NeuroImage: Clinical 12 (2016) 535–541

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Cognitive Slowing in Gulf War Illness Predicts Executive Network Hyperconnectivity: Study in a Population-Representative Sample

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ARTICLE INFO

Article history:
Received 14 November 2015
Received in revised form 6 June 2016
Accepted 24 August 2016
Available online 26 August 2016

Keywords:
functional magnetic resonance imaging
dorsolateral prefrontal cortex
Gulf War Illness
processing speed
functional connectivity
cognitive efficiency

ABSTRACT

Cognitive slowing is a prevalent symptom observed in Gulf War Illness (GWI). The present study assessed the extent to which functional connectivity between dorsolateral prefrontal cortex (DLPFC) and other task-relevant brain regions was predictive of GWI-related cognitive slowing. GWI patients (n = 54) and healthy veteran controls (n = 29) were assessed on performance of a processing speed task (the Digit Symbol Substitution Task; DSST) while undergoing functional magnetic resonance imaging (fMRI). GWI patients were slower on the DSST relative to controls. Bilateral DLPFC connectivity with task-relevant nodes was altered in GWI patients compared to healthy controls during DSST performance. Moreover, hyperconnectivity in these networks predicted GWI-related increases in reaction time on the DSST, whereas hypoconnectivity did not. These results suggest that GWI-related cognitive slowing reflects reduced efficiency in cortical networks.

1. Introduction

Approximately one-third of the 700,000 troops deployed to the 1991 Persian Gulf War developed chronic physical and psychological symptoms known as Gulf War Illness (GWI). To date, it is the most prevalent health condition affecting Gulf War veterans (Research Advisory Committee on Gulf War Veterans' Illnesses, 2008). GWI is characterized by diverse symptomology, affecting digestive (e.g., abdominal pain, chronic diarrhea), integumentary (e.g., idiopathic skin rashes), respiratory (e.g., chronic cough, dyspnea) and nervous systems (e.g., chronic headaches, cognitive impairment, neuropathic pain). Few studies have assessed the neural correlates of the cognitive symptoms experienced by GWI sufferers (Odegard et al., 2013; Tillman et al., 2010, 2012, 2013). However, recent work suggests that cognitive deficits in GWI might arise from executive dysfunction caused by aberrant functioning of prefrontal neural systems (Hubbard et al., 2014).

Executive processes depend upon dorsolateral prefrontal cortex (DLPFC; e.g., Curtis and D'Esposito, 2003; D'Esposito et al., 1995; Goldman-Rakic et al., 1996; Hubbard et al., 2014, 2016; Rypma, 2006; Rypma et al., 1999, 2002; Rypma and D'Esposito, 1999; Rypma and Prabhakaran, 2009). This area directs sensory and motor information and receives and integrates input from an array of specialized cortical structures (Curtis and D'Esposito, 2003; Goldman-Rakic et al., 1984, 1996; Hubbard et al., 2016; Niki et al., 1972; Petrides and Pandya, 1984, 1999; Rypma et al., 2006; Rypma and Prabhakaran, 2009). Indeed, blood-oxygen-level dependent (BOLD) activity changes in DLPFC are known to accompany executive cognitive deficits in GWI (Hubbard et al., 2014).

Prior research has established that connectivity between DLPFC and parietal regions, as well as other task-relevant regions, is predictive of individual differences in fundamental abilities (Jung and Haier, 2007), including cognitive slowing in healthy (Biswal et al., 2010; Rypma et al., 2006; Rypma and Prabhakaran, 2009) and clinical populations (Hubbard et al., 2016). One study, for instance, found that slower performers showed increased DLPFC connectivity, and that significant variance in performance on the DSST could be explained by the degree of DLPFC connectivity (Rypma et al., 2006). These results suggested that slower performers required greater DLPFC connectivity for executive control and monitoring processes. However, it remains unknown whether functional connectivity changes in DLPFC exist in GWI, and whether such changes might predict cognitive slowing in GWI.

In the present study, we assessed cognitive slowing and functional connectivity in GWI. Specifically, we used functional magnetic resonance imaging (fMRI) to assess the extent to which connectivity with DLPFC was altered during processing speed task performance in GWI relative to healthy-control veterans. We further assessed whether

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http://dx.doi.org/10.1016/j.nicl.2016.08.022

GWI-related changes in DLPFC functional connectivity could predict cognitive slowing in these patients.

