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

Monroe P. Turner[a], Nicholas A. Hubbard[a], Lyndahl M. Himes[a], Shawheen Faghihahmadabadi[a], Joanna L. Hutchison[a,b], Ilana J. Bennett[c], Michael A. Motes[a], Robert W. Haley[d], Bart Rypma[a,b,*]

[a]School of Behavioral and Brain Sciences, University of Texas at Dallas, Richardson, TX, USA
[b]Department of Psychiatry, University of Texas Southwestern Medical Center, Dallas, TX, USA
[c]Center for the Neurobiology of Learning and Memory, University of California-Irvine, Irvine, CA, USA
[d]Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, TX, USA

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

* Corresponding author at: School of Behavioral and Brain Sciences, Center for Brain Health, University of Texas at Dallas, 800 West Campbell Road, Richardson, TX 75080, USA.
E-mail address: bart.rypma@utdallas.edu (B. Rypma).

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

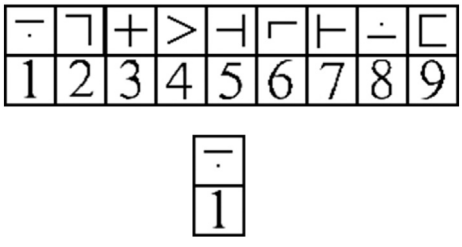

Fig. 1. A sample stimulus array from a single trial of the DSST.