al., 2011). Toxic increases in acetylcholine availability lead to long-term Ch suppression and central and peripheral nervous system dysfunction in GWI (see Chao et al., 2010; Haley et al., 2009; Haley et al., 2013; Haley & Tuite, 2013; Henderson et al., 2002; Li et al., 2011). Repeated, low-level exposure to cholinesterase-inhibiting chemicals, such as those experienced by veterans with GWI, also results in downregulation of the muscarinic M1 and M3 receptor subtypes (e.g., Henderson et al., 2002). Muscarinic Ch transmission has been robustly linked to cognitive processes (see Bartus, 2000; Hasselmo & Sarter, 2011). Specifically, selective action of acetylcholine on the M1 receptor has been shown to mediate working memory (WM) performance (Ragozzino et al., 2012).

WM is a cognitive process that permits moment-to-moment, short-term retention and manipulation of information. The amount of information this process can accommodate is known to have capacity limitations (Baddeley & Hitch, 1974; Cowan, 2001). If the volume of to-be-remembered information exceeds WM capacity ($> 4 \pm 1$ units; Cowan, 2001), central executive strategies are required to reduce the volume of information so as to circumvent capacity constraints (Baddeley & Hitch, 1974). If such strategies are not used, item representations become degraded during maintenance as a result of temporal decay or an inability to keep supracapacity items active through rehearsal. Thus, both performance speed and accuracy (i.e., efficiency) depend on central executive strategies as task demand exceeds WM capacity (e.g., Baddeley & Hitch, 1974). The Ch system has been shown in associational (Baddeley, Bressi, Della Sala, Logie, & Spinnler, 1991; Baddeley, Logie, Bressi, Della Sala, & Spinnler, 1986) and experimental (Rusted, 1988; Rusted & Warburton, 1988) studies to be critical for central executive processes of WM.

In one set of studies, Baddeley et al. (1986) and Baddeley et al. (1991) observed distinct central executive dysfunction in a patient population thought to have Ch aberrations (i.e., patients diagnosed with Alzheimer's disease). Direct antagonism of the Ch system also has been shown to produce performance deficits on tasks that involve central executive function (Rusted, 1988; Rusted & Warburton, 1988). Rusted and Warburton (1988) noted that the underlying WM deficit associated with Ch blockade was an impairment of strategic executive processing in WM. The few studies in which researchers have examined the effects of Ch deficits on neural systems during WM performance have reported functional activity differences within lateral prefrontal cortex (PFC) during Ch antagonism (Dumas et al., 2008; Voss et al., 2012). Researchers have shown that the central executive system is mediated by lateral PFC (D'Esposito et al., 1995; Rypma, 2006; Rypma, Berger, & D'Esposito, 2002; Rypma & D'Esposito, 1999; Rypma, Prabhakaran, Desmond, Glover, & Gabrieli, 1999).

Research has suggested that in high-demand conditions in which WM capacity is exceeded, executive strategies recruited by lateral PFC during the encoding of information aid in performance by compressing high-volume WM loads (Rypma & D'Esposito, 2000; Rypma et al., 1999). Conversely, lateral PFC activity delayed until individuals are attempting to reconstruct/retrieve this information has been shown to be indicative of WM-performance deficits (Rypma & D'Esposito, 1999, 2000). The tendency to bias lateral PFC activity toward encoding has similarly been found to be related to Ch augmentation and enhanced behavioral performance in which retrieval-based strategies have been associated with Ch blockade (see Bentley, Driver, & Dolan, 2011).

In the present study, we examined for the first time the extent to which WM performance and lateral PFC systems are affected in GWI. Using a large sample of GWI patients (GWIPs), we examined task-related blood-oxygen-level-dependent (BOLD) activity in dorsolateral PFC (DLPFC) and ventrolateral PFC (VLPFC) during delayed-response task performance (Sternberg working memory task, SWMT; Sternberg, 1966). The literature reviewed earlier led us to predict that if the central executive system was affected in GWI, we would observe WM-efficiency deficits with increases in task demand (i.e., WM load; Baddeley et al., 1986; Baddeley et al., 1991; Rusted, 1988; Rusted & Warburton, 1988). This literature also led to the prediction that group differences would emerge in lateral PFC activity associated with increased WM load. Use of event-related functional MRI (fMRI) methodology permitted us to test these hypotheses in encoding, maintenance, and retrieval phases of the SWMT. We hypothesized that if the Ch system was affecting the central executive system of WM, GWIPs would defer lateral PFC activation from the encoding period to the retrieval period for high-demand WM loads (Bentley et al., 2011; Rypma & D'Esposito 1999, 2000; Rypma & Gabrieli, 2001; Rypma et al., 2002).

