



Contents lists available at ScienceDirect

Brain, Behavior, & Immunity - Health

journal homepage: www.editorialmanager.com/bbih/default.aspx

Short Communication

Association of the tissue microstructural diffusivity and translocator protein PET in Gulf War Illness

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ARTICLE INFO

Keywords:

REM sleep Behavior disorder
Apolipoprotein E4
Cognitive impairment
Synucleinopathy

ABSTRACT

About a third of all United States veterans who served in the 1991 Gulf War (GW) report a range of chronic health symptoms including fatigue, neurocognitive symptoms, and musculoskeletal pain. There is growing evidence supporting the detrimental effects of maladaptive neuroimmune reactions in this multi-symptom illness. Indeed, recent studies using positron emission tomography (PET) using the radioligand [¹¹C]PBR28, which binds the neuroinflammation marker 18 kDa translocator protein (TSPO), and diffusion magnetic resonance imaging (dMRI) have independently identified the anterior cingulate (ACC) and midcingulate cortices (MCC) as key regions for differentiating GWI veterans from healthy controls (HC). Here, we used integrated (i.e., simultaneous) PET/MRI imaging techniques, paired with dMRI processing methods (neurite density imaging, NDI, and free-water diffusion tensor model to single-shell high-order dMRI), to directly evaluate the relationship between ACC and MCC microstructural tissue parameters, TSPO signal and clinical parameters in the same cohorts of 10 GWI veterans and 19 HCs.

Within the regions evaluated, TSPO signal elevations were associated with restricted diffusivity in the extracellular compartment, while clinical measures were best explained by neurite density and cellular structure complexity measures. Our study is the first to provide evidence of a relationship between PET and dMRI modalities in GWI and suggests that microstructural changes in the ACC and MCC are correlated to mood symptoms and cognitive performances in GWI veterans.

1. Introduction

Approximately one third of the 700,000 U.S. veterans who served in the 1991 Gulf War (GW) experience an array of chronic health symptoms, characterized by fatigue and sleep problems, pain, neurological, cognitive, and mood symptoms, respiratory complaints, gastrointestinal problems, and skin symptoms, collectively termed Gulf War Illness (GWI) (White et al., 2016). Effects of organophosphate (OP) neurotoxicant exposures, such as pesticides, and sarin/cyclosarin nerve agents that were present in the GW theater, possibly coupled with heightened innate immune responses, may give rise to chronic symptom complaints experienced by GWI veterans (Chao et al., 2011; Steele et al., 2012; Sullivan et al., 2018). Findings from animal studies suggest that the exposure to neurotoxicants, stress, and combat-related injuries to the central nervous system (CNS) may induce long-lasting neuroinflammatory responses in

GWI, characterized by dysregulated glial cell activation (Lacagnina et al., 2021; Macht et al., 2019; O'Callaghan et al., 2015). While evidence for neuroinflammation in GWI has until recently been mostly limited to the preclinical literature, in a recent positron emission tomography (PET) study with [¹¹C]PBR28, a second-generation radioligand for the 18 kDa translocator protein (TSPO), our group observed widespread cortical elevations in neuroinflammation. Elevated [¹¹C]PBR28 signal was evident in regions including the anterior and midcingulate cortices (ACC and MCC, respectively), in GWI veterans compared to healthy controls or healthy GW veterans (Alshelh et al., 2020). These abnormal neuro-immune responses appear to trigger downstream macro- and microstructural changes in the brain (Koo et al., 2018). Indeed, diffusion magnetic resonance imaging (dMRI) studies found that microstructural alterations (including the ACC) were associated with elevated levels of peripheral proinflammatory cytokines, and with worse fatigue

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Received 19 June 2021; Received in revised form 1 October 2021; Accepted 2 October 2021

Available online 6 October 2021

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symptoms, in GWI veterans (Cheng et al., 2020).

Despite this converging evidence from separate studies, the relationship between PET neuroinflammatory signals and dMRI measures of microstructural alterations in GWI has never been directly explored in the same individuals.

In this study, we used integrated (i.e., simultaneous) [^{11}C]PBR28 PET/MRI to address this aim. Specifically, we sought to assess if changes in microstructural integrity were related to increased neuroinflammatory signaling in the same brain areas and tissue compartments. We applied two dMRI processing models, neurite density imaging (NDI) and free-water diffusion tensor model (FW-DTI) (Pasternak et al., 2014; Zhang et al., 2012) to single-shell high-order dMRI data collected in GWI veterans (and a healthy control group) from a recent GWI PET study (Alshelh et al., 2020). Furthermore, we compared subjective clinical outcomes with multi-compartment diffusion measures to investigate the relationships between objective brain imaging markers and self-reported health symptoms in GWI veterans.

