Brain and Physiological Markers of Autonomic Function Are Associated With Treatment-Related Improvements in Self-Reported Autonomic Dysfunction in Veterans With Gulf War Illness: An Exploratory Pilot Study

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Abstract

Background: Gulf War Illness (GWI) is a poorly understood condition characterized by a constellation of mood, cognitive, and physical symptoms. A growing body of evidence demonstrates autonomic nervous system (ANS) dysfunction. Few published treatment studies exist for GWI.

Method: We recently completed a randomized controlled trial comparing a 10-week group yoga intervention to 10-week group cognitive behavioral therapy (CBT) for veterans with GWI. Here, we present exploratory data on ANS biomarkers of treatment response from a small pilot exploratory neurophysiological add-on study (n = 13) within that larger study.

Results: Findings suggest that veterans with GWI receiving either yoga or CBT for pain improved following treatment and that changes in biological ANS—especially for the yoga group—moved in the direction of healthy profiles: lower heart rate, higher square root of the mean squared differences between successive R-R intervals (RMSSD), greater parasympathetic activation/dominance (increased high-frequency heart rate variability [HF-HRV], decreased low-frequency/high-frequency [LF/HF] ratio), reduced right amygdala volume, and stronger amygdala-default mode/amygdala-salience network connectivity, both immediately posttreatment and at 6-month follow-up. Biological mechanisms of CBT appeared to underlie improvements in more psychologically loaded symptoms such as self-reported fatigue and energy. Higher tonic arousal and/or more sympathetic dominance (higher skin conductance, lower RMSSD, lower HF-HRV, higher LF/HF ratio) pretreatment predicted greater treatment-related improvements in self-reported ANS for both the yoga and CBT group.

Conclusion: These exploratory pilot data provide preliminary support for the suggestion that treatment (yoga, CBT) is associated with improvements in both biological and self-reported ANS dysfunctions in GWI. The major limitation for these findings is the small sample size. Larger and more controlled studies are needed to replicate these findings and directly compare biomarkers of yoga versus CBT.

Keywords

Gulf War Illness, heart rate variability, amygdala, default mode network, salience network, yoga, cognitive behavioral therapy

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Introduction

Gulf War Illness (GWI) is a poorly understood condition experienced by many veterans who served in the Gulf War in 1990 to 1991.1 GWI is characterized by a constellation of symptoms, including mood disruption, cognitive complaints, chronic pain, chronic fatigue/fibromyalgia, and gastrointestinal problems such as irritable bowel syndrome (IBS).2,3 A growing body of evidence demonstrates autonomic nervous system (ANS) dysfunction in individuals with GWI on both subjective and objective measures. First, veterans with GWI self-report clinically significantly elevated levels of ANS dysfunction.4 Second, diurnal disruptions in cardiac function—specifically high-frequency heart rate variability (HF-HRV)—are consistently observed in individuals with GWI.5,6 Third, structural brain abnormalities are observed in individuals with GWI in regions implicated in ANS regulation such as the amygdala, brain stem, insula, and cingulate cortices.7,8 To date, no published studies have examined resting-state functional connectivity in GWI, though both the default mode network (DMN) and salience network (SN) are implicated in ANS regulation.9

Few published treatment studies exist for GWI, which begs the question whether ANS dysfunction improves with treatment and/or impedes the progress of treatment. In clinical settings, the most common intervention is cognitive behavioral therapy (CBT), the standard (first-line) evidence-based psychological treatment for many of the independent symptoms of GWI, such as mood disturbance,10 chronic pain,11,12 chronic fatigue/fibromyalgia,13 and IBS.14 Outside the GWI field, there is a small but growing body of literature suggesting that CBT may be associated with positive effects on the ANS, including heart rate (HR),15 HRV,16 and amygdala volume,17 though findings are mixed for amygdala-DMN/amygdala-SN connectivity,18–20 and further investigation is warranted for HR/HRV.21

Recently, researchers have begun to explore complementary and integrative interventions for GWI, such as yoga. Yoga is an ancient practice that combines mindfulness meditation with controlled breathing and physical postures.22 Increasingly, research supports the efficacy of yoga for improved psychological well-being, including symptoms associated with GWI such as depression,23 anxiety,24 chronic pain,25,26 cognitive disturbance,27 chronic fatigue/fibromyalgia,28 and IBS.29 Yoga is also associated with improvements in ANS regulation manifesting in a more balanced and less reactive ANS (reduced blood pressure and HR, increased HRV)30,31 as well as increased inhibitory regulation of the amygdala by cortical brain regions (prefrontal cortex, anterior cingulate cortex, and insula).32