Materials and Method

Participants and procedure

Data were collected from 96 GWIPs and 44 matched control participants (MCs). Participants were screened for

GWI using a factor analytic metric that identified unique GWI symptom clusters (Haley, Kurt, & Hom, 1997; Iannacchione et al., 2011). These unique symptom clusters consisted of three primary GWI classes, which were equally represented in the present study. All GWIP diagnoses were confirmed by a physician (R. W. Haley) via diagnostic interview. Syndrome 1 (n = 29) was characterized by problems with attention, memory, reasoning, and depression; Syndrome 2 (n = 36) was characterized by chronic confusion, disorientation, balance disturbance, and impotence; and Syndrome 3 (n = 31) was characterized by joint and muscle pain, fatigue, and extremity paresthesia (Haley et al., 1997; Iannacchione et al., 2011). No behavioral differences were found on the SWMT between these syndrome classes; thus, the syndromes were combined for all subsequent analyses (all ps > .05; see Table S1 in the Supplemental Material available online). MCs were Gulf War veterans without GWI who were age-, sex-, education-, handedness-, and rank-matched with GWIPs (see Table S2 in the Supplemental Material). GWIPs in the present study, compared with MCs, reported significantly greater exposure to chemical nerve gas alarms during deployment, as well as greater use of cholinesterase inhibitors (i.e., pyridostigmine bromide) as prophylaxis for sarin nerve agent exposures (all ps < .001; see Table S2 in the Supplemental Material). Evidence from a large-scale, epidemiological investigation has shown that such indicators significantly increase the risk of GWI (Haley & Tuite, 2013).

Participants were screened for fMRI contraindicators. All procedures were monitored by trained health professionals. Individuals who were deemed high health risks or who met the criteria for traumatic brain injury were excluded from the study. The current work was part of a multi-investigator, multiuniversity study. Two samples of Gulf War veterans, that is, the GW sample, which comprised the Seabees sample (35 GWIPs and 16 MCs) and the National sample (61 GWIPs and 28 MCs), were used in this study. Detailed descriptions of sampling procedures and clinical data for these samples can be found in Haley et al. (1997; Seabees sample) and Haley et al. (2013; National sample). Because our study groups were of unequal sizes, all distributions were scrutinized for violations of the homogeneity of variance assumption. When necessary, degrees of freedom were adjusted to account for unequal variance between groups. All procedures were approved by the institutional review boards of the University of Texas Southwestern Medical Center and the University of Texas at Dallas. Participants consented before undergoing any procedure and received monetary compensation for their participation.

Behavioral measurement

Three runs of the SWMT, each consisting of 54 trials and lasting 5 min per run, were administered during fMRI scanning. Each trial featured three task phases in which participants encoded stimuli of two, four, or six letters (WM Loads 2, 4, and 6 respectively equating to low-, medium- and high-demand WM load), maintained the stimuli while viewing a blank screen, and retrieved the stimuli to judge whether a letter on the decision screen was located within the to-be-remembered set. Each trial consisted of a 4-s encoding period, an 8-s maintenance period, and a 2-s retrieval period. Items were scored as correct or incorrect; accuracy was assessed as percent of correct trials. Reaction time was calculated as the average time it took to complete a correct trial. Trials exceeding 2 standard deviations of a participant's average reaction time were not included in subsequent analyses. A measure of overall WM efficiency was calculated as SWMT accuracy scaled by the speed at which individuals completed the task (i.e., SWMT accuracy / SWMT reaction time). WM capacity (WMC) was also calculated on WM Load 6 (WMC = [hit rate + correct rejection rate − 1] × 6; Cowan, 2001). GWIPs had a median WMC of 4 (median absolute deviation = .83), and MCs had a median WMC of 4.67 (median absolute deviation = .67). Capacity calculations showed that our high-demand condition (i.e., WM Load 6) constituted supracapacity WM performance.

Image acquisition and processing

Imaging data were acquired using a Siemens 3 Tesla magnet with a 12-channel head coil. High-resolution anatomical, magnetization-prepared rapid acquisition of gradient echo (MPRAGE; Brant-Zawadzki, Gillan, & Nitz, 1992) scans were acquired using the following parameters: T1-weighted type, 1-mm isovoxel, 160 slices/volume, sagittal plane, 3.31-ms echo time, 12° flip angle, 256 × 256 matrix, left-to-right acquisition, 281-s scan duration. Functional scans during the SWMT were acquired using the following parameters: BOLD signal type, 3.5-mm isovoxel, 44 slices/volume, 197 volumes/run, transaxial plane, 20-ms echo time, 2,000-ms repetition time, 90° flip angle, 64 × 64 matrix, foot-to-head acquisition, 394-s scan duration across three runs.

Anatomical data were discarded if they featured any artifact that would interfere with spatial localization (e.g., excessive motion issues, magnetic field inhomogeneities, interference caused by metallic implants). Functional data were discarded if they featured an irreconcilable artifact. This quality assurance protocol excluded 10% of the participants from the MC sample and 15% of the participants from the GWIP sample. There was not a significant difference between groups in the numbers of excluded participants (p = .367).

Functional data were processed using Analysis of Functional NeuroImages (Cox, 1996). After T1 saturation time was removed, functional data were corrected for interleaved slice acquisition and motion effects and were aligned to the third functional volume of the first SWMT

run. The MPRAGE image was also spatially aligned to the functional data. Data were spatially smoothed (6-mm full width at half maximum Gaussian kernel) and high-pass filtered at .015625 Hz. If motion-correction parameters indicated presence of movements larger than 1 mm, visual inspection of functional and anatomical alignment was conducted for every time point to ensure that these data were correctly registered.

Task periods versus rest periods were modeled using regressors representing condition and load for a total of nine conditions across three runs. These nine conditions represented encoding, maintenance, and retrieval at WM Loads 2, 4, and 6. Functional data were warped to Talairach space (Talairach & Tournaux, 1988). All three SWMT runs were concatenated, and task regressors derived from these three runs were convolved with a gamma-variate hemodynamic response function and used as independent variables to predict the functional data by means of a generalized linear model. Four a priori regions of interest (ROIs) were placed in standard space for left and right DLPFC (Brodmann's areas 9 and 46) and VLPFC (Brodmann's areas 44, 45, and 47; Brodmann, 1909/2006). Functional data used in subsequent analyses represented average BOLD percent signal change, per condition and load, in the ROIs.