2. Materials and Methods

2.1. Participants

Ninety-seven participants were selected by a three-stage sampling procedure from a nationally representative sample of Gulf War-era US military veterans, stratified by age, education, gender and wartime military rank (Haley et al., 2013). Sixty-six veterans (GWI patients) met the standardized factor case definition of the disease (Haley et al., 1997b; Iannacchione et al., 2011), approximately equally representing the three syndrome variants defined by factor analysis: variant 1, impaired cognition; variant 2, confusion-ataxia; and variant 3, central neuropathic pain. All three variants were included to capture the full spectrum of the disorder (Haley et al., 1997; Iannacchione et al., 2011). All of the cases met the more inclusive CDC case definition (Fukuda et al., 1998), all but 2 met the Kansas case definition without comorbidity exclusions, and approximately half met the original Kansas case definition with comorbidities excluded (Steele, 2000). Thirty-one veterans (healthy controls) met none of the three case definitions. Complete task-performance and functional imaging data were available for 54 GWI patients and 29 healthy controls ($N = 83$); their characteristics are given in Table 1. No participants had a diagnosable neurological condition, such as motor neuron disease, cerebrovascular disease, Parkinson's disease, Guillain-Barré syndrome, or traumatic brain injury.

All procedures were approved by institutional review boards from both the University of Texas at Dallas and the University of Texas Southwestern Medical Center. Participants provided informed consent prior to undergoing any procedure. All procedures were monitored by trained, certified MR technicians who screened participants for contraindications to MR imaging. Upon completion, all participants were compensated monetarily for their participation.

Table 1
Characteristics of the participants included in the analysis.

Characteristic	Controls[a] (N = 29)	GWI cases[a] (N = 54)
Age, mean (SD)	50.4 (7.8)	50.0 (8.0)
Sex		
Male	23 (79)	43 (80)
Female	6 (21)	11 (20)
Handedness		
Right	28 (97)	51 (94)
Left	1 (3)	3 (6)
Education survey response, mean (SD)	5.4 (1.6)	5.2 (1.8)
Deployment to Kuwaiti Theater of Operations		
Deployed	15 (52)	55 (100)
Non-deployed	14 (48)	0 (0)
Wartime rank		
Officer	4 (14)	4 (7)
Enlisted	25 (86)	50 (93)
Syndrome variants of the Factor Case Definition		
Variant 1 (cognitive impairment)	--	18 (33)
Variant 2 (confusion/ataxia)	--	22 (40)
Variant 3 (neuropathic pain)	--	15 (27)
Met CDC criteria for multisymptom illness		
Yes	0 (0)	54 (100)
No	29 (100)	0 (0)
Met Kansas criteria for multisymptom illness		
Yes	0 (0)	30 (56)
No	29 (100)	24 (44)
Met Kansas criteria with no co-morbidity exclusions		
Yes	0 (0)	52 (96)
No	29 (100)	2 (4)

[a] GWI patients met the Factor Case Definition of Gulf War illness, and controls did not meet it. Cells contain N (column %) unless otherwise specified in the row heading.

2.2. Behavioral measurement

Participants completed three runs of an fMRI-adapted digit-symbol substitution task (DSST; Rypma et al., 2006). Each run lasted approximately 5 minutes and consisted of 75 trials. For each trial, a key containing 9 digit–symbol pairs was displayed in the upper half of the viewing screen. In the lower half, a single digit–symbol probe appeared simultaneously (Fig. 1). Participants were instructed to, as quickly and accurately as possible, press a right-thumb button if the probe-pair matched a pair in the key, and to press a left-thumb button if the probe-pair did not match one in the key. The probe-pair matched a pair in the key 50% of the time. Digit-symbol pairings in the key changed from trial to trial. Accuracy was calculated as the proportion of correct responses. Reaction time (RT) was calculated as the average time in ms it took a participant to respond correctly to a trial and was used to assess cognitive slowing.