We recently completed a randomized controlled trial (RCT) comparing a 10-week group yoga intervention to 10-week group CBT for 74 veterans with GWI33 (ClinicalTrials.gov NCT02378025). Briefly, yoga but not CBT was associated with significant improvement in symptoms of chronic pain and fatigue, both at post-treatment and 6-month follow-up. We received pilot funds to conduct an exploratory add-on ANS biomarker neurophysiological study in a small subsample (n = 13; pretreatment and posttreatment) of veterans who participated in the larger RCT. Due to the putative associations between GWI and ANS function, we examined exploratory biomarkers of treatment-related ANS function. Specifically, we investigated cardiac function (HR, HRV) as an index of parasympathetic activation5,6 and sympathetic/parasympathetic balance34 and skin conductance (SCL) as a measure of tonic (resting) arousal.35 We used a region of interest (ROI) approach to focus on structural amygdala volume and resting-state amygdala-DMN/amygdala-SN connectivity due to the robustness of their associations with ANS function and regulation, particularly in GWI.7–9 Due to the limited sample size, we did not directly compare CBT to yoga but rather examined treatment effects separately by group. In view of the extant literature, we hypothesized (i) treatment-related changes in self-reported ANS symptoms (pretreatment vs posttreatment; pretreatment vs 6-month follow-up) would be associated with treatment-related changes in biological ANS function (pre vs post) and (ii) pretreatment biological ANS function would be associated with treatment-related changes in self-reported ANS symptoms (pretreatment vs post-treatment; pre-treatment vs 6-month follow-up).

Methods

Participants

Participants were veterans of the Gulf War recruited from the San Francisco Bay Area via flyers and advertisements. All participants met Fukuda et al.’s2 criteria for GWI and took part in the larger RCT “Treating Chronic Pain in Gulf War Illness” (see Bayley et al. for more details; ClinicalTrials.gov NCT02378025; N = 74 randomly). Thirteen adults (10 M:3 F; 50.31 years [5.07]; yoga = 6) completed the battery of ANS measures pretreatment, with 11 (yoga = 6) returning for the posttreatment assessment battery (1 participant withdrew from the larger RCT prior to completion, 1 participant declined to return for this add-on pilot study) and 8 (yoga = 5) returning for the 6-month follow-up (self-report assessment battery only; 2 participants were lost to follow-up). The groups did not differ pretreatment in age, sex, race-ethnicity, years of education, marital status (Table 1), or self-reported autonomic dysfunction.
Pretreatment data were not available for 1 participant on the cardiac (equipment failure: device slipped off participant, possibly due to movement), 1 participant on the SCL (equipment failure: device slipped off participant, possibly due to movement), 3 participants on the structural magnetic resonance imaging (MRI) (participant movement), and 7 participants on the functional MRI (fMRI) (participant movement) measures. Posttreatment data were not available for 1 participant on the Composite Autonomic Symptom Score (COMPASS) (did not complete), 6 participants on the SCL (equipment failure/human error), and 4 participants on the fMRI (participant movement) measures.

Procedure

The protocol was approved by the Stanford University Institutional Review Board (IRB-21337). The full procedure for the RCT is described elsewhere.33 Briefly, veterans with GWI (including at least moderate to severe chronic pain and 1 or more symptoms from the fatigue and cognition-mood GWI symptom clusters) were randomized into a 10-week 60-minute manualized group treatment intervention for pain (yoga or CBT). All participants were administered multiple clinician-delivered and self-report measures (including the COMPASS and Profile of Mood States [POMS] described below) at pretreatment, posttreatment, and 6-month follow-up. Participants received an additional $100 for participation in this add-on study.

During the scanning session, participants were oriented to the MRI scanner and prepped for the scan. The MRI battery consisted of structural (T1 and T2), resting-state functional (8 min, during which SCL and HR were measured concurrently), and diffusion tensor imaging protocols. Only the structural and functional MRI results are reported here.

Self-Report Measures

**Composite Autonomic Symptom Score.** The COMPASS 31,36 is a brief 31-item self-report measure designed to provide a global autonomic symptom severity score (total; maximum 100) as well as 6 subdomains of autonomic dysfunction: orthostatic intolerance (dizziness and feeling faint), vasomotor (color changes in the skin, such as red, white, and purple), secretomotor (excess sweat or dryness), gastrointestinal (bloating, abdominal cramps/pain, diarrhea, and constipation), bladder (loss of control and difficulty urinating), and pupillomotor (sensitivity to bright light and difficulty focusing eyes). It is based on the longer, well-established 169-item Autonomic Symptom Profile37 and demonstrates high internal consistency (Cronbach's $\alpha = .62–.92$).36 The internal consistency was also high for this study (Cronbach's $\alpha = .81–.96$).

**Short Form of the POMS.** The Short Form of the POMS (POMS-SF) is a brief, 37-item self-report measure of psychological distress based on the longer, well-established 65-item Profile of Mood States.39 Here, we assessed only the POMS tension (tense, on edge, uneasy, restless, nervous, and anxious), POMS vigor (lively, active, energetic, cheerful, full of pep, and vigorous; reverse-scored), and POMS fatigue (worn out, fatigued, exhausted, weary, and bushed) subscales, due to the high loading of autonomic function-related symptoms. The POMS-SF demonstrates high internal consistency (Cronbach’s $\alpha = .62–.92$).36 The internal consistency was also high for this study (Cronbach’s $\alpha = .76–.95$).
Biological ANS Data Acquisition

Peripheral measures. Resting-state HR and SCL were recorded concurrently during the 8-minute resting state fMRI acquisition. Pulse was recorded via a photopulse sensor (eliciting photoplethysmogram [PPG]) attached to the proximal hallux of the right foot and automatically synched to MRI scanner start and stop times. SCLs were recorded in microSiemens (\(\mu\)S) from BIOPAC EDA100C-MRI Smart Amplifier via 2 Ag-AgCl electrodes (with isotonic NaCl electrode paste) placed on the distal phalanges of digits II and IV of the left hand. Recording was triggered by Mac Terminal synchronized with the MRI scanner trigger, and data were digitized with a LabJack UE9 DAQ device.

