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PTSD and Immunological Correlations Of Attention and Working Memory in Gulf War Illness

Mary Jeffrey
Nova Southeastern University, mgtjeffrey@gmail.com

PTSD AND IMMUNOLOGICAL CORRELATIONS OF ATTENTION AND WORKING MEMORY IN GULF WAR ILLNESS

by

Mary Jeffrey

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Date of the Defense

Approved:

Jeffrey Kibler, Ph.D., Chairperson

Travis Craddock, Ph.D.

Amarilis Acevedo, Ph.D.

Christian DeLucia, Ph.D.

Statement of Original Work

I declare the following:

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Name

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Mary Jeffrey

Nova Southeastern University

ABSTRACT

Gulf War Illness (GWI) impacts 25 to 32 percent of those deployed in the 1991 Gulf War (White et al., 2016) and includes symptoms related to fatigue and mood/neurological disturbances. Therefore, it is difficult to ascertain the influence of trauma exposure and chemical exposure when investigating neuropsychological symptoms. This cross-sectional study utilized a group of veterans with and without GWI (n=61) to investigate: 1) the unique impact that GWI has on a survey measure of attention and memory or the Paced Auditory Serial Addition Test (PASAT). We also investigated how PTSD symptoms, followed by fatigue levels, improved the GWI model when predicting performance. Next, we analyzed the unique impact that GWI diagnosis, followed by pro-inflammatory interleukins, would have on reported levels of fatigue.

Although there was not a statistically significant relationship between GWI and the PASAT scores, there was an emerging trend showing GWI as a meaningful effect. The secondary analyses investigating the influence of interleukins on measures of fatigue also only showed GWI diagnosis as significant predictor. Post-hoc analyses were conducted that included pro-inflammatory (INFγ and TNFα) cytokines in another model of GWI. Therefore, a model with the incremental addition of GWI, proinflammatory markers, and PTSD symptoms was tested for its ability to predict worse performance on the PASAT. Results indicated that pro-inflammatory markers were significant across virtually all trials of the PASAT, over and above GWI and PTSD symptom levels. More investigation investigating the linkage between these processes and cytokines are therefore necessary to elucidate these patterns.

Keywords: gulf war illness, post-traumatic stress disorder, working memory

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Chapter I: Statement of the Problem

Gulf War Illness (GWI), also known as chronic multi-symptom illness (CMI; Fukuda et al., 1998) and Gulf War Syndrome (GWS), impacts 25 to 32 percent of those deployed in the 1991 Gulf War (White et al., 2016). GWI varies in case definition. Symptoms identified by researchers (Fukuda et al., 1998; Haley, Kurt, & Hom, 1997; Steele, 2000) include musculo-skeletal pain (i.e., joint pain, joint stiffness, muscle pain), mood/neurological disturbances (i.e., depression, moodiness, anxiety, sleep disturbances, memory problems, word-finding difficulties, attention/concentration problems, gait/balance disturbances), fatigue, pain, respiratory complaints, and gastrointestinal or skin issues. Researchers have identified risk factors leading to GWI, particularly with exposure to chemical agents (e.g., pesticides, depleted uranium, chemical nerve agents, and pyridostigmine bromide [PB]), as well as exposure to combat-related trauma. However, given the retrospective nature of the research, literature remains inconclusive regarding the case criterion and etiology of GWI.

Despite these limitations, research examining the cognitive profile of GWI is necessary given that cognitive problems remain one of the most prevalent symptoms (Smith et al., 2012; Yee et al., 2016). However, memory problems are endorsed by 71.8 percent of veterans with GWI, the second most reported symptom followed by fatigue (Smith et al., 2012). Overall, neurological, neuropsychological, and physiological research has indicated dysfunction in the central nervous system (Steele, 2000; Yee et al., 2016). However, inconsistent definition of case criteria and measurement have not pinpointed definitive trends in cognitive dysfunction. Additionally, research has not shown a definite trend regarding the cognitive impact of GWI while also considering

other relevant factors especially traumatic experiences such as Post-Traumatic Stress Disorder (PTSD). Trauma exposure is associated with problems with memory, attention, and executive functioning (Koçak & Kiliç, 2017). Also, fatigue is the most common symptom reported by GWI and also is associated with cognitive problems in processing speed (Tierskey, Johnson, Lange, Natelson, & Deluca, 1997). Therefore, this study expanded upon existing literature by investigating how GWI and level of PTSD symptoms uniquely contribute to cognitive problems using a neuropsychological measure of attention and working memory. We also investigated how fatigue contributes to performance on the neuropsychological measure. Additionally, we tested the hypothesis that the presence of immunological factors in GWI veterans would be related to measures of fatigue to investigate the biological contributions to fatigue-related cognitive issues.

Chapter II: Review of the Literature

Gulf War Veterans – Psychogenic Etiology Findings

In this section, studies are reviewed that examined those deployed in the Gulf War and analyzed neuropsychological performance along with psychological distress (Axelrod & Milner, 1997; Proctor et al., 2003; Sillanpaa et al. 1997). These researchers found evidence of psychogenic underpinnings to Gulf War-related symptoms over neurological etiology.

Axelrod and Milner (1997) tested 44 male veterans who served in Operation Desert Storm on a comprehensive neuropsychological exam, self-report questionnaires of cognitive symptoms, and psychological questionnaires (see reference for details). Participants had an average age of 33.3 (SD = 9.2) and 13.5 years of education; the majority of the sample was Caucasian (70%). The veterans were tested against normative data. Deficits were evident in two tasks: Grooved Pegboard (Heaton, Grant, & Matthews, 1992; Matthews & Klove, 1964), and the Stroop Test (Golden, 1978). However, analyses returned data indicative of higher psychological distress (as measured by the Minnesota Multiphasic Personality Inventory-Second Edition [MMPI-2; Graham, 1990]), associated with both measures of cognitive decline. Therefore, Axelrod and Milner (1997) compared veterans with and without subjective cognitive complaints. Although results pertaining to cognitive deficits remained significant (i.e., Grooved Pegboard, Stroop) in veterans reporting cognitive changes, psychological variables were also significant and reported to be the stronger finding. Therefore, this study indicated a psychological underpinning to cognitive decline. Limitations of this study included a small sample size (n =44) with the analysis of multiple variables. Researchers justified not using a Bonferroni correction due

to the exploratory nature of the project and its impact on reducing significant findings for group comparisons (Axelrod & Milner, 1997). Additionally, they reported an effect size greater than 0.65 for all t-test analyses. Another limitation pertains to the sample consisting of volunteers over a random sample.

Sillanpaa et al. (1997) investigated neuropsychological and neurological functioning in 49 Gulf War Veterans (GWVs). The sample had an average age of 33.59 years (SD = 9.07), and an average education level of 13.47 (SD = 1.56). The sample was predominately Caucasian (69%) and male (90%). Each veteran completed a MMPI-2, Symptom Check List-90- Revised (SCL-90-R; Derogatis, 1992), neuropsychological symptom checklist (Schinka, 1983), visual analog scale assessing exposure to toxins, Neurobehavioral Evaluation System- Continuous Performance Test (CPT; Letz, 1991), Grip Strength (Reitan & Davison, 1974), Grooved Pegboard, Neurological Screen (Ross, 1985), Finger-Tip Number Writing Perception (Reitan & Davison, 1974; Yeudall, Reddon, Gill, & Stefanyk, 1987), the Wisconsin Card Sorting Test (WCST; Heaton, 1981, 1993), Rey Auditory Verbal Learning Test (RAVLT: Lezak, 1983), Wechsler Adult Intelligence Scale-Revised (WAIS-R; Wechsler, 1981), and State-Trait Anxiety Inventory (STAI; Spielberger, 1983). Additionally, a clinical signs index was created from indices of liver enzymes (aspartate amino transferase, alanine amino transferase), immune system response (i.e., monocytes), and evidence of infection (i.e., labs and clinical examination). Neurocognitive performance was evaluated in comparison to normative data. Analyses were conducted to reflect two models. The first model was created to reflect variables associated with GWS and included (1) age and education, and (2) exposure results (i.e., self-report measure of exposure and clinical signs index). The

second model was created to reflect psychological variables and included (1) trait anxiety (2) subjective complaints, (3) depression, and (4) state anxiety. The first model did not return any significant results once accounting for extraneous variance. However, the second model was significant in that psychogenic factors (i.e., trait anxiety, subjective complaints, depression, and state anxiety) accounted for more variance in neuropsychological performance measuring general cognitive functioning, attention, motor coordination, and executive functioning. Therefore, researchers concluded that a model of psychological factors better accounted for decline in neurocognitive measures. However, limitations of the study included a small sample size (N = 82) which may have reduced power. Researchers also noted restricted range and low variance amongst scores, and the presence of multicollinearity (Sillanpaa et al., 1997). Additionally, the study was unclear regarding how biological measures were collected, the time frame between laboratory testing and the creation of the clinical index.

Proctor et al. (2003) studied neuropsychological measures in male Danish GWVs (N = 215), comparing deployed (n = 143) and non-deployed veterans (n = 72). Proctor et al. (2003) sampled from GWV cohorts identified in a previous study (see Proctor et al., 1998) and had participants undergo a series of neuropsychological tests (see Proctor et al., 2003). The sample had a mean age of 38.8 (SD = 9.7) Mood and affect were measured via the Profile of Mood States (POMS; McNair, Lorr, & Droppleman, 1971). Researchers compared groups across neuropsychological measures, controlling for age as the Gulf War deployed group was older than the control group. Results were not significant for neuropsychological domains. However, there were significant differences on the POMS Fatigue and Confusion scales, with deployed groups reporting a moderate

to high number of GWI-associated symptoms. Therefore, the researchers concluded that there was no evidence of toxin exposure leading to neurocognitive deficits. Rather, psychological symptoms were more likely to be reported. However, this study was composed of Danish soldiers who were not exposed to combat while deployed and may differ from other cohorts (e.g., British, American) given differential exposure to the nerve toxins (e.g., less endorsement of exposure to chemical warfare agents and use of anti-nerve gas pills) and trauma.

Consequently, these researchers concluded that complaints associated with Gulf War deployment were more likely psychogenic (Axelrod & Milner, 1997; Proctor et al., 2003; Sillanpaa et al. 1997). However, psychological functioning was measured through differential measurements (self-report [POMS] versus objective measurements [MMPI-2]) and did not always reflect emotional states (POMS Fatigue and Confusion). Also, inclusive symptoms were extensive and inconsistent with any known criteria for GWI. Additionally, these research studies had small sample sizes with the exception of Proctor et al. (2003), which may have had a sample that was limited in exposure to combat and chemical exposure despite deployment. Therefore, further research expanded on these findings by differentiating groups by GWI diagnosis.

Gulf War Veterans – Neurotoxic Etiology Findings

White et al. (2001) examined central nervous system (CNS) dysfunction in GWVs as measured by neuropsychological tests and specific neurotoxin exposure. Participants (N = 240) were recruited from the Devens cohort, New Orleans cohort, and German-deployed cohort (see Proctor et al., 1998). Veterans underwent an environmental interview, questionnaires (POMS), a neuropsychological test battery (WAIS-R, CPT,

Trail Making Test [TMT; Reitan, 1992], Paced Auditory Serial Addition Test [PASAT; Gronwall & Wrightson, 1975], WCST, Finger Tapping Test [Halstead, 1947], Purdue Pegboard [Purdue Research Foundation, 1948], Wechsler Memory Scale-Revised [WMS-R; Wechsler, 1987], California Verbal Learning Test [CVLT; Delis, Kramer, Kaplan, & Ober, 1987], and Test of Memory Malingering [TOMM; Tombaugh, 1996]) and a psychological diagnostic interview. Groups were divided between those deployed to Gulf War combat locations (n = 193) and those stationed in Germany who did not experience combat and were used as a control group (n = 47). Demographic analyses revealed an average age of 53.8 and education level of 13.7 in the deployed group and an average age of 41.0 and education level of 13.7 in the non-deployed group. Both samples were predominately male (female percentage ranging from 12.8 to 13.1 percent) and Caucasian (non-white sample ranging from 0 to 16.9%). Multivariate regression analyses were used to control for age, education, and gender. Results comparing combat and non-combat GWVs on neuropsychological outcomes showed differences in mood complaints. Regarding neuropsychological outcomes, one measure of sustained attention (CPT) approached significance. However, no individual measure achieved true statistical significance. Of note, additional tests showed moderate effect sizes in measures of attention, executive, and motor functioning (PASAT, WCST, TMT-Trails A, Purdue Pegboard) which suggest that those deployed in the Gulf War had lower cognitive performance. When comparing those exposed or not exposed to toxins, significant differences were found in measures of tension and confusion (POMS), long-term visual memory (WMS-R Visual Reproduction), short-term verbal memory (CVLT), and working memory (WMS-R Digit Span). As the researchers controlled for mood, results

on neuropsychological performance were not fully explained by mood disorders. Therefore, toxin exposure pointed towards specific deficits in domains of attention and memory. However, limitations include difficulty finding significance given the multitude of comparisons.