2.3. Image acquisition and preprocessing

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 et al., 1992) scans were acquired using the following parameters: T1-weighted type, 1 × 1 × 1 mm³ voxel, 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 DSST were acquired using the following parameters: BOLD, gradient-echo signal, 2.97 × 2.97 × 3.5 mm³ voxel, 44 slices/volume, 159 volumes/run, transverse plane, 20 ms echo time, 2000 ms repetition time, 90° flip angle, 64 × 64 matrix, foot-to-head acquisition, 318 s per scan.

Analysis of Functional Neuroimages (AFNI; Cox, 1996) was used to process functional neuroimaging data. Data were de-spiked using AFNI's *3dDespike* program that applies a scaling factor to values larger than 2.5 standard deviations above the mean (spikes) such that they then fall between 2.5 and 4 standard deviations above the mean. This scaling was done to reduce undue effects of outlier signal measurements (Jo et al., 2013). Head motion was corrected by registering functional volumes to the first volume of the first run of the functional task using a six-parameter rigid-body transformation. The MPRAGE volume was aligned to the functional data. The MPRAGE was then transformed to Colin space (Holmes et al., 1998; Van Essen, 2002), where the transformation matrix was applied to warp the functional data into Colin space. Functional volumes within grey matter were then smoothed using a Gaussian kernel (full width at half maximum; FWHM = 3 mm). Signal contributions from white matter and participant motion were labeled as nuisance covariates and removed from further processing using regression analysis (Jo et al., 2013). A high-pass filter (0.015625 Hz) was applied to the data and linear and quadratic trends were removed. Volumes for each participant were visually inspected to ensure pre-processing programs operated as intended. Anatomical

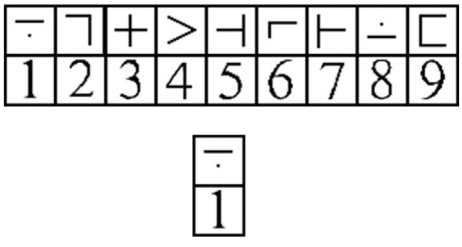

Fig. 1. A sample stimulus array from a single trial of the DSST.

ROI masks were algorithmically delineated via AFNI's Talairach daemon (Cox, 1996) for each participant using Brodmann Area (BA) definitions for grey matter in left and right superior DLPFC corresponding to BA 9 (see Hutchison et al., 2014).

2.4. Image Analyses

2.4.1. DLPFC ΔBOLD

Previous research has shown attenuated BOLD activity in DLPFC for GWI patients compared to healthy controls (Hubbard et al., 2014). The magnitude of linear dependence, as assessed using Pearson correlations, is contingent upon variability (e.g., Alexander et al., 1984). Thus, when comparing two groups on measures of linear dependence, increases in BOLD time-series variability for one group compared to another could bias group differences in connectivity (Hubbard et al., 2016). Thus, prior to assessing group differences in connectivity within DLPFC, we ensured that GWI patients and healthy controls did not significantly differ in DLPFC variability. We thus computed ΔBOLD, that is, the standardized fluctuation of BOLD signal from the mean, within left and right DLPFC for GWI patients compared to healthy controls.

2.4.2. DLPFC connectivity

Using left and right BA 9 as seed regions, we performed voxelwise Pearson product-moment correlations between average BOLD signal time-series data in the seed regions and data in all other grey matter voxels. These correlations indicated how similarly time-series data in the seed region and in any other voxel in the brain varied together through time. Voxels with higher correlation coefficients are considered to be more connected than those with lower coefficients (Biswal et al., 1995, 2010; Friston, 2011; Hubbard et al., 2016). To normalize data distributions, a Fisher z-transformation (Fisher, 1915) was applied to each Pearson correlation, yielding a z-connectivity score with left and right DLPFC, per voxel. Between-group connectivity differences were assessed using independent samples *t*-tests. Cluster-extent-based thresholding was used to correct for familywise error rate (FWER < .05). The AFNI program *3dClustSim* estimated the probability of finding a noise-only cluster featuring faces-touching, contiguous voxels (k), on our specified grid space, with a smoothing kernel of 3 mm, and a p-value of .05 for each voxel within a cluster. At $k \geq 17$, the probability of a noise-only cluster was $p < .05$.