Magnetic resonance imaging. MRI data were collected on a 3T GE Discovery™ MR750 scanner (GE Healthcare, Chicago, IL) with a 32-channel head coil at the

Table 2. Self-Reported Symptoms of Autonomic Nervous System Dysfunction.

| Measure                  | Yoga          | CBT           | All Participants |
|--------------------------|---------------|---------------|------------------|
|                         | n/M %/SD      | n/M %/SD      | n/M %/SD         |
| Pretreatment             |               |               |                  |
| COMPASS Total            | 18.90 11.12   | 21.45 15.52   | 20.27 13.18      |
| Orthostatic intolerance  | 5.33 8.64     | 6.29 7.95     | 5.85 7.94        |
| Vasomotor                | 0.00 0.00     | 0.00 0.00     | 0.00 0.00        |
| Secretomotor             | 3.93 4.16     | 6.43 4.29     | 5.27 4.25        |
| Gastrointestinal         | 5.95 4.33     | 5.36 4.64     | 5.63 4.32        |
| Bladder                  | 1.30 2.67     | 1.43 1.24     | 1.37 1.93        |
| Pupillomotor             | 2.39 .83      | 1.95 1.27     | 2.15 1.07        |
| POMS Tension             | 7.17 7.57     | 9.57 7.21     | 8.46 7.17        |
| Vigor\(^a\)              | 6.83 4.62     | 5.29 4.39     | 6.00 4.37        |
| Fatigue                  | 6.83 6.37     | 10.14 6.36    | 8.62 6.33        |
| Posttreatment            | 6 60.00       | 5 40.00       | 11 100.00        |
| COMPASS Total            | 24.21 18.58   | 36.37 13.51   | 29.08 17.09      |
| Orthostatic intolerance  | 12.00 10.73   | 16.00 5.66    | 13.60 8.88       |
| Vasomotor                | 0.28 0.68     | 0.42 0.83     | 0.33 0.70        |
| Secretomotor             | 2.50 2.11     | 5.36 5.67     | 3.64 3.92        |
| Gastrointestinal         | 6.40 5.88     | 9.15 6.24     | 7.50 5.85        |
| Bladder                  | 0.93 0.84     | 2.78 2.13     | 1.67 1.68        |
| Pupillomotor             | 2.11 0.83     | 2.67 0.54     | 2.33 .75         |
| POMS Tension             | 4.33 6.50     | 10.20 6.42    | 7.00 6.86        |
| Vigor\(^a\)              | 5.00 3.69     | 7.00 6.33     | 5.91 4.89        |
| Fatigue                  | 8.67 5.54     | 9.20 6.98     | 8.91 5.91        |
| 6-Month follow-up        |               |               |                  |
| COMPASS Total            | 21.78 21.87   | 23.85 16.96   | 22.56 18.88      |
| Orthostatic intolerance  | 8.80 12.13    | 5.33 9.24     | 7.50 10.57       |
| Vasomotor                | 0.00 0.00     | 0.00 0.00     | 0.00 0.00        |
| Secretomotor             | 3.00 3.59     | 5.00 4.46     | 3.75 3.76        |
| Gastrointestinal         | 6.25 5.89     | 8.93 5.58     | 7.25 5.53        |
| Bladder                  | 1.33 1.45     | 2.59 1.70     | 1.81 1.56        |
| Pupillomotor             | 2.40 .60      | 2.00 .88      | 2.25 .68         |
| POMS Tension             | 9.80 8.04     | 8.33 7.57     | 9.25 7.34        |
| Vigor\(^a\)              | 5.60 1.82     | 2.33 4.04     | 4.58 3.07        |
| Fatigue                  | 8.40 7.27     | 10.00 6.56    | 9.00 6.57        |

Abbreviations: CBT, cognitive behavioral therapy; COMPASS, Composite Autonomic Symptom Score (COMPASS 31); M: mean; n: number; POMS, Short Form of the Profile of Mood States (POMS-SF); SD: standard deviation.

\(^a\)Reverse-scored (higher scores indicate worse functioning).
sympathetic balance. LF/HF ratio was used as an index of sympathetic/parasympathetic measure of tonic (resting) arousal. As outside the range of 0 to 40, mean SCL (mS) HF-HRV power, relative [n.u.] HF-HRV power, and low-frequency/high-frequency [LF/HF] ratio). Mean HR and RMSSD reflect general autonomic function (typically lower and higher values, respectively, indicate healthier function). HF-HRV values were used as indices of parasympathetic activation and LF/HF ratio was used as an index of sympathetic/parasympathetic balance.