Comparing GWI with Healthy Controls – Psychogenic Etiology Findings

In symptomatic veterans with possible GWI (as defined by Fukuda et al., 1998), results using neuropsychological measures were varied (David et al., 2002). David et al. (2002) investigated neuropsychological patterns amongst 341 United Kingdom Servicemen selected from a large randomized survey (see Unwin et al., 1999). The sample was predominately male with a high school education; the average age was 35. Participants were categorized as ill or healthy based on the Physical Functioning subscale of the Medical Outcome Study Short-Form (SF-36; Ware & Sherbourne, 1992; Ware, Sherbourne, & Davies, 1988). Furthermore, participants were divided by deployment to the Gulf War, to Bosnia, or as an active member that did not participate in either theater. David et al. (2002) assessed general functioning through the WAIS-R, National Adult Reading Test (NART; Nelson, 1991), and Letter-Number Sequencing task of the Wechsler Adult Intelligence Scale-Third Edition (WAIS-III; Wechsler, 1997). Attention was assessed using the PASAT, Sustained Attention to Response Task (SART; Robertson et al., 1997), Stroop Neuropsychological Screening Test (Trenerry, Crosson, DeBoe, & Leber, 1989), and TMT. Memory was assessed using the WMS-R and the Camden Recognition Memory Tests (CRMT; Warrington, 1996). Motor skills were determined using the Purdue Pegboard. In addition, the veterans completed four self-report measures: Cognitive Failures Questionnaire (CFQ; Broadbent, Cooper, Fitzgerald, & Parkes, 1982),

Beck Depression Inventory (BDI; Beck & Steer, 1993), State-Trait Anger Expression Inventory (STAEI; Forgays, Forgays, & Spielberger, 1997), and the Mississippi Combat-Related PTSD Scale (MCRP; Keane, Caddell, & Taylor, 1988). When investigating health status, the researchers found significant associations between depression and the ill group. Therefore, depression was controlled as a confounding factor through an ANCOVA. It was found that, after accounting for depression, worse performance in the ill group was found only in the MCRP. When comparing deployment status, there were no significant results once depression and multiple comparisons were controlled. Therefore, they concluded that there was no significant neuropsychological impairment, but rather, more associations with psychogenic impairment in deployed veterans which may better account for poor performance on neuropsychological measures. However, limitations include crossover effects (i.e., some participants were reassigned as ill or healthy between time intervals of measurements) and no differentiation between levels of symptomatology (David et al., 2002).

Wallin et al. (2009) investigated neuropsychological performance in a sample derived from the National Health Survey of GWVs (Case group = 25, Control = 16) utilizing a stratified random sampling method from a pool of 700,000 veterans. The sample was predominately male (84%) with an average age of 34.5 and predominate education level of 12 years. Wallin et al. (2009) divided groups by veterans reporting GWI symptomatology (using Center of Disease Control criteria) and asymptomatic veterans. Veterans underwent neuropsychological testing (see Wallin et al. 2009) in addition to psychological testing (Personality Assessment Inventory [PAI; Morey, 2007]). Veterans were also assessed on alcohol intake and medical conditions to account

for possible confounding factors. Researchers found no significance amongst neurocognitive testing results. However, there were differences in GWI cases in depression, somatic complaints, and anxiety as measured by the PAI and impairment on the SF-36. Therefore, researchers concluded a stronger influence of psychological factors over neurological factors. Several limitations were present in this study including small sample size (N = 41), the time between study and deployment (12 years post-deployment) and using self-report measures of toxin exposure.

Therefore, both these studies (David et al., 2002; Wallin et al., 2009) further delineated case criteria, with results indicating more psychogenic etiology in GWI veterans. Although differential measures were used to investigate psychological measures, both studies found depression to be a significant factor and possibly distress associated with anxiety or trauma.

Comparing GWI with Healthy Controls – Neurotoxic Etiology Findings

Hom, Haley, and Kurt (1997) investigated veterans with GWI (n = 26) in comparison to a matched GWVs control group (n = 20) on neuropsychological and psychological measures. Sample had an average age of 47.81 and education level of 11.92. Veterans with GWI were selected given their elevated scores on the six factors associated with GWI. Hom et al. (1997) measured neuropsychological performance (see Hom et al. 1997) through an extensive battery. Psychological functioning was measured using the PAI, the Cornell Index (CI; Weider, Wolff, Brodman, Mitteimann, & Wechsler, 1949), and a clinical interview. GWI veterans showed significantly worse performance on measures of overall neurocognitive functioning as reflected in neuropsychological composite scores (Halstead Retain Impairment Index, General Neuropsychological

Deficit Scale, WAIS Full-Scale IQ, Verbal IQ, and Performance IQ); therefore, they demonstrated lower performance as compared to controls on measures of general intelligence, academic abilities, executive functioning, language, visuospatial functioning, and sensorimotor abilities. Notable differences on specific functions were demonstrated in greater impairment in GWI on measures of abstract reasoning and problem-solving/ flexibility. These results point towards deficits in higher-level cognitive abilities or executive functioning. However, results showed no specific neuropsychological deficits or targeted brain dysfunction. Regarding psychological measures, GWI veterans reported more mental and physical complaints as measured by the PAI, similar to patterns seen in general medical patients. The researchers concluded that these results supported the presence of worse neuropsychological (particularly generalized or overall functioning) and psychological functioning in GWI veterans. However, these researchers hypothesized that psychological complaints were secondary to the physical dysfunction consistent with GWI symptoms and did not solely account for GWI presentation. Limitations of the study include a smaller sample size used to test multiple hypotheses.

Anger et al. (1999) investigated psychological and neuropsychological differences via a random pool of GWVs who exhibited otherwise unexplained medical symptoms (i.e., cognitive/psychological changes, gastrointestinal distress, fatigue, muscle pain, joint pain, or skin/mucous membrane lesions). Veterans underwent a medical examination conducted by a physician blind to case designation. Veterans were assigned to controls if they did not endorse any Gulf War-related symptoms. The case sample (n=66) had a mean age of 32.6 and education level of 13.5. The control sample (n = 35) had a mean

age of 30.6 and an education level of 13.8. Both groups (N = 101) completed a series of tests assessing psychological functioning: MCRP, Penn Inventory for PTSD (PIP; Hammarberg, 1992), Post Traumatic Stress Disorder Checklist (PCL; Weathers, Litz, Herman, Huska, & Keane, 1993), SF-36, Beck Anxiety Inventory (BAI; Beck, Epstein, Brown, & Steer, 1988), BDI, Substance Abuse Subtle Screening Inventory (SASSI; Miller, 1988), SCL-90-R, MMPI-2, Positive Affect/Negative Schedule (PANS; Watson, Clark, & Tellegen, 1988), Life Experience Scale (LES; Sarason, Johnson, & Siegel, 1978), and the Combat Exposure Scale (CES; Keane et al., 1989; Wolfe, Brown, Furey, & Levin, 1993). The neurocognitive tests implemented included Simple Reaction Time (Posner, 1978), Selective Attention Test (Anger et al., 1996), Digit Span (Wechsler, 1955), Symbol Digit (Smith, 1968), Serial Digit Learning (Benton, Sivan, Hamsher, Varney, & Spreen, 1994), and the Oregon Dual Task Procedure (ODTP; Binder, 1993; Binder & Kelly, 1996; Binder & Willis, 1991). Anger et al. (1999) found statistically significant differences between controls and Persian Gulf cases on all thirteen measures of psychological functioning. However, neurocognitive results returned significance only for the ODTP after controlling for multiple comparisons. Using these results, researchers divided groups based on speed or "slow cases" and "other cases." Slow cases were identified by a score of two standard deviations above (slower) than the mean ODPT forced choice latency observed in the control group. The slow case subgroup (n = 13) had a mean ODTP latency of three standard deviations (2.7 seconds) than the control group mean (1.7 seconds). Consistent with performance on the ODTP, veterans in the "slow case" group showed slower responses than controls on Symbol Digit, Simple Reaction Time, Digit Span Forward, and Digit Span Backward. Therefore, researchers reported

slower neurobehavioral performance on tasks of memory, attention, and response speed in those with GWI-related symptoms. However, results did not indicate an overall neurobehavioral deficit, as poorer performance was only exhibited in a subgroup of "slow cases" with GWI-related symptoms. Also, these results were not otherwise explained by psychological distress as "slow cases" data were nonsignificant with psychological measures. Additionally, these results were consistent with the literature investigating deficits in individuals with organophosphate poisoning. However, these results may not be generalizable as all veterans were volunteering to participate, which may indicate a group more motivated for treatment or with higher concerns about their health (Anger et al., 1999).

Lange et al. (2001) conducted a study examining GWI and healthy veterans on cognitive functioning. Additionally, Lange et al. (2001) identified and accounted for the presence of PTSD and Major Depressive Disorder (MDD) in a group of 87 GWVs (healthy controls = 39; GWI = 48). Sample consisted of an average age of 34.3 and was predominately composed of males. Both healthy and GWI groups were administered tests sensitive to attention, concentration or informational processing (e.g., CPT, PASAT), verbal and visual memory, abstraction and conceptualization (Category Test), visuoperceptual and perceptual-motor functions, and fine motor functioning. A MANOVA found significant results in attention, concentration, and information processing, as well as abstraction and conceptualization. Tests reflecting attention and information processing (CPT and PASAT) as well as tests of abstraction and concentration (Category test) were significantly different ($p \leq .05$) with GWI veterans showing worse performance than healthy controls. Also, regression analyses were

conducted controlling for psychopathology variables. Results indicated that GWI remained significant on some tests (CPT simple reaction time) but was nonsignificant with other tests (CPT complex reaction time, PASAT). Psychopathology was not correlated with performance on the CPT. Therefore, GWI was the only predictor and remained significant. They concluded that GWI veterans exhibited deficits on attention, concentration, and information processing over and above the impact of psychopathology. Limitations of the study include failure to investigate other etiological sources (i.e., toxin exposure) as well as a lack of generalizability given that the sample comprised of healthcare seeking veterans (Lange et al. 2001).

The results of these studies converge in that researchers point towards cognitive problems associated with either GWI or a subset of GWI veterans. However, these studies diverge on the areas of cognitive weaknesses with one study identifying both global and specific decline and another identifying attention and memory decline in subset of a GWI-population. These studies vary in their design and have small sample sizes which may account for the differences in results. Of note, the diagnosis of GWI also remains inconsistent across modalities (i.e., factors, Fukuda et al.,1998 criteria). Therefore, a strength of later research is the inclusion of more reliable measures of toxin exposure.