2.4.3. Definition of DLPFC hyper- and hypoconnectivity

We hypothesized that GWI-related hyperconnectivity with DLPFC was related to group differences in cognitive slowing. To test this hypothesis, from each participant we extracted the average connectivity z-score from all voxels in regions where GWI patients were significantly more connected with left and right DLPFC than healthy controls. We also extracted the average connectivity z-score in regions where GWI patients were significantly less connected with left and right DLPFC than healthy controls. This approach yielded two summary z-scores for each participant. One z-score represented the average connectivity with left and right DLPFC in regions where GWI patients showed significantly increased connectivity compared to healthy controls (i.e., the hyperconnectivity coefficient). The other z-score represented the average connectivity with left and right DLPFC in regions where GWI patients showed significantly reduced connectivity compared to healthy controls (i.e., the hypoconnectivity coefficient). We then assessed whether hyper- and hypoconnectivity coefficients could predict DSST RT.

2.5. Statistical Analysis

All within-group distributions were examined for outliers. Any observation greater than two standard deviations above or below the mean was removed from that distribution, as reflected by the degrees of freedom in any statistical analysis we performed. Additionally, we used multivariate ordinary least squares regression models in accordance with Baron and Kenny's protocol (Baron and Kenny, 1986). Briefly, this method has four criteria for identifying an intervening variable (Fig. 2). First, the effect of X on Y (i.e., the direct effect) must be significant (path α in Fig. 2). Second, the effect of X on M must be significant (path β in Fig. 2). Third, the effect of M on Y (path τ in Fig. 2) controlling for X must be significant (path α' in Fig. 2). Fourth, the effect of X on Y controlling for M must be non-significant or less than the effect of path α.

3. Results

3.1. DSST Performance

GWI patients and healthy controls did not significantly differ in DSST accuracy ($M_{GWI} = 95.73\,\%$ [$SEM = 0.41\,\%$] vs. $M_{healthy} = 97.03\,\%$ [.56 %]; $t[79] = -1.87$, $p = .066$). Because accuracy on the DSST was high (>95%) and did not differ between groups, all trials were used in neuroimaging analyses. GWI patients ($M_{GWI} = 2223.60$ ms [44.11]) were significantly slower to respond in the DSST compared to healthy controls ($M_{healthy} = 1981.39$ ms [61.26]; $t[80] = 3.21$, $p = .002$).

3.2. DLPFC ΔBOLD

GWI patients ($M_{GWI} = 2.51$ [.06]) did not significantly differ from healthy controls ($M_{healthy} = 2.53$ [.08]) in left DLPFC ΔBOLD ($t[77] = -.186$, $p = .853$). Similarly, no significant group differences were found between GWI patients ($M_{GWI} = 2.48$ [.05]) and healthy controls ($M_{healthy} = 2.47$ [.07]) in right DLPFC ΔBOLD ($t[78] = .115$, $p = .909$). Fig. 3 depicts maps of BOLD signal during task across the entire brain for patients and controls.

3.3. DLPFC connectivity

Results of the connectivity analysis showed that GWI patients had both hyper- and hypoconnectivity with left and right DLPFC during DSST performance compared to healthy controls (Table 2; Fig. 4).

3.4. Relationship between DLPFC connectivity and DSST RT

DLPFC hyperconnectivity coefficients significantly predicted DSST RT ($\beta = 2143.02$, $r = .296$, $t[77] = 2.72$, $p = .008$). DLPFC hypoconnectivity coefficients did not significantly predict DSST RT ($\beta = -1022.02$, $r = -.155$, $t[78] = -1.39$, $p = .169$). Finding that (1)

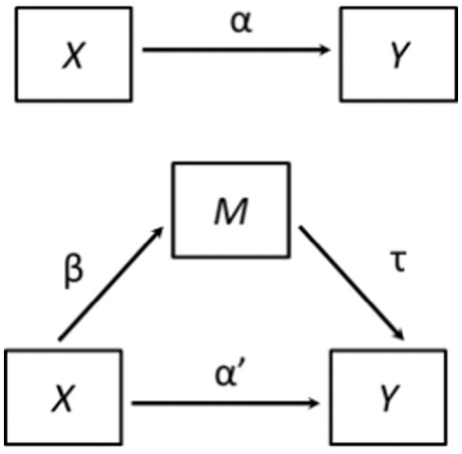

Fig. 2. Baron & Kenny's protocol to identify an intervening variable. X is the independent variable, Y is the dependent variable, M is the intervening variable, α is the effect of X on Y, β is the effect of X on M, τ is the effect of M on Y, and α' is the effect of X on Y controlling for M.