Results

The Seabees and the National samples showed equivalent SWMT performance ($p > .05$; see Table S3 in the Supplemental Material). Data were therefore combined for all subsequent analyses. However, the GW sample was found to have significant interaction effects with some of the functional repeated measures factors, which were likely due to age differences between the samples ($p < .001$). To ensure that the GW sample was not confounded with group effects, we modeled these between-subjects effects holding the GW sample constant in our repeated measures analyses of the functional data (see later discussion).

Behavioral results

Group analyses of SWMT performance revealed that GWIPs were significantly slower (M = 1,626.03 ms, SEM = 36.96) compared with MCs (M = 1,352.95 ms, SEM = 54.31), $t(138) = 4.15$, $p < .001$, and were less accurate (M = .87%, SEM = .01) than were MCs (M = .93%, SEM = .006), $t(137.44) = -5.36$, $p < .001$. GWIPs were also less efficient on the SWMT ($M = 5.6 \times 10^{-4}$, $SEM = 1.5 \times 10^{-5}$) than were MCs ($M = 7.5 \times 10^{-4}$, $SEM = 3.8 \times 10^{-5}$), $t(56.86) = -4.52$, $p < .001$ (see also Table S4 in the Supplemental Material). To test predicted GWIP deficits in WM efficiency as WM load increased, we planned one-tailed t tests to compare each group's change in efficiency from WM Load 2 to WM Load 4 and from WM Load 2 to WM Load 6. Compared with MCs, GWIPs were significantly less efficient as WM load increased both from 2 to 4 items (GWIP: $M = 1.0 \times 10^{-4}$, $SEM = 1.3 \times 10^{-5}$; MC: $M = 1.5 \times 10^{-4}$, $SEM = 1.9 \times 10^{-5}$), $t(83.51) = -2.31$, $p = .012$, and from 2 to 6 items (GWIP: $M = 2.2 \times 10^{-4}$, $SEM = 1.5 \times 10^{-5}$; MC: $M = 2.7 \times 10^{-4}$, $SEM = 2.1 \times 10^{-5}$), $t(85.93) = -1.95$, $p = .028$. A mixed-model analysis of variance (ANOVA) of SWMT efficiency across WM loads confirmed a significant difference in group performance slopes as load increased via a WM Load × Group interaction, Greenhouse-Geisser corrected $F(1.74, 240.04) = 3.45$, $p = .040$.

ROI functional analyses

Four ANOVA models were built to examine percent signal change in BOLD activity across ROIs—left and right DLPFC and left and right VLPFC—as a function of the independent variables, WM load, and WM phase. In all four ROIs, repeated measures ANOVAs showed WM load, WM phase, and WM Load × WM Phase interactions to be significant predictors of change in BOLD signal (ps < .001). To investigate our hypothesis that compared with MCs, GWIPs would defer recruitment of lateral PFC from encoding to retrieval at high-demand load sizes, we added group to the model, holding sample constant. This mixed-model procedure yielded a significant three-way (WM Load × WM Phase × Group) interaction for right DLPFC, Greenhouse-Geisser corrected $F(3.31, 386.86) = 3.36$, $p = .016$, and for right VLPFC, Greenhouse-Geisser corrected $F(3.47, 406.44) = 4.07$, $p = .005$. Levene's tests of equality of error variances for group showed a single group difference in error variance in right DLPFC at WM Load 2 during maintenance. This result did not affect subsequent analyses, which focused on high-demand load conditions. Three-way interactions were not significant for left DLPFC ($p > .05$) or for left VLPFC ($p > .05$). It is important that the GW sample did not affect these results (i.e., WM Load × WM Phase × Group × Sample; $p > .05$), which indicated replicability across the two samples. Significant three-way interactions in right DLPFC and right VLPFC showed that there were differences between GWIPs and MCs as WM load increased and as WM phase changed.

To further model these differences, we built mixed-model ANOVAs for both ROIs, which examined the interaction between WM Phase × Group in each WM load condition, holding sample constant (see Figure 1 for ANOVA results). No group differences were found for WM Loads 2 or 4 in BOLD activity across WM phase for either ROI ($p > .05$). However, mixed models for WM Load 6 were significant for both right DLPFC and right