Investigating Toxin Exposure – Neurotoxic Etiology Findings

Toomey et al. (2009) conducted a study examining GWVs (deployed and non-deployed) on several measures of neuropsychological performance. Random sampling of non-deployed and deployed GWVs was utilized resulting in a sample size of 2,189 GWVs (1,061 deployed, 1,128 non-deployed). The sample consisted of mostly men with

an average age of 39; additionally, the majority of the sample had a high school education and were Caucasian. Veterans underwent the neuropsychological battery designed by the Devens Cohort study except for visual-spatial functioning tasks. Additionally, veterans were assessed on mental health (BDI-II, BAI, PCL) CMI complexes (i.e., similar to GWI diagnosis), and exposure to sarin and cyclosarin (e.g., 2000 Khamisiyah plume analyses and self-reported exposure). Results indicated that deployed veterans performed worse on a test of attention flexibility and motor speed in comparison to non-deployed veterans. Additional analyses showed that toxin exposure was associated with worse performance in verbal memory, visual memory, and psychomotor speed after controlling for psychological variables. However, GWI status was not associated with any notable factor after controlling for psychological variables. A notable limitation of the study included low participation rates, which may underestimate covariates such as psychiatric conditions (e.g., anxiety, schizophrenia, other neurocognitive disorders) as they tend to be less healthcare seeking compared to the research sample. However, the researchers sampled the participants and non-participants on depressive symptoms and did not find a significant difference. Therefore, researchers concluded that both toxin and psychogenic factors might be impacting performance, especially in different neuropsychological domains.

Proctor, Heaton, Herren, and White (2006) examined the relationship between levels of sarin and cyclosarin exposure in GWVs and neurobehavioral functioning. As sarin and cyclosarin are acetylcholinesterase inhibitors, exposure leads to several CNS symptoms (e.g., dizziness, nausea, miosis, blurred vision, vomiting, weaknesses), indicating a mechanism for cognitive deficits. Proctor et al. (2006) used data (N = 140)

from the Devens Cohort Study, a stratified random sample of GWVs, who completed a medical and history questionnaire, a semi-structured environmental interview, neuropsychological testing, and psychological testing (Structural Clinical Interview for DSM [SCID; Spitzer, Williams, Gibbon, & First, 1990], Clinical-Administered PTSD Scale [CAPS; Blake et al., 1995], MCRP, and Brief Symptom Interview [BSI; Derogatis, 1993]). Sarin and cyclosarin exposure were determined through the 2000 Khamisiyah plume analyses or modeled exposure utilizing meteorological modeling information, estimates of rockets deployed, unit location and personal data, exposure thresholds, presence of agent removal mechanisms, and combined toxicity of sarin and cyclosarin. Researchers obtained plume analyses data applicable to the Devens cohort, which gave dosage estimates of exposure for each member. The sample consisted of mostly men with average age of 34.8 and education level of 13 years. Veterans were divided based on exposure to sarin and cyclosarin or high exposure group (> 0.072 mg min/m3 [n = 23]), moderate exposure group (≤ 0.072 mg min/m3 [n = 47]) and no exposure group (n = 70). Neuropsychological measures were analyzed through Student t-tests for continuous variables and through chi-square for categorical variables. Results indicated significant differences in groups on psychomotor and visuospatial abilities (e.g., Purdue Pegboard and Block Design) with higher exposure associated with worse outcomes, or a dose-response with exposure (exposure matching the amount of deficit reported/observed). However, one limitation is the gap between exposure and outcome measurement (4-5 years), thereby making it impossible to determine if it is a delayed or immediate effect. However, this study was conducted before GWI awareness was heightened amongst GWVs, limiting any potential for self-report bias to over-report symptoms.

Overall, both studies were consistent in finding decreased motor speed associated with toxin exposure. However, more research is needed to understand deficits in visuospatial skills as well as the presence of psychological symptoms related to objective and subjective toxin exposure.

Additional Neuropsychological Findings

Janulewicz et al. (2017) conducted a meta-analysis investigating the neuropsychological characteristics of GWI. Studies included in the analysis had GWVs who served from 1990 to 1991, had neuropsychological results reportable in a manner conducive to meta-analyses, and contained a unique sample with a total of 14 studies. Study results were delineated by specific domains including visuospatial abilities, academic achievement, attention/executive functioning, learning/memory, and motor skills using tests that were present in at least three studies in the meta-analysis. Also, two analyses were performed based on the differential samples across studies comparing Gulf-deployed veterans to non-deployed veterans/population norms (Group A) and Gulf-deployed symptomatic versus Gulf-War non-symptomatic veterans (Group B). Group A analyses returned significance in visuospatial abilities, attention/executive functioning, and learning/memory, in which deployed GWVs had worse outcomes over non-deployed veterans. Group B studies had statistically significant differences in domains of visuospatial abilities, attention/executive functioning, and learning/memory, with symptomatic veterans exhibiting worse performance in comparison to asymptomatic veterans. Also, analyses indicated that Block Design, TMT-Trails A, CPT, and CVLT were the most sensitive in discriminating cohorts in Group A and Group B. Limitations reported in the study included difficulties assessing domain-specific findings given the

sparse information reported in included studies, and the overlap between studies that prevented a more diverse sample. Also, data was too limited to assess toxin exposure concerning neuropsychological deficits. Therefore, across studies, deployed GWVs and symptomatic GWVs demonstrate levels of cognitive impairment, particularly in visuospatial abilities, attention/executive functioning, and learning/memory.

Fatigue

Fatigue is the most common symptom associated with GWI (Smith et al., 2012) and could impact cognitive functioning. Although fatigue has not been isolated in studies investigating GWI, fatigue present with a known cognitive impairment has evidenced lowered sustained attention, concentration, processing speed, and reaction time (Fleck et al., 2002; Groopman, 1998). Additionally, chronic fatigue syndrome (CFS), another multiple chemical sensitivity syndrome, is linked to slowed processing speed (Tierskey et al., 1997). Michiels and Cluydts (2001) also investigated neuropsychological functioning in CFS and reported significantly worse processing speed, working memory, and learning abilities. Therefore, fatigue is noteworthy considering the prevalence of fatigue in GWI and its impact on cognitive functioning.

GWI and PTSD

Given the increased risk of trauma exposure in combat, it is not surprising that researchers have found a PTSD prevalence rate of 29 to 39 percent in GWVs (Al-Turkiat & Oheari, 2008; Labbate & Snow, 1992; Sutker, Davis, Uddo, & Ditta, 1995). However, prevalence rates of those with both GWI and PTSD have not been thoroughly investigated. Additionally, controversy surrounds the etiology of GWI, as literature presents conflicting evidence supporting either a psychological or physical underpinning.

Haley (1997) reviewed 19 articles investigating GWI and PTSD research – in this study he found that there were discrepancies between studies as some studies pooled samples from specific military units, others sampled from veteran populations by state, and others sampled treatment-seeking veterans. He also reanalyzed PTSD rates taking into account the sensitivity and specificity of the specific measures used (i.e., MCRP, SCID) and found a very high number of false positive cases. Therefore, he argued that there was a misrepresentation of the amount of true PTSD cases present in veterans with GWI. Ford et al. (2001) also investigated posttraumatic stress symptomatology amongst those with GWI-like symptoms with a random selection of 237 GWI veterans and 113 controls. Ford et al. (2001) had conflicting results, as posttraumatic stress symptomatology was associated with GWI and to a lesser degree war zone trauma and depression. In response to Haley (1997), Ford et al. (2001) supported their finding in that most veterans of the Gulf War had lower levels of posttraumatic stress symptomatology, and therefore, did not meet full criteria for PTSD; additionally, they also reported that posttraumatic stress symptomology does not fully account for their presentation. However, Ford et al. (2001) argued that investigating subclinical aspects of posttraumatic stress has utility given that these symptoms were associated with GWI even when controlling for physical health symptoms, functional impairment, and life stressors. Therefore, additional research investigating other aspects of physical and psychological presentations such as cognition and immunological factors may contribute to understanding the relationship between posttraumatic stress symptoms and GWI.

Vasterling, Brailey, Constans, and Sutker (1998) examined GWVs with PTSD on measures of attention and memory dysfunction. Vasterling et al. (1998) divided GWVs

based on PTSD diagnosed via the SCID (n = 19) and compared them to healthy veterans with no mental disorder diagnoses (n =24). The sample was predominately male (74.4%) with an average age of 25.74 (SD = 9.19) and 14.26 years of education (SD = 2.02). All participants underwent the Letter Cancellation task (Talland, 1965), Stroop Test, CPT, WCST, WAIS-R (Digit Span, Arithmetic), RAVLT, and the Continuous Visual Memory Test (Trahan & Larrabee, 1988). Results from the attention measures showed worse performance on the Arithmetic test and higher commission errors on the CPT in the PTSD group. The PTSD group also had worse performance on scores of the RAVLT measuring intrusions, recognition, and retroactive interference. Researchers hypothesized that the presence of cognitive intrusions (i.e., inability to inhibit thoughts or experiences related to trauma) could contribute to these patterns of symptoms. Using a principal component analysis, the researchers found that cognitive intrusions symptoms, particularly re-experiencing phenomenon, was related to poorer performance on memory and attention measures. Therefore, they hypothesized that PTSD might lead to problems inhibiting wrong answers and filtering information unrelated to the task at hand. Additionally, the researchers found that PTSD-diagnosed veterans had difficulty on measures of sustained attention and mental manipulation over other measures of attention (i.e., selective attention). Of note, the study was limited given that the study had a small sample and their case sample also had co-morbid diagnoses outside of PTSD. Researchers also were unable to compare results with differential clinical samples with mental diagnosis outside of PTSD to differentiate the impact of trauma related stress over general emotional distress. Finally, the researchers noted that cognitive changes may be more evident during heightened arousal (i.e., presence of psychological triggers or

threats) which was not used as a manipulation in this study (Vasterling et al., 1998).

Lindem et al. (2003) investigated neuropsychological performance in conjunction with self-reported chemical exposure and severity of trauma symptoms with a sample of 225 participants (Devens cohort = 141, New Orleans cohort = 37, Germany cohort = 47) comprised of those deployed and non-deployed during the Persian Gulf War. The Germany cohort was used as a comparison group as this cohort was exposed to the military-related stress; however, they did not experience the same combat or environmental exposure as their counterparts stationed in the Gulf War. The sample of participants deployed to the Gulf War (n = 178) had a mean age of 34.9 (SD = 9), a mean education of 13.9 (SD = 2.1), were roughly equivalent in gender (male = 55.9%, female = 44.1%), and predominantly Caucasian (82.2%). The sample of non-deployed veterans had a mean age of 41.0 (SD = 9.1), a mean education of 13.7 years (SD 1.5), were predominantly male (87.2) and Caucasian (100%). Participants were administered the CAPS to determine the level of trauma symptoms and combat exposure was assessed using the CES (Keane et al., 1989; Wolfe et al., 1993) with additional items relevant to the Gulf War (i.e., chemical exposure). Health symptoms were measured with the Expanded Health Symptom Checklist (HSC: Bartone, Ursano, Wright, & Ingraham, 1989). Regarding neuropsychological testing, the veterans underwent tests of general intelligence (i.e., WAIS-R Information), attention and executive functioning (WAIS-R Digit Span, WMS-R Digit Span, CPT, TMT, WCST, PASAT), motor functioning (Finger Tapping Test, Purdue Pegboard), visuospatial constructional abilities (WAIS-R Block Design), verbal memory (WMS-R Verbal Paired Associates, CVLT), visual memory (WMS-R Visual Reproduction), and mood and motivation (POMS, TOMM). Chemical

exposure was assessed through self-report measure and a clinical interview. Partial correlational analyses including all veteran groups found a significance between severity of PTSD symptoms reported and performance in attention, executive functioning, motor functioning, memory, and mood subscales while controlling for age, education, WAIS-R Information score, deployment status, depression, and disability. Partial correlational analyses for Gulf War deployed veterans revealed that severity of PTSD symptoms was significantly correlated with general intellectual ability, sustained attention, motor speed, motor coordination, verbal learning, and mood while controlling for age, education, and WAIS-R Information. The same analysis was conducted for Germany deployed veterans, and there were significant findings in measures of simple attention, sustained attention, and some mood scales. For Gulf War deployed veterans that reported chemical exposure (n = 30), partial correlation analyses showed worse performance in sustained attention, motor speed, and motor coordination even after controlling for age, education, WAIS-R Information, depression, and disability. Additionally, the same analysis was used to investigate PTSD severity and neuropsychological performance in GWVs that denied chemical or biological warfare (CBW) exposure. Results indicated a significant relationship in measures of cognitive tracking, motor speed, motor coordination, and mood.