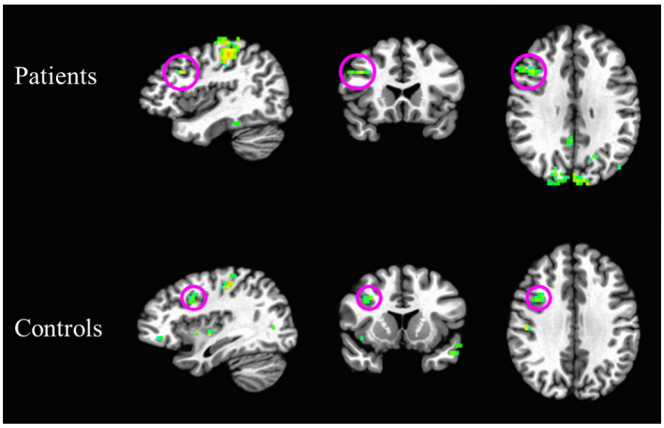

Fig. 3. Group-average activation maps depicting BOLD signal during task (as measured across all trials) for patients (above) and controls (below). Maps depict the top 10% of voxels for the whole brain, with a cluster threshold of k = 10. Circled in magenta are clusters located in DLPFC.

Table 2
Anatomical regions showing hyper- or hypoconnectivity with left or right BA 9.

Anatomical Region (BA)	*x*	*y*	*z*	Voxel count	*t*-value
Left BA 9					
Right Declive	- 24	- 69	- 20	77	-3.101
Right Medial Frontal Gyrus (10)	- 03	- 45	- 09	52	3.692
Right Culmen	- 21	+ 48	- 20	47	-3.716
Right Cerebellar Tonsil	- 15	+ 51	- 41	39	-3.150
Right Tuber	- 30	+ 77	- 27	35	-3.853
Right Cerebellar Tonsil	- 45	+ 51	- 34	34	-2.841
Left Insula (13)	+ 39	+ 30	+ 19	32	3.327
Left Parahippocampal Gyrus (27)	+ 15	+ 33	- 02	32	-4.505
Left Inferior Parietal Lobule (40)	+ 57	+ 42	+ 29	31	3.300
Right Culmen	- 09	+ 48	- 16	31	-3.474
Left Tuber	+ 36	+ 80	- 30	29	-3.471
Right Inferior Semi-Lunar Lobule	- 33	+ 66	- 37	27	-3.291
Right Inferior Frontal Gyrus (47)	- 30	- 30	- 06	23	3.125
Left Superior Temporal Gyrus (38)	+ 36	+ 06	- 16	19	4.190
Right Fusiform Gyrus (37)	- 45	+ 45	- 13	18	-4.273
Right Middle Temporal Gyrus (21)	- 57	+ 06	- 06	17	2.755
Left Insula (47)	+ 33	- 12	+ 01	17	3.595
Right BA 9					
Left Parahippocampal Gyrus (30)	+ 15	+ 36	- 02	384	-4.621
Right Cerebellar Tonsil	- 09	+ 39	- 44	224	-3.748
Left Pyramis	+ 09	+ 80	- 27	221	-4.230
Right Superior Temporal Gyrus (42)	- 65	+ 18	+ 08	53	4.003
Right Tuber	- 30	+ 77	- 27	44	-3.152
Right Middle Frontal Gyrus (9)	- 42	- 30	+ 33	39	3.965
Left Fusiform Gyrus (37)	+ 36	+ 63	- 09	36	-3.426
Right Postcentral Gyrus (3)	- 51	+ 15	+ 40	34	3.037
Right Superior Temporal Gyrus (22)	- 57	- 12	- 06	30	3.713
Left Inferior Semi-Lunar Lobule	+ 21	+ 63	- 44	30	-3.174
Right Inferior Frontal Gyrus (13)	- 36	- 21	+ 08	28	3.484
Left Medial Frontal Gyrus (10)	+ 00	- 50	- 09	26	3.645
Right Middle Frontal Gyrus (6)	- 30	- 06	+ 54	23	2.626
Left Inferior Frontal Gyrus (13)	+ 33	- 09	- 16	22	3.590
Right Middle Frontal Gyrus (45)	- 45	- 24	+ 22	22	3.124
Left Precentral Gyrus (3)	+ 27	+ 21	+ 50	22	3.125
Left Cerebellar Tonsil	+ 12	+ 51	- 37	22	-3.753
Right Fusiform Gyrus (37)	- 48	+ 45	- 13	21	-3.629
Left Middle Temporal Gyrus (39)	+ 48	+ 51	+ 05	21	-2.866
Right Middle Frontal Gyrus (46)	- 54	- 30	+ 19	19	2.669
Left Middle Temporal Gyrus (37)	+ 48	+ 57	- 09	19	-3.537
Left Declive (19)	+ 21	+ 60	- 13	18	-2.685
Right Inferior Parietal Lobule (40)	- 45	+ 36	+ 50	17	3.208