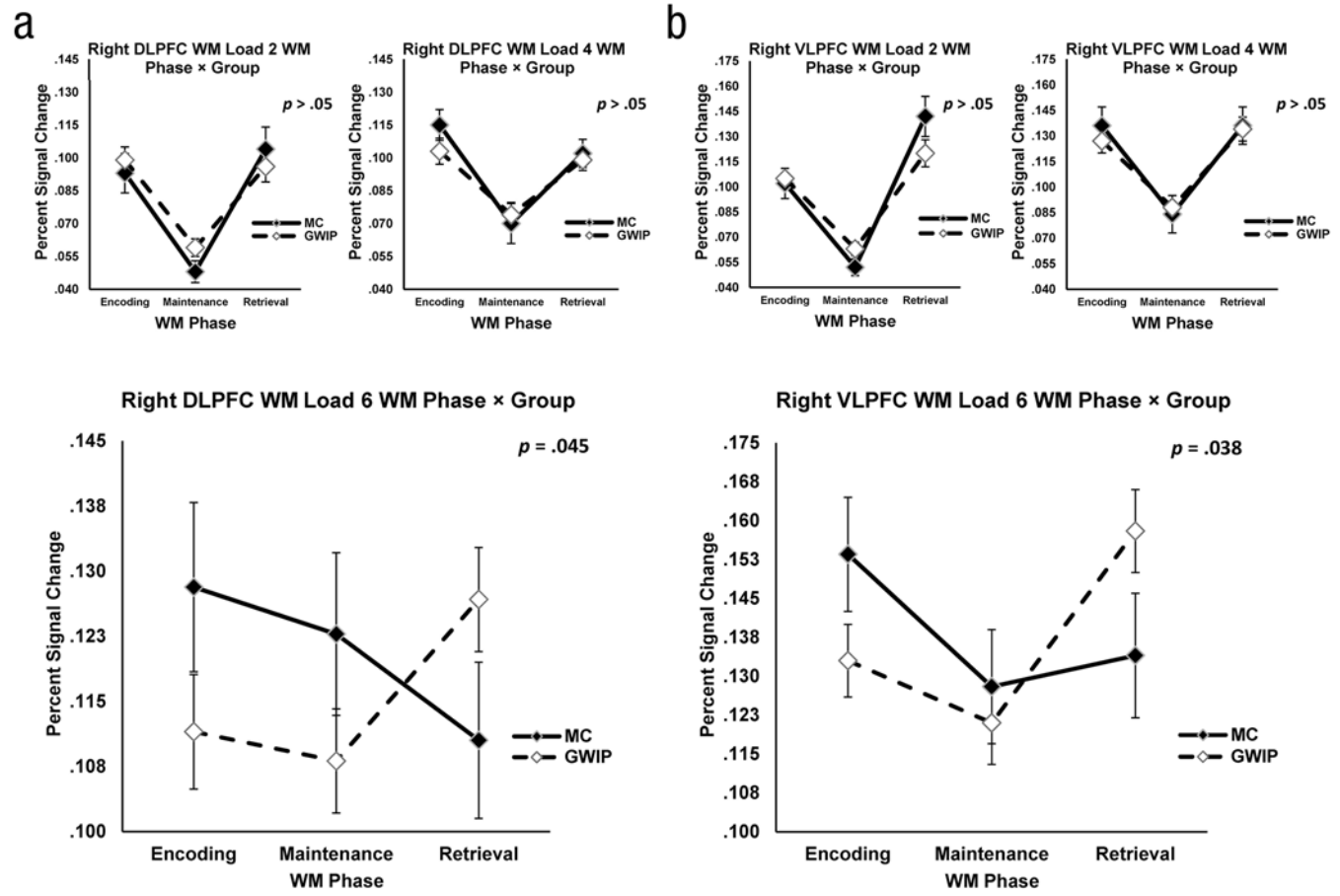

Fig. 1. Repeated measures analyses of working memory (WM) phase by group interactions, including percent signal change during encoding, maintenance, and retrieval at WM Loads 2, 4, and 6 for (a) right dorsolateral prefrontal cortex (DLPFC) and (b) right ventrolateral prefrontal cortex (VLPFC). Error bars represent standard error of the mean, and *p* values represent mixed-model, repeated measures analyses of variance. MC = matched control participant; GWIP = Gulf War Illness patient.

VLPFC activity (see Figure 1). At high-demand WM loads, MCs showed relatively high BOLD percent signal change during the encoding phase, but the BOLD response was attenuated during maintenance and retrieval. In contrast, GWIPs showed relatively depressed encoding and maintenance compared with MCs, but BOLD activity increased during retrieval.

Right DLPFC and right VLPFC WM-phase contrasts

For both groups, peak BOLD activity was observed during high-demand WM loads. However, this peak activity occurred during retrieval for GWIPs and during encoding for MCs. Encoding-retrieval contrasts were used in right DLPFC and right VLPFC to examine the relative change in BOLD activity between these phases (see Figure 2 for group differences in encoding and retrieval activity). These results showed that during high-demand WM, there was less BOLD activity at encoding than at retrieval for GWIPS (encoding – retrieval = negative) compared with MCs (encoding – retrieval = positive). These results suggested that MCs emphasized encoding activity relative to retrieval activity, whereas GWIPs emphasized retrieval activity relative to encoding activity. Differential emphasis on encoding versus retrieval suggested the hypothesis that GWIPs and MCs use different processing strategies during high-demand WM performance.