To further investigate the relationship between PTSD severity and CBW exposure, regression analyses were performed to investigate how PTSD severity and CBW exposure predicted neuropsychological performance while controlling for age, education, and WAIS-R Information. Researchers found that PTSD was associated with poorer performance in general academic ability, sustained attention, motor speed, verbal

learning, visual memory recognition, and mood. CBW exposure was associated with worse performance on sustained attention, verbal memory, visual memory delayed recall, and mood. Researchers concluded that the severity of PTSD contributed to declines in short-term verbal memory (acquisition, retrieval, semantic clustering). Additionally, severity of PTSD suggested difficulties with sustained attention, motor functioning, and intellectual functioning. In regard to CBW exposure, researchers concluded that severity of PTSD was associated with specific tasks of sustained attention, number of perseverative responses in verbal memory tasks, visual memory, and mood measures. Limitations of this examination include the use of cross-sectional analyses over a longitudinal design as it is difficult to determine what neurocognitive weaknesses were present prior to deployment. Additionally, the analyses were dependent on subjective measures of exposure to chemicals over more objective measures (Lindem et al., 2003).

Sullivan et al. (2003) also investigated neuropsychological performance in GWVs with PTSD concerning PB exposure, a chemical linked to neurotoxic effects. Sullivan et al. (2003) used a sample of 260 veterans which were divided into a group that was deployed and seeking treatment (i.e., for cognitive or health symptoms) and a control group (i.e., non-deployed GWVs who were not seeking treatment). Researchers determined toxin exposure through the use of military records and self-report exposure questionnaires. All veterans underwent a neuropsychological battery (see reference for full battery list) in addition to a CAPS to determine PTSD status. In comparison to non-deployed veterans, deployed veterans had worse performance in measures of attention (WAIS-R Digit Span), visuospatial skills (WAIS-R Block Design), and visual memory (Visual Reproduction delay). Also, the veterans endorsed worse mood symptoms.

Veterans exposed to PB showed worse performance on the WCST. However, there was no difference between those with and without PTSD on neuropsychological measures. Therefore, the researchers concluded that deployment and PB exposure led to some notable deficits.

Sullivan et al. (2018) investigated how differing levels of pesticide exposure and PB intake contributed to neuropsychological dysfunction. The researchers recruited veterans with functional knowledge of their exposure to these toxins as they held roles as preventative medical personnel. The sample (n = 159) had an average age of 48, an average education level of 16 years, and were predominately male (87%). Researchers also used Department of Defense environmental exposure reports to divide participants into four groups: group one (i.e., low pesticide, low PB), group two (i.e., high pesticide, low PB), group three (i.e., low pesticide, high PB), and group four (i.e., high pesticide, high PB). All veterans completed several neuropsychological tests. Noteworthy tests include the CPT, CVLT-II, TMT, WCST, Rey-Osterrieth Complex Figure Test (ROCF; Taylor, 1959), Grooved Pegboard, and Finger Tapping Test. Veterans were also assessed for psychological functioning via the POMS and CAPS. GWI was screened for using CMI criteria (Fukuda et al., 1998). The data were analyzed with a series of multivariate and univariate analyses. Univariate analyses of covariance demonstrated that high pesticide/high PB exposure was associated with worse CPT and on the POMS sub scores. These analyses remained significant with PTSD as a covariate, demonstrating a main effect on attention reaction time in comparison to the low pesticide/low PB group. Additionally, high pesticide exposure/low PB exposure was significantly worse on a measure of visual memory (via the ROCF) compared to the low pesticide/high PB and

low pesticide/low PB group. Multivariate analyses were performed with a MANCOVA using a summary score for all cognitive tests as the dependent variables and all four participant groups as the independent variable. Significant differences were found in psychomotor, mood, attention, and memory domains when considering demographic covariates (i.e., age, education, gender). However, psychomotor, attention, and memory domains only remained significant when CMI was added as a covariate when considering the model as a whole. Researchers found that a higher rate of CMI was associated with the high pesticide/high PB group which evidenced worse cognitive performance in attention, motor, and memory domains. These results are consistent with problems in short-term memory, attention, and processing speed in a research investigation of organophosphate exposure amongst pesticide, greenhouse, and livestock employees. Overall, results showed that high pesticide/high PB exposure had worse performance on information processing reaction times, attentional errors and visual memory accompanied by increased mood complaints. Limitations of this study include the multitude of analysis with a smaller sample size, increasing the chance of finding significance. Additionally, it is possible that, although the sample had a sophisticated knowledge of their exposure, their exposures were correlated (i.e., exposure to PB associated with exposure to vaccines, nerve agents, and pesticides). Additionally, pesticide and PB classifications were reliant on self-report exposure

Considering the research on GWVs in regard to PTSD and chemical exposure, there is some consistency in that chemical exposure, per self-report, may negatively impact attention, visual memory, and mood. However, patterns are not necessarily clear given the specific underlying issues in attention (i.e., sustained attention versus

attentional errors). It also remains unclear if there is a pattern specific to the type and variety of exposure. Finally, the Sullivan et al. (2018) study was the only one that considered GWI or CMI as a covariate, limiting the ability to see a trend related to neuropsychological performance and GWI. Future research would benefit from using specific criteria to examine GWI and more objective measures of immunological dysfunction to elucidate neurocognitive performances in GWI with PTSD.

GWI Biomarkers, Trauma, and Neuropsychological Performance

As GWI has been linked to an underlying immunological process via toxin exposure, additional studies associating psychological and neuropsychological functioning in conjunction with immunological performance could further elucidate contributions of cognitive decline. Currently, only one published study has investigated immunological biomarkers (i.e., cytokines, genetic expression data, cortisol) in conjunction with trauma, fatigue, and neuropsychological performance (Broderick et al., 2013). In this study biomarkers were examined under an exercise challenge to prompt immunological response mechanisms in a sample of GWI participants (n = 20) CFS participants (n = 7) and healthy veteran controls (n =22). All participants were male and comparable in age (range of 30 to 55), body mass index, ethnicity, and duration of illness. Participants were administered a variety of measures notably the Davidson Trauma Scale (DTS; Davidson et al., 1997), the Multidimensional Fatigue Inventory (MFI; Smets, Garssen, Bonke, & De Haes, 1995) and the PASAT. Immune response was activated with a standard exercise test using the McArdle protocol (see McArdle et al., 2007). Blood was collected at three time points during the exercise challenge (i.e., prior to exercise challenge, at peak effort measured at VO2 max, and four hours post-exercise challenge).

Sixteen different cytokines were analyzed via blood plasma with a quantitative enzyme-linked immunosorbents assay (ELISA)-based test. Using partial correlation analyses, Broderick et al. (2013) analyzed cytokine correlates with measure results during rest, at peak effort, and during recovery. Results indicates that lower interleukin-10 (IL-10) levels at peak effort was significantly associated with scores on the DTS and lower scores on the PASAT. Results concerning the MFI was more varied and was associated with changes in interleukin 4 (IL-4), interleukin 12 (IL-12), and IL-10. However, this study was also limited in that a small sample was used to conduct a multitude of analyses.

Barker et al. (2015) also conducted a pilot analysis for a poster presentation investigating the biobehavioral differences in GWI participants with and without self-reported trauma. Using the data collected through the exercise challenge study (see Broderick et al., 2013 for details), researchers divided the participants (N = 21) into two groups via K-means clustering based on DTS scores. Additionally, researchers examined how these two groups differed on self-reported health outcome measures (SF-36, MFI) immune cytokine profiles, and autonomic variables (heart rate variability, work percentage predicted) with an ANOVA analysis. Results indicated that the group with higher DTS scores significantly differed ($p < .0.01$) from the lower DTS group in terms of age and SF-36 Social Functioning. Therefore, these results indicated that higher DTS scores were associated with older veterans with self-reported problems with social functioning. Additionally, the group with higher DTS scores showed significant differences ($p < 0.05$) reflecting diminished functioning as a result of health-related issues (SF-36 Vitality, SF-36 Physical Functioning), higher fatigue levels (MFI General Fatigue, MFI Physical Fatigue, MFI Reduced Activity, MFI Reduced Motivation), and

cardiac output (work percentage predicted). Of note, some measure results approached significance ($p < 0.06$) indicating that those with higher DTS scores had higher IL-4 concentrations at peak exercise and four hours post-exercise, higher heart rate variability, and poorer emotional role functioning (SF-36 Emotional Role Functioning). However, considering the small sample size, the p-value had limited value given that the study was underpowered. Considering these results, the researchers hypothesized that veterans with trauma-based symptoms may have higher levels of IL-4 at peak exercise and four hours post exercise. However, more research is necessary to understand if IL-4 was elevated based on trauma over age-related IL-4 elevations.

Although the literature is not abundant, these two studies are indicative of a possible immunological process that may be contributing to problematic psychological patterns (i.e., poor social and emotional functioning, low motivation), fatigue, and worse attention processes (i.e., PASAT). Therefore, further research investigating interleukin as a biomarker in conjunction with psychological and cognitive measures may elucidate more patterns to understand the unique contributions of biological versus psychological factors in GWI presentation.

Summary of the Literature

GWI is chronic, multi symptom illness, impacting the health of a significant amount of GWVs; however, the etiology and treatment of GWVs remains somewhat elusive, prompting the demand for more research. Research investigating the neuropsychological underpinnings of GWI is especially needed given the prevalence of cognitive symptoms in GWVs, possibly the second most reported symptom in GWI (Smith et al., 2012).

Early studies of neuropsychological functioning and GWVs focused more on the etiology of these symptoms with conflicting results pointing either towards a psychogenic or neurological cause. These studies did not use an established criterion and compared groups based on their deployment status (deployed, non-deployed) and/or symptom presence (reporting symptoms, not reporting symptoms). Some researchers found that their group of interest (deployed or symptom reporting) endorsed higher psychological distress (Axelrod & Milner, 1997; Proctor et al., 2003; Sillanppa et al., 1997). However, this research did not necessarily clarify neuropsychological performance in GWI as it is understood in current literature, as symptoms were not classified into a specific diagnosis. Additionally, other studies that controlled for trauma (Proctor et al., 2003) did not utilize a sample that was exposed to combat, and therefore, may not reflect the same etiology as those exposed to combat and chemical exposure. One researcher comparing GWVs (White et al., 2001) found evidence of a neurotoxin impact in GWVs leading to worse neuro-cognitive performance. However, there was still evidence of higher psychological distress in addition to poorer performance specifically in attention and memory tests. Therefore, these conflicting findings prompted further research that delineated GWI through more testable operational definitions.

Despite the efforts to establish criteria for GWI, researchers continued to find mixed results on the etiology of GWI centering on the debate of a psychogenic or neurotoxic underpinning. David et al. (2002) found substantial evidence of psychogenic nature of GWI using the Fukuda et al. (1998) criteria. With the use of an extensive mood and neuropsychological batteries, they found depression confounded the results between GWI and neuropsychological test performance. Wallin et al. (2009) expanded on these

findings and only found differences in GWI on depression, somatic complaints, and anxiety. However, additional research (Hom et al., 1997) also eluded to more physiological causes. Earlier research showed more impairment in general scores of neuropsychology tests (i.e., Halstead-Reitan Index, Weschler Indexes), which made it difficult to ascertain the different neurological areas and pathways that were impaired. In addition, researchers (Anger et al., 1999) investigated different levels of symptoms related to the Gulf War comparing those with slower reaction times to those who were not impaired on processing speed. Those GWVs with slower times also had memory impairment, pointing towards difficulty with basic processing and encoding skills. Nevertheless, focusing on criteria or the presence of Persian-related symptoms did not necessarily clarify the etiology of GWI. Differences in findings could account for different samples as well as differing measures for neuropsychological and psychological functioning.