x, *y* and *z* are the Talaraich coordinates of the peak voxel in each cluster. T-values are independent-samples *t*-score of the peak voxel of each cluster. Significance was assessed at $p = .01$, $k \geq 6$, familywise error rate < .05. Positive t-values indicate hyperconnectivity, and negative t-values indicate hypoconnectivity.
Anatomical regions are the Brodmann areas nearest the peak voxel (with 5 mm).

GWI patients had significantly longer RT than healthy controls, (2) GWI patients had significantly greater DLPFC hyperconnectivity than controls, and (3) the DLPFC hyperconnectivity coefficient significantly predicted DSST RT, we sought to test whether the relationship between the DLPFC hyperconnectivity coefficient and group differences in DSST RT suggested the presence of an intervening variable between the group variable and DSST RT (e.g., Baron and Kenny, 1986). To test this, we utilized multiple regression predicting DSST RT from patients' group status and the hyperconnectivity coefficient. The overall model was significant ($F[2, 76] = 5.73$, $p = .005$, R^2 adj = .13). Examination of the individual factors showed that when controlling for DLPFC hyperconnectivity, patients' group status was no longer a significant predictor of DSST RT ($\beta = -95.08$, $t[76] = -1.94$, $p = .056$).

3.5. Parietal Connectivity and DSST RT

The finding that DLPFC hyperconnectivity was a significant intervening variable in the group-performance relationship suggests a central role for DLPFC in GWI-related cognitive slowing. Because activation-performance relationships have been observed in parietal cortex in previous work (e.g., Rypma et al., 2006; Rypma and Prabhakaran, 2009), we performed similar analyses using left and right BA 7 (corresponding to superior parietal lobule and precuneus) as seed regions to assess the specificity of the DLPFC results. We performed the same steps as above for DLPFC (cluster thresholding was identical to DLPFC). The only difference between our parietal cortex connectivity analyses and those we performed for DLPFC was that in the parietal analyses, we excluded voxels within DLPFC because DLPFC-parietal connectivity had already been determined in the DLPFC seed analysis.

Consistent with DLPFC analyses, GWI patients had both hyper- and hypoconnectivity with left and right BA 7 during DSST performance compared to healthy controls (Fig. 4; see also Supplementary Material). Inconsistent with DLPFC analyses, neither BA 7 hyperconnectivity coefficients ($\beta = 272.43$, $r = .03$, $t[78] = .27$, $p = .786$), nor hypoconnectivity coefficients ($\beta = 267.75$, $r = .04$, $t[79] = .38$, $p = .707$), significantly predicted DSST RT. Due to the absence of this relationship, there was no need to test whether parietal connectivity was an intervening variable in the relationship between group and DSST RT (Baron and Kenny, 1986).

4. Discussion

In this study, we compared processing speed and functional connectivity during DSST performance for GWI patients and healthy veteran controls. We assessed whether GWI-related changes in DLPFC functional connectivity were related to GWI patients' reductions in processing speed compared to controls. There were three principle results. First, RT of GWI patients during DSST performance was slower than that of controls, while accuracy did not differ between groups. Second, GWI patients showed both hyper- and hypoconnectivity between DLPFC and other regions throughout the brain compared to controls. Third, hyperconnectivity with DLPFC in these other regions predicted group differences in DSST RT. Hypoconnectivity was not predictive of these RT group differences. No such results were observed for connectivity with parietal cortex. Our results suggest that cognitive slowing in GWI results from inefficient connectivity within executive networks.