Skin conductance. Data were recorded with the amplifier gain set to 5 μS/V, so raw data extracted in Excel were multiplied by 5 to obtain SCL in microSiemens. Data outside the range of 0 to 40 μS were removed following standard practice in the field and as recommended by the equipment manufacturer. Mean SCL (μS) was extracted as a measure of tonic (resting) arousal. As mean SCL may be artificially elevated by spontaneous responses, we also extracted minimum SCL as a confirmatory measure of tonic (resting) arousal.

MRI Data Processing

Structural MRI (amygdala). ROI analyses were conducted using voxel-based morphometry in FMRIB’s Software Library (FSL) v.4.1.8 (http://www.fmrib.ox.ac.uk/uk/fsl/). Preprocessing included removal of nonbrain tissues using Brain Extraction Tool (BET), segmentation into gray matter, white matter, and cerebellar fluid using FMRIB’s Automated Segmentation Tool (FAST4), and normalization to an average template using a linear registration tool (Montreal Neurologic Institute [MNI] 152 standard 2 mm template [voxel size = 2 x 2 x 2 mm]).

fMRI (resting-state connectivity). Analyses were conducted using FSL v.4.1.8 (http://www.fmrib.ox.ac.uk/uk/fsl/). Preprocessing included conversion from Digital Imaging and Communications in Medicine (DICOM) and reorientation to standard space, motion scrubbing using a voxel-specific mean frame wise displacement threshold of 0.5, and removal of nonbrain tissues using BET. Functional data were collected with reversed phase-encode blips. The susceptibility-induced off-resonance field was estimated in FSL from the resultant pairs, producing in a single corrected image. Further preprocessing using FSL’s MELODIC included motion correction (MCFLIRT) with 6 movement parameters (3 translations and 3 rotations), high-pass filter of 100, nonlinear registration between fMRI, T1-weighted anatomical and standard MNI 152 space (2 mm³) images, and spatial smoothing (Gaussian kernel of 5 mm FWHM). No slice-time correction or intensity normalization was performed.

Sphere masks for DMN (xyz = 2, –14, 34; Figure 2(A)) and SN (xyz = –6, 14, 32; Figure 2(B)) were created in MNI standard space based on peak MNI coordinates from a previous study. Amygdala masks were created as per the structural analysis (Figure 1). Functional data were linearly transformed from native into standard space, and intensity normalization was run with a whole brain mode value of 10 000. Functional data at rest were obtained by extracting the mean time series from the amygdala, DMN, and SN ROIs. Spearman’s rho correlations were computed between ROIs (amygdala-DMN and amygdala-SN) for each participant’s pretreatment and posttreatment scan. Fisher z transformations were applied to each pretreatment/posttreatment correlation to obtain an estimate of the strength of functional connectivity.

Analyses

All analyses were conducted in IBM SPSS Statistics 21 with significance threshold set at P < .05. Due to the exploratory nature of the study, we did not control for multiple comparisons and we report trend-level associations where .05 < P < .10 and r or β > .50 (ie, ≥
moderate effect size), to inform future studies with larger sample size. While sample size precluded direct comparison of differences between the treatment interventions (ie, yoga vs CBT), all analyses were conducted separately by treatment group to highlight differential patterns for further investigation in larger studies.

For hypothesis 1 (treatment-related changes in self-reported ANS will be associated with treatment-related changes in biological ANS function), separate exploratory bivariate correlations were conducted between change scores (pretreatment minus posttreatment, pretreatment minus 6-month follow-up) of self-reported ANS (COMPASS and POMS) and change scores (pretreatment minus posttreatment) of biological ANS (mean HR, RMSSD, HF-HRV, LF/HF ratio, mean SCL, minimum SCL, amygdala volume, resting-state amygdala-DMN connectivity, and resting-state amygdala-SN connectivity). All self-reported ANS measures were scored such that higher scores indicate worse functioning; thus, the higher the change score value, the greater the treatment-related improvement in functioning.

For hypothesis 2 (pretreatment biological ANS function will be associated with treatment-related changes in self-reported ANS), separate exploratory regression analyses were conducted with pretreatment biological ANS (mean HR, RMSSD, HF-HRV, LF/HF ratio, mean SCL, minimum SCL, amygdala volume, resting-state amygdala-DMN connectivity, and resting-state amygdala-SN connectivity) as the independent (predictor) variables and pre/posttreatment change scores (pretreatment minus posttreatment) and pre/follow-up change scores (pretreatment minus 6-month follow-up) on self-reported ANS (COMPASS, POMS) as the dependent variables.