Of note, these studies did not specifically address the level of neurotoxicity exposure, as differing levels of toxins can have a mild to severe impact on physiological functioning. Additional research was conducted comparing groups based on sarin/cyclosarin exposure via self-report and found reported higher exposure to sarin/cyclosarin was associated with lower performance in a visuospatial and motor functioning task. Further research partially supported this finding as toxin exposure was associated with reduced motor speed. However, toxin exposure also impacted scores reflecting poor attentional flexibility. Therefore, based on the different methods (i.e., sampling, operational definition of toxin) and differing neuropsychological measures used, toxin exposure may have an impact on some neuropsychological processes, but

more research is needed before definitive conclusions can be made.

To address these conflicting findings, Janulewicz et al. (2017) conducted a meta-analysis from GWI neuropsychological research. They compared data from deployed and non-deployed veterans as well as deployed veterans that were symptomatic and asymptomatic. When comparing deployed and non-deployed veterans, they found worse performance in deployed veterans in visuospatial abilities, attention/ executive functioning and learning/memory. When comparing asymptomatic and symptomatic veterans, symptomatic veterans had similar results, supporting the idea that symptomatic veterans present with neuropsychological deficits.

Lastly, as PTSD has a high prevalence rate in GWVs, this review also included research investigating PTSD and GWVs in relation to neuropsychological performance. Vasterling et al. (1998) divided GWVs based on the presence or absence of PTSD and found worse performance in the PTSD group on measures of different components of memory (i.e., working memory, intrusions, recognition, and interference) and attention. They found that these memory and attention issues were possibly related to the presence of cognitive intrusions, particularly in the re-experience of trauma (Vasterling et al., 1998). Lindem et al. (2003) also investigated PTSD in relation to cognitive performance and chemical exposure. They found that GWVs with PTSD had worse performance on general intellectual ability, sustained attention, motor speed, verbal learning, and mood measures. Sullivan et al. (2003) investigated PTSD and the deployment status of veterans on neurocognitive performance, finding that deployed veterans with PTSD more likely had problems with attention, visuospatial skills, and visual memory as well as higher endorsement of mood distress. Therefore, GWVs with PTSD likely will show some

neurocognitive impairment, especially in regard to memory and attention.

Although research is varied on GWI, there remains preliminary evidence of possible neuropsychological deficits. The etiology of these results remains unclear as both emotional and true neurological damage have been identified as causes. Given the complexity of retrospective analyses, it may be a combination of psychological and biological factors. However, research has improved to support evidence of GWI leading to neurological deficits measurable through neuropsychological batteries, particularly in areas including attention, memory, motor functioning, and executive functioning. Notable improvements include the use of established criteria and measuring toxin exposure. However, future research would benefit from continuing to use established criteria when investigating neuropsychological performance in GWI. GWI research would also benefit from including self-report and modeled measures of toxin exposure. However, increased use of bio marker research may also be a helpful introduction to GWI neuropsychological research. For instance, research on cytokine profiles of GWI have shown immunological homeostatic shifts, which lends credence to a neurological etiology in GWI (Craddock et al., 2015). Finally, there has been a lack of research investigating GWI and PTSD together in conjunction with neuropsychological results. Therefore, it is difficult to understand how these two diagnoses create neuropsychological profiles, given that they both lead to poorer performance on neuropsychological measures. This lack of research is especially problematic for practicing neuropsychologists given the high prevalence of PTSD in their patient population as well as the possibility of encountering a patient who has GWI.

Additionally, limited research on objective measures of immunological

functioning (i.e., cytokines), psychological status, and GWI indicate that differential levels of cytokines in GWI veterans may be related to problematic psychological patterns (i.e., poor social and emotional functioning, low motivation), fatigue, and worse attention processes (i.e., PASAT). Therefore, these studies support the utility of investigating biological markers alongside psychological measures to better understand the biological and psychological contributions to GWI presentation as demonstrated in a test of attention and working memory.

Purpose

The purpose of the present dissertation project was to investigate how veterans diagnosed with GWI perform on measures of cognition, while considering their level of fatigue and PTSD symptoms. Both GWI and PTSD-related symptoms have been associated with neuropsychological decline. However, it remains unclear how GWI and PTSD symptoms uniquely contribute to cognitive decline. It is also difficult to accurately measure neurocognitive performance in GWI given that GWI often presents with fatigue. Fatigue leads to lower performance in cognitive measures (Tierskey et al., 1997), and can be misattributed to neurologically mediated deficits.

The present study also incorporated measures of immunological performance and its impact on fatigue levels. Specifically, we investigated the unique contributions of IL-4 and IL-10 levels on measures of reported fatigue. The same measures of fatigue were included in the neuropsychological analyses, to link fatigue as expressed by immunological processes in GWI to neuropsychological performance.

Therefore, this study is an examination of the influence of GWI, PTSD-related symptoms, and fatigue on a neuropsychological measure of sustained attention and

working memory (i.e., PASAT). Additionally, this study investigated fatigue and its association with interleukin levels to further understand immunological processes of fatigue that could contribute to cognitive performance on the PASAT.

Chapter III: Methods

All study materials and procedures were approved by the Institutional Review Board (IRB) of the University of Miami. Ethics review and approval for data analysis was also obtained via the IRB of the University of Alberta. Given the de-identified nature of the data received by the investigator, separate IRB approval via the Nova Southeastern University was not necessary. Recruitment occurred between April 2006 and May 2008 through the Miami Veterans Administration Medical Centers, clinics, and the local veteran community.

Participants

Participants were selected from a de-identified, archival database gathered through the Gulf War Illness Consortium based in Florida. Inclusion criteria mandates participants must have served between August 1990 and July 1991. Those with a history of a prior central nervous system or psychiatric diagnosis that would significantly impact cognitive functions (i.e., stroke, epilepsy, Alzheimer's Dementia, schizophrenia) were excluded. Veterans were placed in the GWI group if they met criteria for case definition (Fukuda et al., 1998). Case definition was defined as moderate to severe symptoms persisting for six months or longer in at least three of the following domains: respiratory, gastrointestinal, neuropsychological, sleep disturbances, and pain (Steele, 2000). All other veterans were placed in the control group if they had no exclusionary diagnoses. Veterans in the control group were matched by age, ethnicity, and BMI to GWI counterparts.

Data for the study was derived from an original sample of 99 male veteran participants. However, some veterans (n = 29) did not have the necessary immunological

data for the desired analyses. We excluded veterans with higher PTSD symptoms from the healthy group (n = 8) to ensure a valid healthy control group. As such, sixty-two male participants, with an age range of 30 to 58, comprised the complete data including the PASAT, MFI, DTS, and cytokines of interest. However, some measures had missing data, which impacted the utilized sample population as analyses were conducted listwise.

Measures

Paced Auditory Serial Addition Test (PASAT). The PASAT is a test of working memory, divided attention and information processing speed appropriate for those aged 16 to 74. The examinee played a tape recording with a random array of numbers ranging from 1 to 9. The participant was instructed to consecutively add pairs of numbers so that each number is added to the number spoken previously. The participant undergoes four trials in total with each trial incrementally increasing the speed of the numbers, thereby decreasing the time allotted for the participant to process the information and respond. The trial speed between number exposure is 2.4 seconds for the first trial, 2.0 seconds for the second trial, 1.6 seconds for the third trial, and 1.2 seconds for the last trial (Gronwall, 1977). Regarding reliability, the PASAT has evidenced high internal consistently (Cronbach's alpha = .90; Crawford, Obansawini, & Allan, 1998) and test-retest reliability over three months (r = .83-.96; Sjogren, Thomsen, & Olsen, 2000). In terms of validity, the PASAT has also demonstrated adequate convergent validity compared to other measures of attention including the Auditory Consonant Trigrams, d2 Test, TMT, Visual Search and Attention Test, and Stroop test (Gronwall & Wrightson, 1981; Sherman, Strauss, & Spellacy, 1997). Additionally, the PASAT has shown convergent validity with choice reaction time tasks (Deary, Langan, Hepburn, & Frier,

1991; Schachinger, Cox, Linder, Brody, & Keller, 2003). In terms of construct validity, a factor analysis has shown that PASAT loads onto a three-factor model of attention, immediate memory, and information processing (Larrabee & Curtiss, 1995). Cronbach's alpha for the all trials of the PASAT for this sample was .923, which demonstrates a high level of consistency for this analysis.

Multidimensional Fatigue Inventory (MFI). The MFI is a 20 item self-report measure designed to assess fatigue within five subscales: General Fatigue, Physical Fatigue, Mental Fatigue, Reduced Motivation, and Reduced Activity. Higher scores on the measure reflect higher levels of acute fatigue. The MFI has adequate internal consistency with a Cronbach's alpha of .84. Additionally, the MFI showed construct validity as the five-factor model of fatigue was supported by confirmatory factor analysis. Finally, convergent validity was somewhat supported ($0.22 < r < 0.78$) when compared to the Visual Analogue Scale measuring fatigue (Smets et al., 1995). Cronbach's alpha for this sample (.95) also showed a high level of internal consistency.

Davidson Trauma Scale (DTS). The DTS is a self-rated measure of PTSD criteria and further delineates the severity and frequency of these symptoms. The use of this measure is supported by sufficient test-retest reliability ($r = 0.86$) and internal consistency ($r = 0.99$) as well as good convergent and divergent validity with the SCID (Davidson et al., 1997). Additionally, researchers found that a cutoff score within the range of 68-72 provided optimal diagnostic accuracy given that the sample matched the veteran prevalence rate (12-13%) and accurately classified 90% of the cases with PTSD (McDonald, Thompson, Stratton, & Calhoun, 2014). However, even though this score is supportive of a PTSD diagnosis, it is not sufficient to determine PTSD. In this current

study, the DTS was used as a measure of the level of PTSD symptoms to investigate PTSD symptoms as a spectrum rather than use it as a screening measure to assign a diagnosis without an accompanying clinical interview.

Procedures

Participants were given a full explanation of the requirements, benefits, and costs of the study. If the participant understood these parameters, the study investigator or IRB-approved delegate obtained informed consent. The participant was also reminded of the aspects of the study and his rights as a participant. After consent was obtained, participants received a physical examination and a medical history was gathered - including a GWI symptom checklist. Following the examination, the veteran completed pertinent questionnaires including the MFI and the DTS. Next, all veterans were assessed using the PASAT. Immune response was stimulated through a standardized exercise challenge test (see Broderick et al., 2013 for details). Blood was drawn prior to exercise, at peak effort as measured by VO2 max, and four hours post-exercise. In addition, MFI was measured prior to exercise, at peak exercise, and four hours post-exercise. For each blood sample, plasma was separated within two hours of collection and stored at -80 degrees Celsius until processing. A total of 16 cytokines (including IL-10 and IL-4) were analyzed with Quansys reagents and instruments. These cytokines were identified through a quantitative ELISA plate or through distinct patterns of antibodies in a 96-well plate array. To compare between subject groups, data was adjusted previously to account for the range of the standard curve and exposure time for reliable comparisons at both high and low cytokine concentrations (see Broderick et al., 2013 for further statistical and methodological descriptions).

After collecting data, each case was assigned a specific code number to ensure that no personal identifying information was contained in research materials. An electronic code, which matched materials linked to personal health information, was used only for patient tracking/safety purposes and password protected. All data were kept in locked file cabinets accessible only to authorized staff. Data are coded without any personal health information.

Hypotheses

The present study had two overarching hypotheses, with sub-hypothesis within each major question. First, it was hypothesized that 1a) a GWI diagnosis, higher levels of PTSD symptoms, and higher fatigue symptoms would lead to poorer performance on a survey measure of attention and working memory (PASAT). Additionally, it was predicted that 1b) GWI diagnosis would be the most important factor leading to worse testing performance over and above demographic factors, severity of PTSD, and severity of fatigue. Next, it was hypothesized that 1c) PTSD symptom severity would be the second most important factor leading to poorer performance on measures of attention and working memory.

The second overarching hypothesis was that 2a) the presence of GWI and elevated levels of IL-10 and/or IL-4 would lead to higher endorsement of fatigue in the MFI including Physical Fatigue, Mental Fatigue, Reduced Activity, Reduced Motivation and General Fatigue.