One possible explanation for these findings is a pathologically altered central cholinergic system. Epidemiologic studies have linked GWI to environmental exposure to chemicals that inhibit acetylcholinesterase (AChE), including organophosphate pesticides, pyridostigmine bromide, and sarin nerve gas (Chao et al., 2010, 2014; Golomb, 2008; Haley and Kurt, 1997; Haley et al., 2009, 2013; Haley and Tuite, 2013; Heaton et al., 2007; Henderson et al., 2002; Li et al., 2011; Tuite and Haley, 2013). AChE is an enzyme necessary for degradation of the neurotransmitter acetylcholine. When AChE is inactivated, the resulting buildup of excess acetylcholine causes sustained excess stimulation,

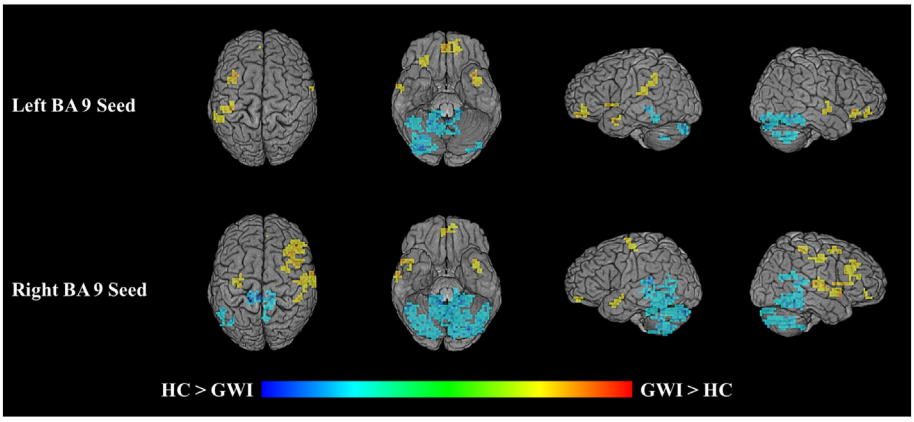

Fig. 4. Differences in connectivity on between veterans with Gulf War illness (N = 54) and matched controls (N = 29) on the DSST while undergoing fMRI. Results of seed-based connectivity analyses, using left and right BA 9 as seed regions. Voxels depict group differences in connectivity with the seed region in GWI patients relative to controls during DSST performance. Voxels appearing yellow and orange indicate hyperconnectivity; voxels appearing cyan and blue indicate hypoconnectivity.

preventing neurons from returning to resting equilibrium and leading to excitotoxic damage. Other populations with documented poisoning by sarin nerve gas (Yokoyama et al., 1998) or organophosphate pesticides (Ecobichon, 1994) have chronic symptoms and neuropsychological abnormalities similar to those reported in GWI.

Executive cognitive function depends on the central cholinergic system, which modulates both processing speed and functional connectivity (Baddeley et al., 1986, 1991; Bartus, 2000; Hasselmo and Sarter, 2011; Ragozzino et al., 2012; Ricciardi et al., 2013; Rusted, 1988; Rusted and Warburton, 1988; see Hubbard et al., 2014). Further, it is known that alterations to the cholinergic system can lead to changes in both functional connectivity and cognitive functioning (Ricciardi et al., 2013). Ricciardi et al. (2013), for instance, assessed the effects of acute cholinergic augmentation on behavioral performance and functional connectivity. Participants performed a selective attention task during fMRI scanning immediately following administration of intravenous physostigmine (an acetylcholine enhancer) or saline placebo. Results showed that participants who received physostigmine were faster (i.e., showed decreased RT) than those who received a placebo, and showed reduced connectivity in prefrontal regions during the task relative to the placebo group. These results suggest that enhancement of the cholinergic system increases the efficiency of cognitive and neural processes. Recent studies have identified increased functional connectivity in early-moderate Alzheimer's disease (Jiang et al., 2016; Kurth et al., 2015; Serra et al., 2016; Sui et al., 2015), also characterized by central cholinergic function loss (Mufson et al., 2008) and slowed DSST RT (Lafont et al., 2010; Rapp and Reischies, 2005). Similarly, GWI patients are known to have abnormal cholinergic function (Haley et al., 2009, 2013; Li et al., 2011) that could affect those DLPFC functions that control executive processes necessary for problem solving, reasoning, planning, and working memory (e.g., Braver, 2012; Chao et al., 2014; Fuster, 1995; Hubbard et al., 2014, 2016; Prabhakaran et al., 2001; 2011; Rypma and Prabhakaran, 2009; Shokri-Kojori et al., 2012).