Results

Hypothesis 1 (Biological and Self-Reported ANS Treatment-Related Associations): Treatment-Related Changes in Self-Reported ANS Symptoms Will Be Associated With Treatment-Related Changes in Biological ANS Function

Yoga group. Change in general autonomic function from pretreatment to posttreatment was associated with treatment-related change on total COMPASS (global...
autonomic dysfunction severity; pre- to 6-month follow-up [RMSSD]: r = -.86, P = .030), COMPASS secretomotor subscale (excess sweat or dryness; pretreatment to posttreatment [mean HR; trend]: r = -.76, P = .080), COMPASS bladder (loss of control, difficulty urinating; pretreatment to posttreatment [mean HR; trend]: r = .76, P = .080; pre- to 6-month follow-up [mean HR]: r = .93, P = .024; [RMSSD]: r = -.99, P = .001), POMS fatigue (tense, on edge, uneasy, restless, nervous, and anxious; pre- to 6-month follow-up [mean HR]: r = .98, P = .002; [RMSSD; trend]: r = -.86, P = .062), POMS vigor (lively, active, energetic, cheerful, full of pep, and vigorous; pre- to 6-month follow-up [RMSSD]: r = .92, P = .025), and POMS fatigue (worn out, fatigued, exhausted, weary, and bushed; pretreatment to posttreatment [mean HR]: r = .73, P = .098; Table 3).

Change in parasympathetic activation was associated with change on total COMPASS (pretreatment to posttreatment [absolute HF-HRV, ms²; trend]: r = -.75, P = .084; pre- to 6-month follow-up [absolute HF-HRV, ms²]: r = -.92, P = .009), COMPASS orthostatic intolerance (pretreatment to posttreatment [absolute HF-HRV, ms²; trend]: r = -.79, P = .063; pre- to 6-month follow-up [absolute HF-HRV, ms²]: r = -.99, P = .002), COMPASS vasomotor (pretreatment to posttreatment [relative HF-HRV (n.u.); r = -.91, P = .011), COMPASS secretomotor (pretreatment to posttreatment [absolute HF-HRV, ms²; trend]: r = .73, P = .099), COMPASS bladder (pretreatment to 6-month follow-up [relative HF-HRV (n.u.); r = -.88, P = .049), POMS tension (pretreatment to 6-month follow-up [relative HF-HRV (n.u.; trend]: r = -.86, P = .064), and POMS vigor (pre- to 6-month follow-up [absolute HF-HRV, ms²; trend]: r = .88, P = .051).

Change in sympathetic/parasympathetic balance (LF/HF ratio) was associated with change on COMPASS bladder (pretreatment to posttreatment [trend]: r = .77, P = .076; pre- to 6-month follow-up: r = .88, P = .047) and POMS fatigue (pretreatment to posttreatment [trend]: r = -.77, P = .073).

Change in tonic arousal (mean SCL) was associated with change on POMS fatigue (pretreatment to posttreatment [trend]: r = .99, P = .083).

Change in amygdala volume was associated with change on total COMPASS (pretreatment to posttreatment [right]: r = .82, P = .048; pre- to 6-month follow-up [right]: r = .87, P = .023), COMPASS orthostatic intolerance (pretreatment to 6-month follow-up [right]: r = .97, P = .006), COMPASS pupillomotor (sensitivity to bright light, difficulty focusing eyes; pre- to 6-month follow-up [left]: r = .92, P = .028), and POMS vigor (pre- to 6-month follow-up [right; trend]: r = -.87, P = .052).
Change in amygdala-DMN connectivity was associated with change on total COMPASS (pretreatment to posttreatment [right; trend]: \( r = -0.82, \ p = 0.092 \); pret- to 6-month follow-up [right]: \( r = -0.97, \ p = 0.005 \); [left]: \( r = -0.89, \ p = 0.045 \)), COMPASS orthostatic intolerance (pretreatment to posttreatment [mean HR]: \( R^2 = 0.78, \ \beta = 0.88, \ p = 0.047 \)), COMPASS pupillometer (pretreatment to 6-month follow-up [RMSSD; trend]: \( R^2 = 0.67, \ \beta = -0.82, \ p = 0.092 \)), and POMS vigor (pretreatment to 6-month follow-up [RMSSD]: \( R^2 = 0.85, \ \beta = 0.92, \ p = 0.027 \); Table 4).

Pretreatment parasympathetic activation predicted treatment-related change on COMPASS vasomotor (pretreatment to posttreatment [relative HF-HRV (n. u.]): \( R^2 = 0.71, \ \beta = -0.84, \ p = 0.036 \)), COMPASS gastrointestinal (pretreatment to posttreatment [absolute HF-HRV, ms\(^2\); trend]: \( R^2 = 0.64, \ \beta = -0.80, \ p = 0.057 \); pret- to 6-month follow-up [absolute HF-HRV, ms\(^2\): \( R^2 = 0.81, \ \beta = -0.90, \ p = 0.039 \)), and COMPASS pupillometer (pretreatment to 6-month follow-up [absolute HF-HRV, ms\(^2\): \( R^2 = 0.78, \ \beta = -0.88, \ p = 0.049 \); [relative HF-HRV (n.u.): \( R^2 = 0.88, \ \beta = -0.94, \ p = 0.019 \)).

Pretreatment sympathetic-parasympathetic balance (LF/HF ratio) predicted change pre- to 6-month follow-up on COMPASS pupillometer (\( R^2 = 0.82, \ \beta = 0.91, \ p = 0.034 \)).