2. Materials and methods

2.1. Participants

Brain imaging outcomes from 10 veterans with GWI (2 females, 49.6 ± 3.1 years old [mean \pm SD]) and 19 healthy controls (HC, 11 females, 44.1 ± 13.04 years old) were obtained from an established GWI biorepository and were included for the analysis. GWI case status was defined by the Kansas GWI case criteria, which requires multiple or moderate-to-severe chronic symptoms reported in at least three out of six symptom domains (fatigue, somatic pain, neurological cognitive, gastrointestinal, respiratory, and skin abnormalities) (Steele, 2000). Clinical outcomes including self-reported scales of pain, mood and cognitive testing of sustained attention including the Short-Form McGill Pain Questionnaire (SF-MPQ2), Patient-Reported Outcomes Measurement Information System (Promis-29), Conner's Continuous Performance Test III (CPT3), and -because GWI shares some of the core symptoms reported by patient suffering from fibromyalgia-the 2011 American College of Rheumatology (ACR) Fibromyalgia Diagnostic Criteria survey were also obtained from the repository for analysis (Cella et al., 2010; Conners et al., 2000; Dworkin et al., 2009; Wolfe et al., 2011).

2.2. Procedures

We processed the single-shell, high-order dMRI data (b -value = 3000 s/mm^2 , 60 gradient directions, TR/TE/voxel size: 119 msec/8000 msec/ $2.5 \times 2.5 \times 3 \text{ mm}$) acquired in the GWI PET study by Alshelh et al. (2020) and shared through the Boston Biorepository and Integrative Network (BBRAIN) for GWI (Keating et al., submitted). Microstructural diffusion indices reporting neurite density (ND), orientation dispersion (OD), and isotropic diffusion (IsoVF) were reconstructed using the NDI model in a similar protocol as described previously (Cheng et al., 2020). FW-DTI derived measures, free-water corrected fractional anisotropy (FW-FA), and free-water corrected mean diffusivity (FW-MD), were extracted using the single shell free-water elimination diffusion tensor model (Pasternak et al., 2014). Reconstructed diffusion maps from NDI and FW-DTI models were then linearly registered to the Montreal Neurological Institute 152 (MNI152) structural template and projected to hemispheric cortical surfaces (Greve et al., 2014). For the PET analysis, standardized uptake value ratio (SUVr) images were generated from data collected over the 60-90 min post-injection [^{11}C]PBR28 PET interval, preprocessed and transformed to MNI152 space, as previously described (Alshelh et al., 2020; Loggia et al., 2015; Zurcher et al., 2015). The two regions of interest (ROI), ACC and MCC, were structures that displayed significantly elevated [^{11}C]PBR28 PET signal and significant microstructural alterations in GWI veterans compared to healthy controls in previous studies (Alshelh et al., 2020;

Cheng et al., 2020). Both ROIs were projected to the standard space cortical surfaces using the same method as the reconstructed dMRI maps. Mean dMRI measures and SUVr values were then extracted from these regions. Clinical variables were also obtained as described by Alshelh et al. (2020).

Partial correlations were performed to assess the relationship between dMRI measures and (1) [^{11}C]PBR28 signal (controlling for sex, age, and TSPO genotype polymorphism, which predicts binding affinity to the PET radioligand) (Owen et al., 2012) and (2) clinical variables (controlling for sex and age). Significant p-values ($p < 0.05$) were reported along with Spearman correlation coefficients (ρ).

3. Results

In the whole group ($N = 29$) analysis, elevated [^{11}C]PBR28 PET signal was significantly correlated with lowered IsoVF and OD in the MCC (IsoVF: $\rho = -0.498$, $p = 0.008$; OD: $\rho = -0.386$, $p = 0.047$) and lowered FW-MD in the ACC ($\rho = -0.382$, $p = 0.049$). The same patterns were also found in MCC IsoVF and ACC FW-MD analysis performed within GWI veterans (Fig. 1). Other multi-compartment diffusion measures did not show significant patterns to [^{11}C]PBR28 PET signals in either ROI.