Superior WM performance of MCs relative to GWIPs might occur because MCs implement a more efficient high-demand encoding-based strategy than do GWIPs. In testing this hypothesis, we found that greater high-demand BOLD activity in right DLPFC and right VLPFC during encoding significantly predicted greater WM efficiency (DLPFC: $\beta = 0.067$, $p = .035$, $r^2 = .037$; VLPFC: $\beta = 0.105$, $p < .001$, $r^2 = .106$), whereas no substantive predictive relationship was found between high-demand BOLD activity during maintenance (DLPFC: $\beta = 0.030$, $p =$

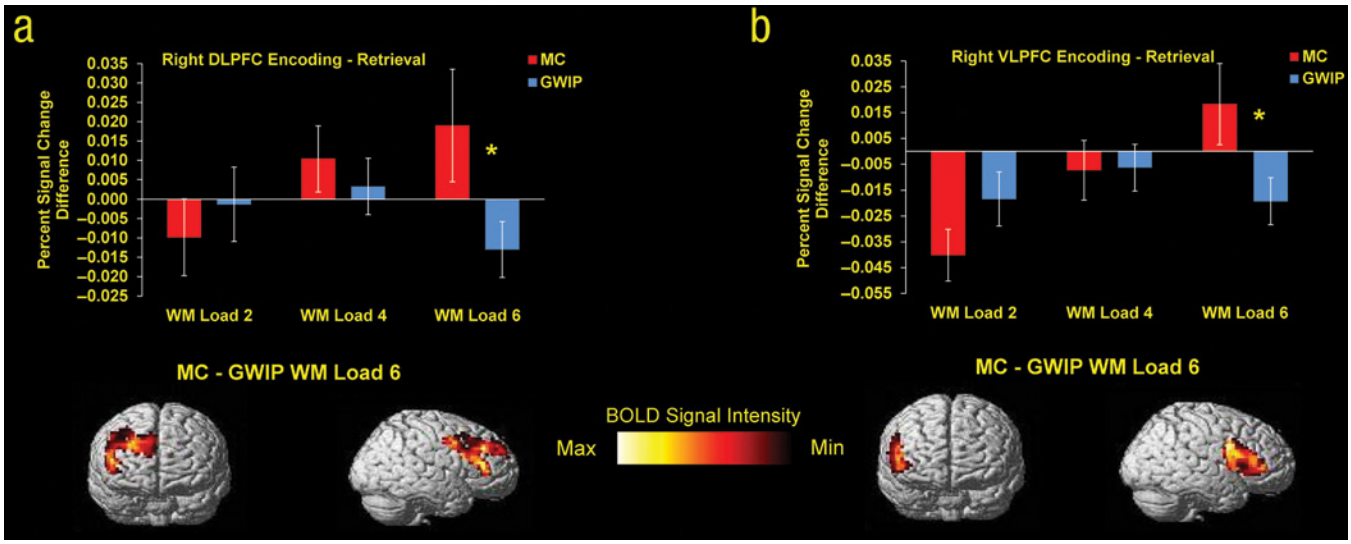

Fig. 2. Group differences in encoding and retrieval processing strategies across working memory (WM) loads, including a bar graph of percent signal change difference between encoding and retrieval across WM loads and MC–GWIP contrast of percent signal change difference in encoding and retrieval strategies at WM Load 6 for (a) right dorsolateral prefrontal cortex (DLPFC) and (b) right ventrolateral prefrontal cortex (VLPFC). Error bars represent standard error of the mean. MC = matched control participant; GWIP = Gulf War Illness patient; BOLD = blood oxygen level dependent. *$p < .05$.

.374, $r^2 = .007$; VLPFC: $\beta = 0.048$, $p = .080$, $r^2 = .026$) or retrieval (DLPFC: $\beta = 0.040$, $p = .278$, $r^2 = .010$; VLPFC: $\beta = 0.032$, $p = .219$, $r^2 = .012$). These results suggest that greater lateral PFC BOLD activity during high-demand encoding predicted greater WM efficiency. As GWIPs shifted high-demand processing away from encoding and toward retrieval, it is likely that this retrieval-based processing strategy resulted in less efficient performance.

Discussion

In this study, we compared GWIPs with MCs on WM performance and lateral PFC activation to test hypotheses of reduced PFC-related WM function. To our knowledge, this fMRI study is one of very few to evaluate GWIPs (see Calley et al., 2010; Gopinath et al., 2012; Odegard et al., 2013). Consistent with our hypotheses, our results showed WM-performance deficits in GWIPs as well as group-differential BOLD activation in right DLPFC and right VLPFC during WM. There were significant differences between groups in WM efficiency and PFC activity, as well as WM Load × Group interactions on WM efficiency and WM Load × WM Phase × Group interactions on right lateral PFC activity. Furthermore, the results that GWIPs deferred neural processing of high-demand WM loads from the encoding to the retrieval phase of the SWMT. Functional imaging and behavioral results supported our hypothesis regarding central executive dysfunction in GWIPs compared with MCs.

Behavioral results showed that as WM load size increased from two items, GWIPs had significantly greater declines in efficiency relative to MCs. This result and the observed WM Load × Group efficiency interaction showed that GWIPs evinced a behavioral signature of central executive dysfunction. Taken together, the present findings suggest that reduced WM efficiency with increasing WM load is attributable to an inability to strategically manipulate information for later retrieval, which results in information degradation or loss (cf. Rypma & D'Esposito, 1999; Salthouse, 1996). Behavioral results also implicate overall WM deficits in GWIPs, which possibly reflects additional short-term storage deficits (Golomb, 2008; Horn, Haley, & Kurt, 1997). Lateral PFC BOLD activity further suggests a pattern of mediation of these executive processes by the Ch system.