Pretreatment tonic arousal (minimum SCL) predicted change pre- to 6-month follow-up on COMPASS orthostatic intolerance (trend: \( R^2 = 0.67, \ \beta = 0.82, \ p = 0.089 \)).

Pretreatment amygdala volume predicted treatment-related change on total COMPASS (pretreatment to posttreatment [right]: \( R^2 = 0.66, \ \beta = 0.81, \ p = 0.049 \); pret- to 6-month follow-up [right]: \( R^2 = 0.73, \ \beta = 0.86, \ p = 0.030 \)), COMPASS orthostatic intolerance (pretreatment to 6-month follow-up [right]: \( R^2 = 0.91, \ \beta = 0.95, \ p = 0.013 \)), and COMPASS pupillometer (pretreatment to posttreatment [left]: \( R^2 = 0.90, \ \beta = 0.95, \ p = 0.004 \)).

Pretreatment amygdala-DMN connectivity predicted treatment-related change on total COMPASS (pretreatment to posttreatment [left]: \( R^2 = 0.88, \ \beta = 0.94, \ p = 0.018 \)), COMPASS orthostatic intolerance (pretreatment to posttreatment [left]: \( R^2 = 0.95, \ \beta = 0.93, \ p = 0.025 \)), POMS tension (pretreatment to posttreatment [left]: \( R^2 = 0.95, \ \beta = -0.98, \ p = 0.005 \)), POMS vigor (pretreatment to posttreatment [right; trend]: \( R^2 = 0.68, \ \beta = -0.82, \ p = 0.087 \)), and POMS fatigue (pretreatment to 6-month follow-up [left]: \( R^2 = 0.95, \ \beta = 0.97, \ p = 0.005 \)).

Pretreatment left amygdala-SN connectivity predicted change pre- to 6-month follow-up on total COMPASS (\( R^2 = 0.94, \ \beta = 0.97, \ p = 0.006 \)), COMPASS orthostatic intolerance (\( R^2 = 0.97, \ \beta = 0.99, \ p = 0.002 \)), and POMS vigor (\( R^2 = 0.86, \ \beta = -0.93, \ p = 0.023 \)). There were no other biological ANS predictors of self-reported ANS treatment-related change for the yoga group.

**Hypothesis 2 (Biological ANS Treatment Markers):** Pretreatment Biological ANS Function Will Be Associated With Treatment-Related Changes in Self-Reported ANS Symptoms

**Yoga group.** Pretreatment general autonomic function predicted treatment-related change on total COMPASS (pretreatment to 6-month follow-up: [RMSSD]: \( R^2 = 0.76, \ \beta = -0.87, \ p = 0.024 \)), COMPASS secretomotor (pretreatment to posttreatment [mean HR]: \( R^2 = 0.99, \ \beta = -1.00, \ p < 0.01 \)), COMPASS gastrointestinal (pretreatment to posttreatment [RMSSD]: \( R^2 = 0.75, \ \beta = -0.87, \ p = 0.025 \); pret- to 6-month follow-up [RMSSD]: \( R^2 = 0.89, \ \beta = -0.94, \ p = 0.017 \)), COMPASS bladder (pretreatment to 6-month follow-up [mean HR]: \( R^2 = 0.78, \ \beta = 0.88, \ p = 0.047 \)), COMPASS pupillometer (pretreatment to 6-month follow-up [RMSSD; trend]: \( R^2 = 0.67, \ \beta = -0.82, \ p = 0.092 \)), and POMS vigor (pretreatment to 6-month follow-up [RMSSD]: \( R^2 = 0.85, \ \beta = 0.92, \ p = 0.027 \); Table 4).

Pretreatment parasympathetic activation predicted treatment-related change on COMPASS vasomotor (pretreatment to posttreatment [relative HF-HRV (n. u.]): \( R^2 = 0.71, \ \beta = -0.84, \ p = 0.036 \)), COMPASS gastrointestinal (pretreatment to posttreatment [absolute HF-HRV, ms\(^2\); trend]: \( R^2 = 0.64, \ \beta = -0.80, \ p = 0.057 \); pret- to 6-month follow-up [absolute HF-HRV, ms\(^2\): \( R^2 = 0.81, \ \beta = -0.90, \ p = 0.039 \)), and COMPASS pupillometer (pretreatment to 6-month follow-up [absolute HF-HRV, ms\(^2\): \( R^2 = 0.78, \ \beta = -0.88, \ p = 0.049 \); [relative HF-HRV (n.u.): \( R^2 = 0.88, \ \beta = -0.94, \ p = 0.019 \)).

Pretreatment sympathetic-parasympathetic balance (LF/HF ratio) predicted change pre- to 6-month follow-up on COMPASS pupillometer (\( R^2 = 0.82, \ \beta = 0.91, \ p = 0.034 \)).

Pretreatment tonic arousal (minimum SCL) predicted change pre- to 6-month follow-up on COMPASS orthostatic intolerance (trend: \( R^2 = 0.67, \ \beta = 0.82, \ p = 0.089 \)).