Chapter IV: Results

Overview

The hierarchical regression analyses were conducted through multiple steps. First, education was recoded via dummy coding with elementary school used as the baseline. The first analyses was designed to measure how GWI status, PTSD symptoms, and fatigue, would impact scores on the PASAT. Age and education were the first variables in the model (Block 1) to account for confounding sources of variance. Second, the categorical variable of condition as defined by either healthy control or GWI was entered (Block 2). The next block included the PTSD symptoms variable as measured by the DTS (Block 3). Finally, fatigue, as measured by the overall score of the MFI (General Fatigue), was included in the final Block (Block 4). These analyses were applied to all four trials of the PASAT.

The next analysis was designed to measure how health condition (i.e., GWI or healthy control), then cytokine variables (i.e., IL-10 and IL-4) impacted how veterans reported their fatigue on the MFI. Condition was added as the first variable (Block 1). The next block (Block 2) consisted of interleukin IL-10 and IL-4 levels. These analyses were applied to all sub scores of the MFI including Physical Fatigue, Mental Fatigue, Reduced Activity, Reduced Motivation, and General Fatigue.

For all analyses, the alpha level was set to .05. Additionally, given the smaller sample sizes (and the inverse association between sample size and statistical significance levels), effect sizes were also reported to provide meaningful information about the magnitude of effects. The effect sizes for full models of regression were based on the R^2 statistic and ΔR^2; coefficient effect sizes were determined by squared semi-partial

correlations (r_{sp}^2). The values (Cohen, 1988) were interpreted with following cutoffs: ≥ .02 (small) , ≥ .13 (medium) , and ≥ .26 (large).

Descriptive Characteristics

The sample included only male participants who were veterans of the Gulf War. The sample was predominately Caucasian (n = 44; 72.1%), with one participant who identified as Asian and 16 participants who identified as African American. A sample consisted of a relatively equivalent amount of non- Hispanic/Latino participants (n = 33), and Hispanic/Latino participants (n = 28). Age grouping revealed 20 participants were between the ages 30 to 39 (32.3%), 34 participants were between the ages 40 to 49 (54.8%), and eight participants were between 50 and 58 (12.9%). Education level also varied, as 1 participant completed elementary school (1.7%), 24 participants had a high school diploma (40.7%), 26 participants had a four-year college degree (44.1%), and 8 participants had a doctoral degree (12.9%). See Table 1 for more details on participant characteristics between health conditions.

Table 1
Demographic Characteristics Between Health Conditions

Characteristic	GWI (n = 31)		Healthy Controls (n = 31)	
	n	% of group	n	% of group
Age				
30-39	10	32.26	10	32.26
40-49	18	58.06	16	51.61
50-58	3	9.68	5	16.13
Race*				
White	21	67.74	23	76.67
Asian	1	3.23	0	0
African American	9	29.03	7	23.33
Ethnicity*				
Hispanic/Latino(a)	13	41.94	15	50
Not Hispanic/Latino(a)	18	58.06	15	50
Education*				
Elementary School	1	3.23	0	0
High School	12	38.71	12	40
College	14	45.16	14	46.67
Doctorate	4	12.90	4	13.33

Note: *These demographics were not documented for one healthy control participant

Additionally, analyses between the GWI and control group produced means on all key measures including the DTS, MFI, and PASAT (see Table 2). Of note, the investigator reported on all sub scores of the DTS to demonstrate where both groups fell on particular PTSD symptom clusters (i.e., intrusive symptoms, avoidance, and hypervigilance). However, only the total DTS score was utilized in the overall hierarchical analyses of interest.

Table 2
Key Measure Means Between Health Conditions

Measure	GWI (n = 31)		Healthy Controls (n = 31)	
	Mean	SD	Mean	SD
DTS*				
Intrusion	23.06	10.88	3.35	7.20
Avoidance	29.58	16.88	2.84	6.82
Hypervigilance	26.39	10.13	3.94	8.79
Total	79.03	35.18	10.13	20.61
MFI				
Physical Fatigue	60.14	24.41	13.33	15.64
Mental Fatigue	65.86	27.69	15.00	21.15
Reduced Activity	53.88	25.00	16.40	16.28
Reduced Motivation	52.82	26.69	13.33	13.33
General Fatigue	65.42	22.56	17.88	16.81
PASAT				
Trial 1	35.86	12.21	38.28	13.69
Trial 2	33.18	10.16	37.17	12.05
Trial 3	28.50	10.16	32.55	9.39
Trial 4	21.14	10.20	25.17	7.84

Note: *DTS scores in the healthy control group are likely lower in means given the exclusion of veterans (n = 8) with high PTSD levels (DTS score >70) to ensure a healthy control group

Differences between the GWI and control group on demographic variables were analyzed using a one-way ANOVA. Age was not statistically significant when comparing the control group (M = 43, SD = 6.53) and the GWI group (M = 43, SD = 6.53), $F(1, 60) = .132$, $p = .717$, $\eta^2 = .002$. Education was not statistically significant when considering the control group and the GWI group for the following educational levels: high school, $F(1, 57) = .101$, $p = .751$, $\eta^2 = .002$; college, $F(1, 57) = .031$, $p = .862$, $\eta^2 = .001$, and

doctorate, $F(1, 57) = .023$, $p = .880$, $\eta^2 = > .001$. A chi-square test was used to test if groups differed by race $X^2 (1, N = 62) = .576$, $p = .78$ and by ethnicity $X^2 (1, N = 62) = .527$, $p = .61$. There were no statistically significant differences seen between individuals with GWI and healthy controls.

PASAT Results by Condition, PTSD Symptoms, and Fatigue

In the first set of hierarchical regression models, the four trials of the PASAT were analyzed in separate models. Predictor blocks were held constant across models: Block 1 (Age, Education), Block 2 (GWI or Healthy Control), Block 3 (PTSD symptoms), Block 4 (Fatigue symptoms) with the full model consisting of all blocks. Tables 3 through 9 present selected statistical information from the analyses.

PASAT Trial 1. Regression models were used on available data (n = 48). The full model for PASAT Trial 1 was nonsignificant, $R^2 = .189$, 95% CI [.028, .350], $F(7, 40) = 1.330$, $p = .262$, adjusted $R^2 = .047$. The first predictor block – including age and education – was nonsignificant, $R^2 = .178$, $F(4, 43) = 2.324$, $p = .072$, adjusted $R^2 = .101$; however, it demonstrated a medium effect. The addition of health condition on the second predictor block did not account for significant incremental variance in Trial 1, $\Delta F(1, 42) = .146$, $p = .704$, $\Delta R^2 = .003$. The addition of PTSD in the third block also did not provide significant incremental variance in Trial 1, $\Delta F (1, 42) = .259$, $p = .614$, $\Delta R^2 = .005$. Finally, the addition of the last block, fatigue level, failed to produce significant incremental variance, $\Delta F (1, 40) = .152$, $p = .699$, $\Delta R^2 = .003$. In the final model, age was associated with lower scores ($r_{sp} = -.208$, 95% CI [-.465, .081]) with a small effect ($r_{sp}^2 = 0.04$). Education at the high school level ($r_{sp} = .164$, 95% CI [-.126, .428]; $r_{sp}^2 = 0.03$), college level ($r_{sp} = .136$, 95% CI [-.154, .405]; $r_{sp}^2 = 0.02$), and the doctoral level ($r_{sp} =$

.216, 95% CI [-.073, .471]; r_{sp}^2 =0.05) were positively associated with the PASAT with small effect. Health condition (r_{sp} = .044, 95% CI [-.243, .324]; r_{sp}^2 = 0.00), PTSD symptoms (r_{sp} = -0.04, 95% CI [-.320, .247]; r_{sp}^2 = 0.00), and fatigue symptoms (r_{sp} = -0.06, 95% CI [-.338, .228]; r_{sp}^2 =0.00) did not show a statistical or meaningful association.

Table 3
PASAT Trial 1

	Model 1		Model 2		Model 3		Model 4	
Variable	B	r_{sp}^2	B	r_{sp}^2	B	r_{sp}^2	B	r_{sp}^2
Constant	50.230		52.714		48.370		47.916	
Age	-.643	.07	-.665	.07	-.583	.04	-.573	.04
Edu. Level								
High School	15.367	.03	14.265	.02	15.794	.03	16.459	.03
Collegiate	12.039	.02	11.202	.01	12.305	.02	13.194	.02
Doctoral	21.040	.05	20.126	.04	21.070	.04	21.733	.05
Condition [a]			-1.458	.00	.941	.00	2.110	.00
PTSD Level [b]					-.037	.01	-.022	.00
Fatigue [c]							-.047	.00
R^2	.178		.181		.186		.189	
$R^{2\ adj}$	.101		.083		.067		.047	
F	2.324		1.851		1.559		1.330	
ΔR^2	.178		.003		.005		.003	
Δ F	2.314		.146		.259		.152	

Note. *p < .05, **p <.001, [a] Case designation (GWI or Healthy Control), [b] PTSD level (PTSD-related symptoms from DTS total), [c] Fatigue (as designated by MFI General Fatigue); B indicates unstandardized coefficient, r_{sp}^2 indicates a semi-partial correlation squared

PASAT Trial 1 Reanalysis without Outliers. Assumption testing of the data revealed two potential outliers which were excluded for the following analysis (n = 46). The analysis interpretation did not change as the full model for PASAT 1 remaining nonsignificant (see Table 4 for comparison values). There was no notable change in ΔR^2, as it did not produce significant or meaningful results. Regarding semi-partial correlations, age (r_{sp} = -.254, 95% CI [-.507, .039]; r_{sp}^2 =0.06) continued to have a small negative impact on PASAT scores as stipulated in the previous analysis. Education at the high school level (r_{sp} = .165, 95% CI [-.132, .434]; r_{sp}^2 =0.02) and the doctoral level (r_{sp} = .217, 95% CI [-.078, .477]; r_{sp}^2 =0.047) still exhibited a small meaningful and positive

association with the PASAT.

PASAT Trial 1 Reanalysis with Recoding. PASAT data was reanalyzed to include the participant with elementary level education (n =1) by combining his data with other participants with a high school education. There were no major changes to data with the exception of high school education level having a nonmeaningful effect score which was previously a small effect size (r_{sp}^2 =0.03); this same change was seen in the data without outliers as high school education was previously a small effect size (r_{sp}^2 =0.02).

Table 4
PASAT Trial 1 with and without Outliers

	Model 1		Model 2		Model 3		Model 4	
Variable	B	r_{sp}^2	B	r_{sp}^2	B	r_{sp}^2	B	r_{sp}^2
Constant	50.23		52.71		48.37		47.92	
	(49.89)		(52.35)		(48.4)		(47.97)	
Age	-.64	.07	-.67	.07	-.58	.04	-.57	.04
	(-.64)	(.06)	(-.65)	(.07)	(-.58)	(.04)	(-.57)	(.04)
Education								
High Sch	15.37	.03	14.27	.02	15.79	.03	16.46	.03
	(15.71)	(.03)	(14.51)	(.02)	(15.84)	(.03)	(16.38)	(.03)
College	12.04	.02	11.20	.01	12.31	.02	13.19	.02
	(12.07)	(.02)	(11.16)	(.01)	(12.18)	(.02)	(12.99)	(.02)
Doctoral	21.04	.05	20.13	.04	21.07	.04	21.73	.05
	(21.07)	(.05)	(20.08)	(.04)	(20.95)	(.04)	(21.57)	(.05)
Cond. [a]			-1.46	.00	.94	.00	2.11	.00
			(-1.60)	(.00)	(.61)	(.00)	(1.75)	(.00)
PTSD [b]					-.04	.01	-.02	.00
					(-.03)	(.00)	(-.02)	(.00)
Fatigue [c]							-.05	.00
							(-.04)	(.00)
R^2	.178		.181		.186		.189	
	(.174)		(.178)		(.182)		(.184)	
$R^{2\ adj}$	.101		.083		.067		.047	
	(.094)		(.075)		(.056)		(.033)	
F	2.32		1.851		1.559		1.330	
	(2.16)		(1.727)		(1.444)		(1.222)	
ΔR^2	.18		.003		.005		.003	
	(.17)		(.003)		(.004)		(.002)	
Δ F	2.31		.146		.259		.152	
	(2.16)		(.163)		(.089)		(.089)	