Table 1 lists the results of partial correlation analyses between clinical variables and multi-compartment diffusion measures in GWI veterans. Positive correlations were evident between (1) CPT3 scores and OD in both ACC (detectability $p = 0.043$, omission errors $p = 0.018$, variability $p = 0.048$) and MCC (detectability $p = 0.032$, omission errors $p = 0.043$, commission errors $p = 0.046$), (2) CPT3 HRT block change test and ND in the ACC ($p = 0.044$), (3) SFMPQ-2 sensory sum and ND in the MCC ($p = 0.027$), and (4) ACR total score and OD in the ACC ($p = 0.016$). Negatively correlations were found between (1) Promis-29 anxiety domain scores and IsoVF in the ACC ($p = 0.042$), (2) CPT3 scores and ND in the MCC (detectability $p = 0.03$, omissions $p = 0.022$), and (3) CPT3 HRT and OD in the MCC ($p = 0.05$).

4. Discussion

Our study revealed significant relationships between the upregulation of the neuroinflammatory marker TSPO, detected by [^{11}C]PBR28 PET signals, and decreased extracellular isotropic diffusivity (IsoVF), reduced cellular complexity (OD), and lowered cellular packing density (FW-MD), in the ACC and MCC of GWI veterans. This study is an extension to our previous analyses, which showed elevated levels of the neuroinflammatory marker TSPO in a widespread set of brain regions in GWI (Alshelh et al., 2020). The neuroinflammatory marker TSPO is normally expressed at low levels but becomes dramatically upregulated -predominantly in activated glial cells-during neuroinflammatory responses (Rupperecht et al., 2010). TSPO signal elevations observed in diseases such as fibromyalgia and GWI (Albrecht et al., 2019; Alshelh et al., 2020) suggest that dysregulated glial activation may contribute to the pathophysiology of GWI, as suggested by the preclinical literature. The present study is the first to report dMRI correlates of GWI neuroinflammation. The negative correlations between OD or IsoVF and [^{11}C]PBR28 PET signal in the MCC suggested hindered isotropic diffusivity, which could arise from local glial activation or immune cell infiltration (Yi et al., 2019; Zhang et al., 2012). In fact, decreased OD and IsoVF was shown to reflect chronic stages of microglia-mediate neuroinflammation, which corroborate findings from previous studies (Alshelh et al., 2020; Yi et al., 2019). We also observed a similar pattern between elevated [^{11}C]PBR28 PET signal and lowered FW-MD in the ACC, which suggested decreased cellular packing density that could be reflecting gliosis or cytoarchitecture disruption (Pasternak et al., 2014). In recent GW studies, biomarkers indicating the presence of neuronal injury and gliosis were detected in GWI veterans 30 years after the war, and in GW rat models, the disruption of oligodendrocyte development and changes in glial morphology were identified as key components in studying the chronic

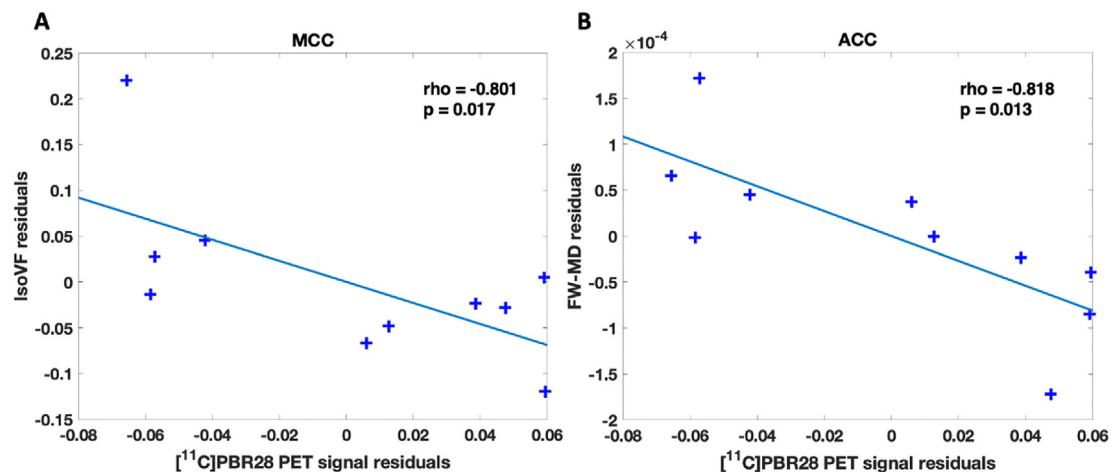


Fig. 1. Multi-compartment diffusion measures correlated with [^{11}C]PBR28 PET signals in the ACC and MCC in GWI veterans. Scatter plots illustrate the negative correlations between the neuroinflammation marker TSPO ([^{11}C]PBR28 PET signal) and (A) the isotropic diffusion measure (IsoVF) in the MCC, or with (B) the free-water corrected mean diffusivity (FW-MD) in the ACC. Results are plotted using TSPO genotype-, sex-, and age-controlled [^{11}C]PBR28 PET signal and age- and sex-controlled diffusion measures. Partial correlation coefficients (ρ) are shown in the plots with p-values. MCC = midcingulate cortex; ACC = anterior cingulate cortex.