In a review of 63 functional imaging studies of Ch modulation of cognition, Bentley et al. (2011) hypothesized that within PFC, the Ch system aids in neural processing during high-demand conditions. Their review suggested that Ch augmentation increased activity within neural executive systems (particularly DLPFC) under high-demand conditions. This observation supports the hypothesis of a relationship between acetylcholine availability and additional recruitment of executive prefrontal processes when cognitive systems are at capacity (cf. Bentley et al., 2011). In the present study, group differences in BOLD activity across task phases were observed only in high-demand/supracapacity conditions. Differences in allocation of BOLD resources occurred during encoding and retrieval phases in right DLPFC and right VLPFC. Compared with MCs, GWIPs showed a greater shift in BOLD activity away from encoding and toward

retrieval processes in right DLPFC and right VLPFC during supracapacity WM. Additionally, greater supracapacity BOLD activity during encoding in right DLPFC and right VLPFC predicted greater WM efficiency, which suggests that GWIPs' retrieval-based strategy might not facilitate supracapacity WM performance. Indeed, researchers have shown that encoding and retrieval strategies are mediated by Ch availability (see Bentley et al., 2011).

During episodic memory, Ch augmentation is associated with an increase in neural activity in medial temporal lobe while individuals are encoding information (e.g., Kukolja, Thiel, & Fink, 2009). Ch augmentation is also associated with a decrease in activity in medial temporal lobe during retrieval (e.g., Kukolja et al., 2009). Ch antagonism has been shown to have the opposite effect by attenuating encoding and facilitating retrieval processes (see Bentley et al., 2011). Accordingly, it has been postulated that the Ch system might mediate enhancement of incoming information by inhibiting interference from parallel internal (retrieval) processes (Hasselmo, 1995; Hasselmo & Giocomo, 2006; Hasselmo & McGaughy, 2004). Animal and computational models also indicate that high acetylcholine levels potentiate encoding by inhibiting feedback "noise" from internal processing (e.g., Hasselmo, 1995; Hasselmo & McGaughy, 2004). During supracapacity WM conditions, it is likely that Ch signals to and from lateral PFC follow a similar pattern as those in medial temporal lobe.

Lateral PFC is innervated by the Ch system via lateral ascending fibers from the basal forebrain (Selden, Gitelman, Salamon-Murayama, Parrish, & Mesulam, 1998). Moreover, basal forebrain is thought to be employed via descending fibers from PFC when executive control of mental resources is required (Sarter, Gehring, & Kozak, 2006). Ch ascending fibers to lateral PFC and descending fibers to basal forebrain have been proposed as mediating executive functions in the cortex when increased effort is necessary (Sarter et al., 2006). Damage to this basal forebrain–lateral PFC circuit in GWI, as a result of exposure to Ch-disruptive agents, would inhibit GWIPs' ability to adequately recruit encoding processes during high-demand WM. This failure would place inordinate demands on retrieval processes to scan a larger and more degraded memory set, thereby reducing accuracy and increasing reaction time (i.e., reducing efficiency).

The present results showed behavioral deficits and deferred activation of lateral prefrontal processing for high-demand (i.e., supracapacity) WM loads in GWIPs. Impairment of the Ch system in GWIPs is posited as contributing to the maladaptive central executive processing strategies observed in GWIPs. Impairments to the Ch system probably exert effects in brain regions outside of lateral PFC. Exploration of these effects awaits future research. The present results lend insight into the cognitive changes associated with GWI and suggest future directions examining the central executive sequelae of patient populations with Ch deficits, for example, patients diagnosed with Alzheimer's disease (Terry & Buccafusco, 2003), autism (Deutsch, Urbano, Neumann, Burket, & Katz, 2010), and schizophrenia (AhnAllen, 2012).

Author Contributions

N. A. Hubbard contributed to all aspects of data analysis and wrote the manuscript. J. L. Hutchison contributed to aspects of data analysis and manuscript writing. M. A. Motes contributed to aspects of data analysis, data collection, and manuscript preparation. E. Shokri-Kojori and R. M. Brigante contributed to aspects of data analysis and manuscript preparation. I. J. Bennett contributed to data collection. R. W. Haley and B. Rypma contributed to study design and manuscript preparation.

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Declaration of Conflicting Interests

N. A. Hubbard, J. L. Hutchison, M. A. Motes, I. J. Bennett, R. M. Brigante, E. Shokri-Kojori, and B. Rypma declared that they had no biomedical financial interests or conflicts of interest with respect to their authorship or the publication of this article. R. W. Haley received an honorarium from Targeted Medical Pharma, Inc. for a review of a Food and Drug Administration application for a nonpharmaceutical medication to treat fatigue, with possible benefit to Gulf War Illness patients.

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Supplemental Material

Additional supporting information may be found at http://cpx.sagepub.com/content/by/supplemental-data

References

AhnAllen, C. G. (2012). The role of the alpha7 nicotinic receptor in cognitive processing of persons with schizophrenia. *Current Opinion in Psychiatry*, *25*, 103–108.

Baddeley, A. D., Bressi, S., Della Sala, S., Logie, R., & Spinnler, H. (1991). The decline of working memory in Alzheimer's disease. *Brain*, *114*, 2521–2542.

Baddeley, A. D., & Hitch, G. J. (1974). Working memory. In G. Bower (Ed.), *Recent advances in learning and motivation 8* (pp. 47–90). New York, NY: Academic Press.

Baddeley, A., Logie, R., Bressi, S., Della Sala, S., & Spinnler, H. (1986). Dementia and working memory. *Quarterly Journal of Experimental Psychology: Section A*, *32*, 603–618.

Bartus, R. T. (2000). On neurodegenerative disease, models, and treatment strategies: Lessons learned and lessons forgotten a generation following the cholinergic hypothesis. *Experimental Neurology*, *163*, 495–529.