Note. *p < .05, **p <.001, Analysis without outliers within parentheses, [a] Case designation (GWI or Healthy Control), [b] PTSD level (PTSD-related symptoms from DTS total), [c] Fatigue (as designated by MFI General Fatigue); B indicates unstandardized coefficients, Abbreviations were also used. High Sch = High School, Cond. = Condition. r_{sp}^2 indicates a semi-partial correlation squared

PASAT Trial 2. Regression models were used on available data (n = 48). The full model for PASAT Trial 2 was nonsignificant, $R^2 = .171$, 95% CI [.014, .328] $F(7, 40) = 1.181$, $p = .335$, adjusted $R^2 = .026$. The first predictor block with age and education was nonsignificant, $R^2 = .136$, $F(4, 43) = 1.691$, $p = .170$, adjusted $R^2 = .056$; however, there was a medium effect. The addition of health condition on the second predictor block did not account for significant incremental variance in Trial 2, $\Delta F(1, 42) = .955$, $p = .334$, $\Delta R^2 = .019$; there was an approaching small effect. The addition of PTSD in the third block also failed to produce significant incremental variance in Trial 2, $\Delta F(1, 41) = .732$, $p = .397$ $\Delta R^2 = .015$. The addition of the last block with fatigue level did not significantly contribute to the model with incremental variance, $\Delta F(1, 40) = .063$, $p = .803$, $\Delta R^2 = .001$. In the final model, age was associated with lower scores ($r_{sp} = -.126$, 95% CI [-.396, .164]) with a small effect ($r_{sp}^2 = 0.02$). Education at the high school level ($r_{sp} = .12$, 95% CI [-.170, .391]; $r_{sp}^2 = 0.01$), college level ($r_{sp} = .094$, 95% CI [-.195, .368]; $r_{sp}^2 = 0.01$), and the doctoral level ($r_{sp} = .191$, 95% CI [-.098, .451]; $r_{sp}^2 = 0.04$) were positively associated with the PASAT. Only education at the doctoral level produced a small meaningful effect. Health condition ($r_{sp} = .022$, 95% CI [-.264, .304]; $r_{sp}^2 = 0.00$), PTSD symptoms ($r_{sp} = -0.091$, 95% CI [-.366, .198]; $r_{sp}^2 = 0.01$), and fatigue symptoms ($r_{sp} = -0.036$, 95% CI [-.317, .251]; $r_{sp}^2 = 0.00$) did not show a statistical or meaningful association.

Table 5
PASAT Trial 2

	Model 1		Model 2		Model 3		Model 4	
Variable	B	r_{sp}^2	B	r_{sp}^2	B	r_{sp}^2	B	r_{sp}^2
Constant	41.834		47.452		41.018		40.760	
Age	-.379	.03	-.429	.04	-.307	.02	-.301	.02
Edu. Level								
High School	10.291	.02	12.013	.01	10.062	.01	10.441	.01
Collegiate	7.664	.01	11.656	.00	7.404	.01	7.909	.01
Doctoral	17.019	.04	12.214	.03	16.350	.04	16.727	.04
Condition [a]			-3.296	.02	.256	.00	.920	.00
PTSD Level [b]					-.055	.01	-.046	.01
Fatigue [c]							-.027	.00
R^2	.136		.155		.170		.171	
$R^{2\ adj}$	.056		.055		.049		.026	
F	1.691		1.543		1.399		1.181	
ΔR^2	.136		.019		.015		.001	
Δ F	1.691		.955		.732		.063	

Note. *p < .05, **p <.001, [a] Case designation (GWI or Healthy Control), [b] PTSD level (PTSD-related symptoms from DTS total), [c] Fatigue (as designated by MFI General Fatigue); B indicates unstandardized coefficients, β indicates standardized coefficients, r_{sp}^2 indicates a semi-partial correlation squared

PASAT Trial 2 Reanalysis without Outliers. The overall model of age, education, condition, PTSD symptoms and fatigue (n = 46) did not significantly predict changes on the second trial of the PASAT when analyzed without outliers, $R^2 = .145$, 95% CI [-.018, .308], $F(7, 38) = 1.146$, $p = .356$, adjusted $R^2 = .022$. There were no changes in any of the hierarchical models. The first model ($R^2 = .145$) held a medium effect size. However, the second model ($\Delta R^2 = .018$) approached a small effect with the addition of health condition. Semi-partial correlation interpretation also did not change without outliers.

PASAT Trial 2 Reanalysis with Recoding. Reanalysis with the original data revealed that Model 1 R^2 and Model 1 ΔR^2 with age and education had a small effect ($R^2 = .120$) which was previously a medium effect size ($R^2 = .136$). Additionally, Model 2 ΔR^2 was interpreted as a small effect size ($\Delta R^2 = .026$), which was previously non-meaningful ($\Delta R^2 = .019$). Without outliers, there were similar results in that Model 1 R^2 and Model 1 ΔR^2 had a small effect (.127) rather than medium effect (.145) and Model 2

ΔR^2 was interpreted as a small effect (.026) over a non-significant effect (.018).

Table 6
PASAT Trial 2 with and without Outliers

	Model 1		Model 2		Model 3		Model 4	
Variable	B	r_{sp}^2	B	r_{sp}^2	B	r_{sp}^2	B	r_{sp}^2
Constant	41.83		47.45		41.02		40.76	
	(42.73)		(47.72)		(42.17)		(42.12)	
Age	-.38	.03	-.43	.04	-.31	.02	-.30	.02
	(-.4)	(.03)	(-.44)	(.04)	(-.33)	(02)	(-.33)	(.02)
Education								
High Sch	10.29	.02	12.01	.01	10.06	.01	10.44	.01
	(11.05)	(.02)	(8.62)	(.01)	(10.49)	(.02)	(10.56)	(.01)
College	7.66	.01	11.66	.00	7.40	.01	7.91	.01
	(7.6)	(.01)	(5.77)	(.01)	(7.2)	(.01)	(7.3)	(.01)
Doctoral	17.02	.04	12.21	.03	16.35	.04	16.73	.04
	(16.95)	(.04)	(14.95)	(.03)	(16.18)	(.03)	(16.25)	(.03)
Cond. [a]			-3.3	.02	.26	.00	.92	.00
			(-3.3)	(.02)	(-.15)	(.00)	(-.009)	(.00)
PTSD [b]					-.06	.01	-.05	.01
					(-.05)	(.01)	(-.05)	(.00)
Fatigue [c]							-.03	.00
							(-.005)	(.00)
R^2	.136		.155		.170		.171	
	(.145)		(.163)		(.174)		(.174)	
$R^{2\ adj}$	.056		.055		.049		.026	
	(.062)		(.059)		(.047)		(.022)	
F	1.691		1.543		1.399		1.181	
	(1.740)		(1.561)		(1.372)		(1.146)	
ΔR^2	.136		.019		.015		.001	
	(.145)		(.018)		(.011)		(.000)	
Δ F	1.691		.955		.732		.063	
	(1.740)		(.867)		(.519)		(.002)	

Note. *p < .05, **p <.001, Analysis without outliers within parentheses, [a] Case designation (GWI or Healthy Control), [b] PTSD level (PTSD-related symptoms from DTS total), [c] Fatigue (as designated by MFI General Fatigue); B indicates unstandardized coefficients, Abbreviations were also used. High Sch = High School, Cond. = Condition. r_{sp}^2 indicates a semi-partial correlation squared

PASAT Trial 3 Analysis. The full model for PASAT Trial 3 (n = 48) was nonsignificant, $R^2 = .194$, 95% CI [.032, .356], $F(7, 40) = 1.375$, $p = .242$, adjusted $R^2 = .053$. The first predictor block (i.e., age and education) was nonsignificant, $R^2 = .136$, $F(4, 43) = 1.691$, $p = .170$, adjusted $R^2 = .056$; a medium effect was observed. The addition of health condition in Block 2 did not account for significant incremental variance in Trial 3, $\Delta F(1, 42) = .713$, $p = .403$, $\Delta R^2 = .014$. The third block, with PTSD symptoms, also failed to produce significant incremental variance in Trial 3, $\Delta F(1, 41) = .204$, $p = .654$

$\Delta R^2 = .004$. The addition of the last block with fatigue level did not significantly contribute to the model with incremental variance, $\Delta F(1, 40) = .736$, $p = .396$, $\Delta R^2 = .015$. For the overall model, age did not produce a meaningful effect ($r_{sp} = -.107$, 95% CI[-.380, .183], $r_{sp}^2 = 0.01$). Education at the high school level ($r_{sp} = .264$, 95% CI [-.022, .510]; $r_{sp}^2 = 0.07$), college level ($r_{sp} = .217$, 95% CI [-.072, .472]; $r_{sp}^2 = 0.05$), and the doctoral level ($r_{sp} = .257$, 95% CI [-.029, .504]; $r_{sp}^2 = 0.07$) were positively associated with the PASAT and all produced a small meaningful effect. Health condition ($r_{sp} = .031$, 95% CI [-.255, .312]; $r_{sp}^2 = 0.00$), PTSD symptoms ($r_{sp} = -0.001$, 95% CI [-.285, .283]; $r_{sp}^2 = 0.00$), and fatigue symptoms ($r_{sp} = -0.112$, 95% CI [-.384, .178]; $r_{sp}^2 = 0.01$) did not show a statistical or meaningful association.

Table 7
PASAT Trial 3

	Model 1		Model 2		Model 3		Model 4	
Variable	B	r_{sp}^2	B	r_{sp}^2	B	r_{sp}^2	B	r_{sp}^2
Constant	24.882		28.964		26.090		25.349	
Age	-.253	.02	-.289	.02	-.234	.01	-.218	.01
Edu. Level								
High School	19.332	.08	17.520	.06	18.532	.06	19.617	.07
Collegiate	14.805	.05	13.429	.04	14.159	.04	15.608	.05
Doctoral	18.918	.07	17.416	.06	18.040	.06	19.122	.07
Condition [a]			-2.396	.01	-.809	.00	1.097	.00
PTSD Level [b]					-.024	.00	.000	.00
Fatigue [c]							-.077	.01
R^2	.161		.175		.179		.194	
$R^{2\ adj}$	.083		.077		.059		.053	
F	2.064		1.783		1.491		1.375	
ΔR^2	.161		.004		.004		.004	
ΔF	2.064		.713		.204		.736	

Note. *p < .05, **p <.001, [a] Case designation (GWI or Healthy Control), [b] PTSD level (PTSD-related symptoms from DTS total), [c] Fatigue (as designated by MFI General Fatigue); B indicates unstandardized coefficients, β indicates standardized coefficients r_{sp}^2 indicates a semi-partial correlation squared

PASAT Trial 3 Reanalysis without Outliers. The overall model of age, education, condition, PTSD symptoms and fatigue (n = 46) did not produced significance within the third trial of the PASAT without outliers, $R^2 = .172$, 95% CI [.013, 331] $F(7, 38) = 1.322$, $p = .267$, adjusted $R^2 = .048$. However, a change was seen in that the second

model was approaching a meaningful effect ($\Delta R^2 = .018$). As before, the first model ($R^2 = .172$) held a medium effect size. Squared semi-partial correlations showed a difference from the previous analysis as in the second model the health status of the veteran (i.e., either GWI or healthy control) approached a meaningful effect with a negative association for PASAT Trial 3 scores ($r_{sp} = -.134$, 95% CI [-.408, .163]; $r_{sp}^2 = 0.018$).

PASAT Trial 3 Reanalysis with Recoding. Model 1 R^2, Model 1 ΔR^2, Model 2 R^2, Model 3 R^2, and Model 4 R^2 returned a small effect (Model 1 $R^2/\Delta R^2 = .086$, Model 2 $R^2 = .116$, Model 3 $R^2 = .116$, Model 4 $R^2 = .124$) which was previously a medium effect size (Model 1$R^2/\Delta R^2 = .161$, Model 2 $R^2 = .175$, Model 3 $R^2 = .179$, Model 4 $R^2 = .174$). Additionally, Model 2 ΔR^2 reanalysis resulted in a small effect size (.030) which was previously non-meaningful (.004). For the final model semi-partial correlates, reanalysis showed differences in age, ($r_{sp}^2 = 0.036$, previously non-significant), high school level of education (non-significant, previously $r_{sp}^2 = .07$) and doctoral level of education (non-significant, previously $r_{sp}^2 = .07$).