An important question concerns the role that hyperconnectivity plays in GWI-related cognitive slowing. Under the assumption that damage to the central cholinergic system reduces neural signaling strength, possibly due to reduced ACh release at synapses (Golomb, 1999, 2008) or mitochondrial-related energetic impairments (Koslik et al., 2014; Kannurpatti et al., 2015; White et al., 2016), additional neural cell assemblies might be recruited to maintain function. In the present results, these additional neural cell assemblies might be manifested as hyperconnectivity with DLPFC. Such added circuitry would be expected to slow RT (e.g., Rypma et al., 2006; Rypma and Prabhakaran, 2009) as we observed here.

An alternative explanation might follow compensation-based models wherein recruitment of additional cognitive resources serves to minimize age- and disease-related performance deficits (Cabeza, 2002; Park and Reuter-Lorenz, 2009; Reuter-Lorenz and Cappell, 2008). Such compensation mechanisms are hypothesized to optimize performance through broader recruitment of available neural and cognitive resources. However, compensation-based models would have predicted greater connectivity associated with faster DSST performance, which we did not observe. Additional research is needed to understand relationships between BOLD signal, functional connectivity, and performance, particularly if they are to inform development of GWI treatment strategies.

Efficiency explanations conceptualize brain and behavior changes in terms of departures from ideal system function. Models of cognitive efficiency (e.g., Cerella, 1991; Hutchison et al., 2013a,b; Neubauer and Fink, 2009; Salthouse, 1996; Verhaeghen et al., 2002; Vernon, 1983) have suggested that optimal performance results from simultaneously maximizing the speed of cognitive processes and minimizing expenditure of cognitive resources. In this view, cognitive performance depends upon information transmission across a network of processing nodes wherein information relay across fewer nodes allows more direct processing paths and thus faster information processing. Inefficiency results from increases in the number of connections required to traverse nodes and leads to increases in neural activity and slowing of information processing (cf. Hebb, 1949; McClelland et al., 1986; Rypma and D'Esposito, 1999).

5. Conclusion

This study was the first to assess functional connectivity and processing speed in GWI patients. The slowing of reaction time and hyperconnectivity with DLPFC we observed in GWI patients suggest that their cognitive slowing is due to reductions in neural efficiency. Because DLPFC is central to executive cognitive functions, cognitive impairment experienced by GWI sufferers may be due to alterations to DLPFC connectivity evoked by ACh deficits. These findings thus support the conclusion that one of the most troublesome symptoms of GWI, cognitive slowing, is due to abnormal DLPFC functioning. That the study was performed in a sample of cases and controls drawn from a representative sample of Gulf War-era veterans strengthens the importance of this finding to the broader Gulf War veteran population. More generally, this finding establishes that GWI-related cognitive slowing is due to a pathological process, representing objective brain impairment.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.nicl.2016.08.022.

Authors' contributions

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Conflicts of Interest

Authors report no conflicts of interest.

Acknowledgements and Funding

This research was supported in part by IDIQ contract VA549-P-0027 (to R. W. Haley), awarded by the Department of Veterans Affairs Medical Center, Dallas, TX; the National Institutes of Health (Grant 1R01AG029523 to B. Rypma), and the Friends of Brain Health (to N. A. Hubbard); U.S. Army Medical Research and Materiel Command grant number DAMD17-01-1-0741 (to R. W. Haley); and Grant Number UL1RR024982-05, titled North and Central Texas Clinical and Translational Science Initiative, from the National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH) and NIH Roadmap for Medical Research. 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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