Table 1
GWI multi-compartment diffusion measures correlations with clinical variables.

	ACC			MCC	
	ND	IsoVF	OD	ND	OD
Promis29 Raw score:	0.216	-0.724*	-0.416	0.601	-0.674
Anxiety					
SF-MPQ2: Sensory Sum	-0.369	-0.604	-0.111	0.765*	-0.532
Conner's CPT3: Detectability	-0.345	0.593	0.723*	-0.755*	0.751*
Conner's CPT3: Omissions	-0.040	0.647	0.797*	-0.780*	0.722*
Conner's CPT3: Commissions	-0.371	0.525	0.501	-0.656	0.716*
Conner's CPT3: Hit Reaction Time (HRT)	0.272	-0.502	-0.198	0.466	-0.707*
Conner's CPT3: Variability	-0.551	0.423	0.711*	-0.455	0.510
Conner's CPT3: HRT Block Change	0.720*	0.202	-0.327	-0.191	0.174
ACR Total score	-0.146	0.623	0.806*	-0.469	0.354

Partial correlation coefficients are reported, significant ($p < 0.05$) results are bolded. * $p < 0.05$.

neuroinflammatory responses in GWI (Abou-donia et al., 2020; Belgrad et al., 2019). Indeed, our findings on the relationship between [^{11}C]PBR28 signal and dMRI measures confirmed that neuroinflammatory responses may be accompanied by microstructural diffusion alterations in GWI.

Interestingly, while our prior PET analyses didn't reveal statistically significant association with clinical variables, our multi-compartment dMRI measures extracted from the same ACC/MCC regions were correlated with measures of pain, anxiety, and cognitive performance, all symptom domains commonly affected in GWI veterans (Janulewicz et al., 2017; Jeffrey et al., 2019; Sullivan et al., 2018; White et al., 2016). Our results showed that lower IsoVF and OD in the ACC were associated with worse anxiety, while higher ND in the MCC was related to higher pain severity.

GWI veterans often report sensorimotor deficits and memory impairments, often coupled with heightened innate immune responses that give rise to chronic symptom complaints (Chao et al., 2011; Janulewicz et al., 2017; Jeffrey et al., 2019; Sullivan et al., 2018). Furthermore, animal models of GWI show that stress combined with exposure to

chemicals present in the GW theater (pesticides, and sarin/cyclosarin nerve agents) produces GWI symptoms greater than exposure to chemicals alone and causes neuronal cell death in the cingulate cortex (O'Callaghan and Miller, 2019). These changes in the cingulate cortex cause neurobehavioral changes similar to those observed in GWI veterans (Abdullah et al., 2012; Macht et al., 2019). In our study, higher rates of CPT3 detectability, omission and commission errors, and response variabilities were found to correlate with higher OD and lower ND in GWI veterans, whereas slower and varying response rates were associated with lower OD and higher ND. Similar results were reported in other studies, which documented an association between reduced gray and white matter volumes and higher rates of CPT3 omission errors in GW veterans exposed to chemical warfare agents (Chao et al., 2011). Lower ND accompanied with higher OD could reflect decreases in overall volume on the microscopic level and increases in diffusion tortuosity (Colgan et al., 2016), while higher ND has been linked to less efficient information processing capacity (Genç et al., 2018). However, our ability to precisely interpret multi-compartment dMRI measures is limited, particularly as the relationship between microstructural alterations and dMRI measures can vary depending on the etiology of the disease.

In the current study, we demonstrated the presence of changes in microstructural environments of the ACC and MCC, associated neuro-inflammatory signals and behavioral measures, in a small GWI sample. However, the current PET analysis method, using SUVR images from data collected over the 60-90 min post-injection [^{11}C]PBR28 PET interval, was determined from studies on chronic pain and amyotrophic lateral sclerosis, therefore, would require further validation in larger GW veteran cohorts (Loggia et al., 2015; Zurcher et al., 2015). Future studies with a larger GW veteran cohort and post-mortem human studies will be required to shine more light on the neurobiological correlates of neuroinflammation in GWI.

Declaration of competing interest

None.

Acknowledgments

This work is supported in part by DoD-W81XWH1810549 (KS), DoD-W81XWH-17-1-0440 (BBK), DoD-W81XWH2010236 (BBK), DoD-W81XWH-14-1-0543 (MLL), R01-NS094306-01A1 (MLL), and R01-NS095937-01A1 (MLL).

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