Bentley, P., Driver, J., & Dolan, R. J. (2011). Cholinergic modulation of cognition: Insights from human pharmacological functional neuroimaging. *Progress in Neurobiology*, *94*, 360–388.

Brant-Zawadzki, M., Gillan, G. D., & Nitz, W. R. (1992). MPRAGE: A three dimensional, T1-weighted, gradient-echo sequence—Initial experience in the brain. *Radiology*, *182*, 769–775.

Brodmann, K. (2006). *Brodmann's localization in the cerebral cortex: The principles of comparative localization in the cerebral cortex based on cytoarchitectonics* (L. J. Garey, Trans.). New York, NY: Springer. (Original work published 1909)

Calley, C. S., Kraut, M. A., Spence, J. S., Briggs, R. W., Haley, R. W., & Hart, J. (2010). The neuroanatomic correlates of semantic memory deficits in patients with Gulf War Illness: A pilot study. *Brain Imaging and Behavior*, *4*, 248–255.

Chao, L. L., Rothlind, J. C., Cardenas, V. A., Meyerhoff, D. J., & Weiner, M. W. (2010). Effects of low-level exposure to sarin and cyclosarin during the 1991 Gulf War on brain function and brain structure in U.S. veterans. *Neurotoxicology*, *31*, 493–501.

Cowan, N. (2001). The magical number 4 in short-term memory: A reconsideration of mental storage capacity [Target article and commentaries]. *Behavioral & Brain Sciences*, *24*, 87–185.

Cox, R. W. (1996). AFNI: Software for analysis and visualization of functional magnetic neuroimages. *Computers and Biomedical Research*, *29*, 162–173.

D'Esposito, M., Detre, J. A., Alsop, D. C., Shin, R. K., Atlas, S., & Grossman, M. (1995). The neural basis of the central executive system of working memory. *Nature*, *378*, 279–281.

Deutsch, S. I., Urbano, M. R., Neumann, S. A., Burket, J. A., & Katz, J. A. (2010). Cholinergic abnormalities in autism: Is there a rationale for selective nicotinic agonist interventions? *Clinical Neuropharmacology*, *33*, 114–120.

Dumas, J. A., Saykin, A. J., McAllister, T. W., McDonald, B. C., Hynes, M. L., & Newhouse, P. A. (2008). Nicotinic versus muscarinic blockade alters verbal working memory-related brain activity in older women. *American Journal of Geriatric Psychiatry*, *16*, 272–282.

Ecobichon, D. J. (1994). Organophosphorus ester insecticides. In D. J. Ecobichon & R. M. Joy (Eds.), *Pesticides and neurological diseases* (2nd ed., pp. 171–250). Boston, MA: CRC Press.

Golomb, B. A. (2008). Acetylcholinesterase inhibitors and Gulf War Illness. *Proceedings of the National Academy of Sciences, USA, 105*, 4295–4300.

Gopinath, K., Gandhi, P., Goyal, A., Jiang, L., Fang, Y., Ouyang, L., . . . Haley, R. (2012). fMRI reveals abnormal central processing of sensory and pain stimuli in ill Gulf War veterans. *Neurotoxicology*, *33*, 261–271.

Haley, R. W., Charuvastra, E., Shell, W. E., Buhner, D. M., Marshall, W. W., Biggs, M. M., . . . Vernino, S. (2013). Cholinergic autonomic dysfunction in veterans with Gulf War Illness: Confirmation in a population-based sample. *JAMA Neurolology*, *70*, 191–200.

Haley, R. W., Kurt, T. L., & Hom, J. (1997). Is there a Gulf War Syndrome? Searching for syndromes by factor analysis of symptoms. *Journal of the American Medical Association*, *277*, 215–222.

Haley, R. W., Spence, J. S., Carmack, P. S., Gunst, R. F., Schucany, W. R., Petty, F., . . . Trivedi, M. H. (2009). Abnormal brain response to cholinergic challenge in chronic encephalopathy from the 1991 Gulf War. *Psychiatry Research*, *171*, 207–220.

Haley, R. W., & Tuite, J. J. (2013). Epidemiological evidence of health effects from long-distance transit of chemical weapons fallout from bombing early in the 1991 Persian Gulf War. *Neuroepidemiology*, *40*, 178–189.

Hasselmo, M. E. (1995). Neuromodulation and cortical function: Modeling the physiological basis of behavior. *Behavioural Brain Research*, *67*, 1–27.

Hasselmo, M. E., & Giocomo, L. M. (2006). Cholinergic modulation of cortical function. *Journal of Molecular Neuroscience*, *30*, 133–135.

Hasselmo, M. E., & McGaughy, J. (2004). High acetylcholine levels set circuit dynamics for attention and encoding and low acetylcholine levels set dynamics for consolidations. *Progress in Brain Research*, *145*, 207–231.

Hasselmo, M. E., & Sarter, M. (2011). Modes and models of forebrain cholinergic neuromodulation of cognition. *Neuropsychopharmacology*, *36*, 52–73.

Henderson, R. F., Barr, E. B., Blackwell, W. B., Clark, C. R., Conn, C. A., Kalra, R., . . . Mash, D. C. (2002). Response of rats to low levels of sarin. *Toxicology and Applied Pharmacology*, *184*, 67–76.