Pretreatment amygdala volume predicted treatment-related change on total COMPASS (pretreatment to posttreatment [right]: \( R^2 = 0.66, \ \beta = 0.81, \ p = 0.049 \); pret- to 6-month follow-up [right]: \( R^2 = 0.73, \ \beta = 0.86, \ p = 0.030 \)), COMPASS orthostatic intolerance (pretreatment to 6-month follow-up [right]: \( R^2 = 0.91, \ \beta = 0.95, \ p = 0.013 \)), and COMPASS pupillometer (pretreatment to posttreatment [left]: \( R^2 = 0.90, \ \beta = 0.95, \ p = 0.004 \)).

Pretreatment amygdala-DMN connectivity predicted treatment-related change on total COMPASS (pretreatment to posttreatment [left]: \( R^2 = 0.88, \ \beta = 0.94, \ p = 0.018 \)), COMPASS orthostatic intolerance (pretreatment to posttreatment [left]: \( R^2 = 0.95, \ \beta = 0.93, \ p = 0.025 \)), POMS tension (pretreatment to posttreatment [left]: \( R^2 = 0.95, \ \beta = -0.98, \ p = 0.005 \)), POMS vigor (pretreatment to posttreatment [right; trend]: \( R^2 = 0.68, \ \beta = -0.82, \ p = 0.087 \)), and POMS fatigue (pretreatment to 6-month follow-up [left]: \( R^2 = 0.95, \ \beta = 0.97, \ p = 0.005 \)).

Pretreatment left amygdala-SN connectivity predicted change pre- to 6-month follow-up on total COMPASS (\( R^2 = 0.94, \ \beta = 0.97, \ p = 0.006 \)), COMPASS orthostatic intolerance (\( R^2 = 0.97, \ \beta = 0.99, \ p = 0.002 \)), and POMS vigor (\( R^2 = 0.86, \ \beta = -0.93, \ p = 0.023 \)). There were no other biological ANS predictors of self-reported ANS treatment-related change for the yoga group.

**CBT group.** Due to missing data, regression analyses were not possible for the CBT group for the cardiac or structural MRI predictors of long-term treatment-related changes (pretreatment to 6-month follow-up) in self-reported ANS symptoms (COMPASS/POMS), nor any of the
Table 4. Summary of Biological ANS Treatment Markers for Self-Reported ANS by Treatment Group (Hypothesis 2).

| Biological ANS | (Pre to Post) | (Pre to 6 months) |
|----------------|---------------|-------------------|
| Yoga           | CBT           | Yoga             |
| Mean HR (12/10) | Mean HR (12/10) | N/A              |
| RMSSD (12/10)  | RMSSD (12/10)  | N/A              |
| LF-HF (12/10)  | LF-HF (12/10)  | N/A              |
| SCL (12/4)     | SCL (12/4)     | N/A              |
| Amygdala (10/10) | Amygdala (10/10) | N/A              |
| Amyg-DMN (6/6) | Amyg-DMN (6/6) | N/A              |
| Amyg-SN (6/6)  | Amyg-SN (6/6)  | N/A              |

| ΔPOMS (β)     | ΔPOMS (β)     | ΔPOMS (β)  |
|---------------|---------------|------------|
| N/A           | N/A           | N/A        |
| N/A           | N/A           | N/A        |
| N/A           | N/A           | N/A        |
| N/A           | N/A           | N/A        |

| ΔCOMPASS (β)  | ΔCOMPASS (β)  | ΔCOMPASS (β) |
|---------------|---------------|--------------|
| N/A           | N/A           | N/A          |
| N/A           | N/A           | N/A          |
| N/A           | N/A           | N/A          |
| N/A           | N/A           | N/A          |

| ΔLF/HF        | ΔLF/HF        | ΔLF/HF  |
|---------------|---------------|---------|
| N/A           | N/A           | N/A     |
| N/A           | N/A           | N/A     |
| N/A           | N/A           | N/A     |

Abbreviations: Amygdala volume; Amygdala-DMN, amygdala-default mode network connectivity; Amygdala-SN, amygdala-salience network connectivity; ANS anxious nervous system; CBT, CBT cognitive behavioral therapy.
left amygdala-SN connectivity. There were, however, some discrepancies for the yoga group in that improvements in self-reported energy (POMS vigor and fatigue) were more strongly associated with treatment-related increases in amygdala volume and arousal (higher average HR, lower RMSSD, lower HR-HRV, and higher LF/HF ratio) and decreases in amygdala-DMN connectivity. Weaker left amygdala-DMN connectivity at pretreatment predicted short-term improvements in self-reported restless and anxiety and higher HRV and weaker left amygdala-SN connectivity at pretreatment predicted long-term improvements in self-reported energy.

For the CBT group, treatment-related improvements in self-reported fatigue were associated with treatment-related increases in parasympathetic activation (HF-HRV), while improvements in self-reported energy were associated with decreased parasympathetic activation (ie, higher arousal). Higher pretreatment tonic arousal (mean/minimum SCL) predicted greater treatment-related improvements in self-reported ANS function both short term and long term. There was also a trend for poorer pretreatment general biological ANS function (lower HRV [RMSSD]) to predict short-term improvements in self-reported energy.

Higher resting HR is associated with poorer physical and mental health. Similarly, lower RMSSD, lower HF-HRV, and higher LF/HF ratio are associated with poorer physical and mental health, independent of aging. The present findings of treatment-related improvements—reductions in average resting HR, increases in HRV and parasympathetic activation/dominance—for the yoga group are consistent with previous yoga and exercise intervention studies. Increases in parasympathetic activation were also observed in the CBT group, which supports a small but growing body of literature suggesting CBT may also be associated with these positive effects on the ANS.

Extant literature are mixed regarding relative amygdala volume size and associations with psychopathology, though one recent study demonstrated reduced amygdala volume in veterans with GWI. The present findings of associations between improved self-reported ANS and treatment-related reductions in amygdala volume in the yoga group are therefore intriguing and difficult to interpret. Treatment-related reductions in amygdala volume have been observed following yoga and meditation, CBT for social anxiety, and mindfulness-based stress reduction, suggesting the current findings are consistent with existing treatment-intervention literature outside the GWI field.

Increased amygdala-DMN/amygdala-SN connectivity in the yoga group was associated with—and predicted—short- and long-term improvements in self-reported ANS function, consistent with past observations during mindfulness practice. Although missing data precluded analyses for the CBT group, previous findings for CBT are mixed, with studies demonstrating either decreased or increased amygdala-DMN/amygdala-SN connectivity, supporting further investigation. The present findings highlight the importance of concurrently exploring both structural and functional brain responses to treatment.

Interestingly, where inconsistencies occurred in the pattern of findings for the yoga group, these were typically for self-reported energy and fatigue on the POMS (vs self-reported symptoms of autonomic dysfunction on the COMPASS). At the same time, where treatment-related associations between biological and self-reported ANS occurred for the CBT group, these were also typically for the POMS rather than COMPASS. While we chose only those subscales with the highest loading of autonomic (dys)function (tension, vigor, and fatigue), the POMS is more accurately a measure of psychological distress. Thus, for CBT, biological mechanisms of treatment action may underlie more psychologically loaded symptom improvements, whereas for yoga, these biomarkers appear to demonstrate different patterns of association for symptoms with—versus without—psychological loading. Due to the small sample and high proportion of missing data, further investigation is needed to confirm this theory.

Data for both the yoga and CBT group suggest that veterans with GWI who have higher tonic arousal and/or more sympathetic dominance—higher SCL, lower RMSSD, lower HF-HRV, and higher LF/HF ratio—may obtain the greatest benefits from treatment. Given that higher SCL is associated with anxiety and lower RMSSD, lower HF-HRV, and higher LF/HF ratio are associated with poorer physical and mental health, one interpretation of these findings is that poorer pre-treatment biological ANS function predicts greater relative treatment response. There is an overall paucity of studies examining pretreatment predictors of response to yoga and extant findings for CBT are mixed: lower symptom severity and more adaptive ANS function pre-treatment may be predictive of either better or worse treatment outcome, highlighting the need for further exploration.

These exploratory pilot data provide preliminary support for the suggestion that treatment (yoga, CBT) is associated with improvements in both biological and self-reported ANS dysfunctions in GWI. The major limitations for these findings are the small sample size and large amount of missing data, which also prevented group analyses directly comparing treatment-related changes in ANS between yoga and CBT. It should also be noted that since the MRI environment is potentially anxiety-inducing, it is possible that some of the treatment-related improvements in biological ANS
measures were driven by habituation to the MRI environment rather than treatment per se.⁶⁷,⁶⁸ Although outside the scope of this study, other studies using a nontreatment (wait-list) or healthy control comparison group have observed stronger amygdala effects for the active treatment condition (CBT) in individuals with emotional disorders,⁶⁹ suggesting that treatment effects occur over and above potential test–retest habituation. Larger and more controlled studies are needed to replicate these findings in individuals with GWI and directly compare biomarkers of yoga versus CBT.

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Authors’ Contributions

DCM was responsible for writing the manuscript with significant contributions from all other authors. PJB is principal investigator and executive manager of this randomized controlled trial (RCT). PJB conceptualized and designed the RCT, and DCM conceptualized and designed this brain and physiological autonomic nervous system measures add-on study. DCM was one of the cognitive behavioral therapy providers and collected the data. DCM, CME, and DDD analyzed the data. DS provided consultation on data analysis and content. All authors read and approved the final manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Notes

a. The rate of fMRI data loss from participant movement is high given our small sample size. Individuals with chronic pain are known to be more susceptible to movement artifact in fMRI than healthy controls. There is a paucity of fMRI studies on veterans with GWI so it remains to be seen whether their pain is qualitatively or quantitatively different from individuals with non-GWI chronic pain; this small pilot study suggests they may be at least more susceptible to fMRI movement artifact.

b. We share the MRI scanner with multiple research teams at Stanford University. One user made unauthorized changes to the Mac Terminal settings that control SCL recordings via synchronization with the MRI scanner trigger resulting in no SCL recordings (ie, data loss) across all saved paradigms. This human error affected multiple projects and teams (including our study) and was not discovered by Stanford Cognitive and Neurobiological Imaging staff until months later.

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