Horn, J., Haley, R. W., & Kurt, T. L. (1997). Neuropsychological correlates of Gulf War syndrome. *Archives of Clinical Neuropsychology*, *12*, 531–544.

Iannacchione, V. G., Dever, J. A., Bann, C. M., Considine, K. A., Creel, D., Carson, C. P., . . . Haley, R. W. (2011). Validation of a research case definition of Gulf War Illness in the 1991 US Military population. *Neuroepidemiology*, *37*, 129–140.

Kukolja, J., Thiel, C. M., & Fink, G. R. (2009). Cholinergic stimulation enhances neural activity with encoding but reduces neural activity associated with retrieval in humans. *Journal of Neuroscience*, *29*, 8119–8128.

Li, X., Spence, J. S., Buhner, D. M., Hart, J., Jr., Cullum, C. M., Biggs, M. M., . . . Haley, R. W. (2011). Hippocampal dysfunction in Gulf War veterans: Investigation with ASL perfusion MR imaging and physostimine challenge. *Radiology*, *261*, 218–225.

Odegard, T. N., Cooper, C. M., Farris, E. A., Arduengo, J., Bartlett, J., & Haley, R. (2013). Memory impairment exhibited by veterans with Gulf War Illness. *Neurocase*, *19*, 316–327.

Ragozzino, M. E., Artis, S., Singh, A., Twose, T. M., Beck, J. E., & Messer, W. S., Jr. (2012). The selective M1 muscarinic cholinergic agonist CDD-0102A enhances working memory and cognitive flexibility. *Journal of Pharmacology and Experimental Therapeutics*, *340*, 588–594.

Research Advisory Committee on Gulf War Veterans' Illnesses. (2008). *Gulf War Illness and the health of Gulf War veterans*. Washington, DC: Department of Veterans Affairs. Retrieved from http://www1.va.gov/RAC-GWVI/Committee_Documents.asp

Rusted, J. M. (1988). Dissociative effects of scopolamine on working memory in healthy young volunteers. *Psychopharmacology*, *96*, 487–492.

Rusted, J. M., & Warburton, D. M. (1988). The effects of scopolamine on working memory in healthy young volunteers. *Psychopharmacology*, *96*, 145–152.

Rypma, B. (2006). Factors controlling neural activity during delayed-response task performance: Testing a memory organization hypothesis of prefrontal function. *Neuroscience*, *139*, 223–225.

Rypma, B., Berger, J. S., & D'Esposito, M. (2002). The influence of working-memory demand and subject performance on prefrontal cortical activity. *Journal of Cognitive Neuroscience*, *14*, 721–731.

Rypma, B., & D'Esposito, M. (1999). The roles of prefrontal brain regions in components of working memory: Effects of memory load and individual differences. *Proceedings of the National Academy of Sciences, USA*, *96*, 6448–6563.

Rypma, B., & D'Esposito, M. (2000). Isolating the neural mechanisms of age-related changes in human working memory. *Nature Neuroscience*, *3*, 509–515.

Rypma, B., & Gabrieli, J. D. E. (2001). Functional neuroimaging of short-term memory: The neural mechanisms of mental storage. *Behavioral & Brain Sciences*, *24*, 143.

Rypma, B., Prabhakaran, V., Desmond, J. E., Glover, G. H., & Gabrieli, J. D. (1999). Load dependent roles of frontal brain regions in the maintenance of working memory. *NeuroImage*, *9*, 216–226.

Salthouse, T. A. (1996). The processing-speed theory of adult age differences in cognition. *Psychological Review*, *103*, 403–428.

Sarter, M., Gehring, W. J., & Kozak, R. (2006). More attention must be paid: The neurobiology of attentional effort. *Brain Research Reviews*, *51*, 145–160.

Selden, N. R., Gitelman, D. R., Salamon-Murayama, N., Parrish, T. B., & Mesulam, M.-M. (1998). Trajectories of cholinergic pathways within the cerebral hemispheres of the human brain. *Brain*, *121*, 2249–2257.

Sternberg, S. (1966). High-speed scanning in human memory. *Science*, *153*, 652–654.

Talairach, J., & Tournaux, P. (1988). *Co-planar stereotaxic atlas of the human brain*. New York, NY: Thieme.

Terry, A. V., Jr., & Buccafusco, J. J. (2003). The cholinergic hypothesis of age and Alzheimer's disease-related cognitive deficits: Recent challenges and their implications for novel drug development. *Journal of Pharmacology and Experimental Therapeutics*, *306*, 821–827.

Tuite, J. J., & Haley, R. W. (2013). Meterological and intelligence evidence of long-distance transit of chemical weapons fallout from bombing early in the 1991 Persian Gulf War. *Neuroepidemiology*, *40*, 160–177.

Voss, B., Thienel, R., Reske, M., Kellermann, T., Sheldrick, A. J., Halfter, S., . . . Kircher, T. T. J. (2012). Cholinergic blockade under working memory demands encountered by increase rehearsal strategies: Evidence from fMRI in healthy subjects. *European Archives of Psychiatry and Clinical Neuroscience*, *262*, 329–339.

Yokoyama, K., Araki, S., Murata, K., Nishikitani, M., Okumura, T., Ishimatsu, S., & Takasu, N. (1998). Chronic neurobehavioral and central and autonomic nervous system effects of Tokyo subway sarin poisoning. *Journal of Physiology–Paris*, *92*, 317–323.