Without outliers, there were similar results in that Model 1 R^2, Model 1 ΔR^2, Model 2 R^2, Model 3 R^2, and Model 4 R^2 revealed a small effect (Model 1 $R^2/\Delta R^2 = .089$, Model 2 $R^2 = .126$, Model 3 $R^2 = .126$, Model 4 $R^2 = .127$) which was previously a medium effect size (Model 1$R^2/\Delta R^2 = .172$, Model 2 $R^2 = .190$, Model 3 $R^2 = .192$, Model 4 $R^2 = .196$). Model 2 ΔR^2 reanalysis resulted in a small effect size (.037) which was previously non-meaningful (.018). Lastly, semi-partial correlation effect sizes revealed that doctoral education was now non-meaningful, which was previously a small effect size (.06).

Table 8
PASAT Trial 3 with and without Outliers

	Model 1		Model 2		Model 3		Model 4	
Variable	B	r_{sp}^2	B	r_{sp}^2	B	r_{sp}^2	B	r_{sp}^2
Constant	24.88		28.96		26.09		25.35	
	(23.96)		(28.14)		(26.44)		(25.97)	
Age	-.25	.02	-.29	.02	-.23	.01	-.22	.01
	(-.23)	(.02)	(-.26)	(.02)	(-.23)	(.01)	(-.22)	(.01)
Education								
High Sch	19.33	.08	17.52	.06	18.53	.06	19.62	.07
	(20.22)	(.08)	(18.18)	(.06)	(18.75)	(.07)	(19.35)	(.07)
College	14.81	.05	13.43	.04	14.16	.04	15.61	.05
	(14.88)	(.05)	(13.34)	(.04)	(13.78)	(.04)	(14.67)	(.04)
Doctoral	18.92	.07	17.42	.06	18.04	.06	19.12	.07
	(18.99)	(.07)	(17.32)	(.06)	(17.69)	(.06)	(18.37)	(.06)
Cond. [a]			-2.4	.01	-.81	.00	1.1	.00
			(-2.7)	(.02)	(-1.78)	(.00)	(-.52)	(.00)
PTSD [b]					-.02	.00	.00	.00
					(-.02)	(.00)	(-.002)	(.00)
Fatigue [c]							-.08	.01
							(-.04)	(.00)
R^2	.161		.175		.179		.19	
	(.172)		(.190)		(.192)		(.196)	
$R^{2\ adj}$	.083		.077		.059		.05	
	(.092)		(.089)		(.067)		(.048)	
F	2.064		1.783		1.491		1.38	
	(2.133)		(1.878)		(1.54)		(1.32)	
ΔR^2	.161		.004		.004		.004	
	(.172)		(.018)		(.001)		(.004)	
Δ F	2.064		.713		.204		.74	
	(2.133)		(.881)		(.070)		(.202)	

Note. *p < .05, **p <.001, Analysis without outliers within parentheses, [a] Case designation (GWI or Healthy Control), [b] PTSD level (PTSD-related symptoms from DTS total), [c] Fatigue (as designated by MFI General Fatigue); B indicates unstandardized coefficients, Abbreviations were also used. High Sch = High School, Cond. = Condition. r_{sp}^2 indicates a semi-partial correlation squared

PASAT Trial 4 Analysis. The full model for PASAT Trial 4 (n = 48) was nonsignificant, R^2 = .238, 95% CI [.068, .408], F(7, 40) = 1.784, p = .117, adjusted R^2 = .105. The first predictor block with age and education was nonsignificant, R^2 = .184, F(4, 43) = 2.426, p = .062, adjusted R^2 = .108; a medium effect was observed. The addition of health condition in the second predictor block did not add significant incremental variance in Trial 4, $\Delta F(1, 42) = 1.023$, p = .318, ΔR^2 = .019; however, an approaching small effect size was observed. The third block which added PTSD symptoms failed to

produce significant incremental variance in Trial 4, $\Delta F(1, 41) = 1.801$, $p = .187$ $\Delta R^2 = .034$; a small effect was observed. The addition of the fatigue in the last block did not significantly contribute to the model with incremental variance, $\Delta F(1, 40) = .048$, $p = .828$ $\Delta R^2 = .001$. For the overall model, age did not produce a meaningful effect ($r_{sp} = -.022$, 95% CI [-.304, .264]; $r_{sp}^2 = 0.09$). Education showed a small effect across all levels including high school ($r_{sp} = .353$, 95% CI [.077, .579]; $r_{sp}^2 = 0.12$), college ($r_{sp} = .31$, 95% CI [.028, .546]; $r_{sp}^2 = 0.10$), and the doctoral level ($r_{sp} = .348$, 95% CI [.071, .575]; $r_{sp}^2 = 0.12$) which were positively associated with scores. PTSD symptoms ($r_{sp} = -.176$, 95% CI [-.438, .114]; $r_{sp}^2 = 0.03$) showed a small meaningful effect and was negatively associated with scores. Health condition ($r_{sp} = .035$, 95% CI [-.252, .316]; $r_{sp}^2 = 0.00$), and fatigue symptoms ($r_{sp} = 0.03$, 95% CI [-.256, .311]; $r_{sp}^2 = 0.00$) did not show a statistical or meaningful association.

Table 9
PASAT Trial 4

	Model 1		Model 2		Model 3		Model 4	
Variable	B	r_{sp}^2	B	r_{sp}^2	B	r_{sp}^2	B	r_{sp}^2
Constant	8.339		12.549		5.335		5.496	
Age	-.135	.01	-.172	.01	-.035	.00	-.039	.00
Edu. Level								
High School	22.546	.13	20.677	.11	23.217	.13	22.981	.12
Collegiate	19.438	.10	18.019	.09	19.851	.10	19.536	.10
Doctoral	22.928	.13	21.378	.11	22.946	.13	22.711	.12
Condition [a]			-2.470	.02	1.512	.00	1.098	.00
PTSD Level [b]					-.061	.03	-.066	.03
Fatigue [c]							.017	.00
R^2	.184		.204		.237		.238	
$R^{2\ adj}$	.108		.109		.125		.105	
F	2.426		2.146		2.123		1.784	
ΔR^2	.184		.019		.034		.001	
ΔF	2.426		1.023		1.801		.048	

Note. *p < .05, **p <.001, [a] Case designation (GWI or Healthy Control), [b] PTSD level (PTSD-related symptoms from DTS total), [c] Fatigue (as designated by MFI General Fatigue); B indicates unstandardized coefficients, β indicates standardized coefficients

PASAT Trial 4 Reanalysis without Outliers. The full model of age, education, condition (GWI versus healthy control), PTSD symptoms and fatigue, on Trial 4

continued to be non-significant, $R^2 = .248$, 95% CI [.075, .421], $F(7, 38) = 1.789$, $p = .118$, adjusted $R^2 = .109$. Additionally, subsequent models including variables of interests were not significant. However, the overall effect of Model 1 with age and education levels had a medium effect ($R^2 = .198$) and significance ($p = .054$). The second model, including health condition, somewhat approached a clinical effect ($\Delta R^2 = .018$), pointing towards a possible trend with GWI diagnosis and poorer performance on PASAT. The third model, which included PTSD symptoms, continued to hold a small effect regarding model change ($\Delta R^2 = .028$). For the last model, there was a change in the magnitude as the high school education changed from a small to a medium effect ($r_{sp}^2 = .13$).

PASAT Trial 4 Reanalysis with Recoding. Model 1 R^2, Model 1 ΔR^2, Model 2 R^2, Model 3 R^2, and Model 4 R^2 had a small effect (Model 1 $R^2/\Delta R^2 = .051$, Model 2 $R^2 = .096$, Model 3 $R^2 = .108$, Model 4 $R^2 = .113$) which was previously interpreted as a medium effect size (Model 1$R^2/\Delta R^2 = .184$, Model 2 $R^2 = .204$, Model 3 $R^2 = .237$, Model 4 $R^2 = .238$). Additionally, Model 2 ΔR^2 reanalysis resulted in a small effect size (.046) which was previously non-meaningful (.019); however, Model 3 ΔR^2 reanalysis returned a non-significant effect size (.012), which was beforehand interpreted as a small effect (.034). For the final model semi-partial correlates, reanalysis showed differences in high school level of education (non-significant, previously $r_{sp}^2 = .12$), doctoral level of education (non-significant, previously $r_{sp}^2 = .12$), and PTSD symptoms (non-significant, previously $r_{sp}^2 = .03$).

When analyzed without outliers, there were similar results in that Model 1 R^2, Model 1 ΔR^2, Model 2 R^2, Model 3 R^2, and Model 4 R^2 revealed a small effect (Model 1 $R^2/\Delta R^2 = .058$, Model 2 $R^2 = .102$, Model 3 $R^2 = .111$, Model 4 $R^2 = .122$) from a

previously medium effect size (Model 1R^2/ ΔR^2 = .198, Model 2 R^2 = .216, Model 3 R^2 = .244, Model 4 R^2 = .248). Furthermore, Model 2 ΔR^2 reanalysis returned a small effect size (.044) which was previously non-meaningful (.018) and Model 3 ΔR^2 returned a non-significant effect which was previously small (.028). For the final model semi-partial correlates, reanalysis showed differences in high school level of education (non-significant, previously r_{sp}^2 = .13), doctoral level of education (non-significant, previously r_{sp}^2 = .12), and PTSD symptoms (non-significant, previously r_{sp}^2 = .03).

Table 10
PASAT Trial 4 with and without Outliers

	Model 1		Model 2		Model 3		Model 4	
Variable	B	r_{sp}^2	B	r_{sp}^2	B	r_{sp}^2	B	r_{sp}^2
Constant	8.34		12.55		5.34		5.5	
	(9.14)		(12.83)		(6.25)		(6.64)	
Age	-.14	.01	-.17	.01	-.04	.00	-.04	.00
	(-.15)	(.01)	(-.18)	(.01)	(-.06)	(.00)	(-.06)	(.00)
Education								
High Sch	22.55	.13	20.68	.11	23.22	.13	22.98	.12
	(23.13)	(.14)	(21.33)	(.11)	(23.55)	(.13)	(23.05)	(.13)
College	19.44	.10	18.02	.09	19.85	.10	19.54	.10
	(19.38)	(.10)	(18.03)	(.09)	(19.72)	(.10)	(18.97)	(.09)
Doctoral	22.93	.13	21.38	.11	22.95	.13	22.71	.12
	(22.87)	(.13)	(21.39)	(.11)	(22.84)	(.12)	(22.27)	(.12)
Cond. [a]			-2.47	.02	1.51	.00	1.1	.00
			(-2.41)	(.02)	(1.28)	(.00)	(.23)	(.00)
PTSD [b]					-.06	.03	-.07	.03
					(-.06)	(.03)	(-.07)	(.03)
Fatigue [c]							.02	.00
							(.04)	(.00)
R^2	.184		.204		.237		.238	
	(.198*)		(.216)		(.244)		(.248)	
$R^{2\ adj}$	.108		.109		.125		.105	
	(.120*)		(.118)		(.128)		(.109)	
F	2.426		2.146		2.123		1.784	
	(2.537*)		(2.208)		(2.098)		(1.789)	
ΔR^2	.184		.019		.034		.001	
	(.198*)		(.018)		(.028)		(.004)	
Δ F	2.426		1.023		1.801		.048	
	(2.537*)		(.910)		(1.430)		(.193)	

Note. *p < .05, **p <.001, Analysis without outliers within parentheses, [a] Case designation (GWI or Healthy Control), [b] PTSD level (PTSD-related symptoms from DTS total), [c] Fatigue (as designated by MFI General Fatigue); B indicates unstandardized coefficients, β indicates standardized coefficients. Abbreviations were also used. High Sch = High School, Cond. = Condition.

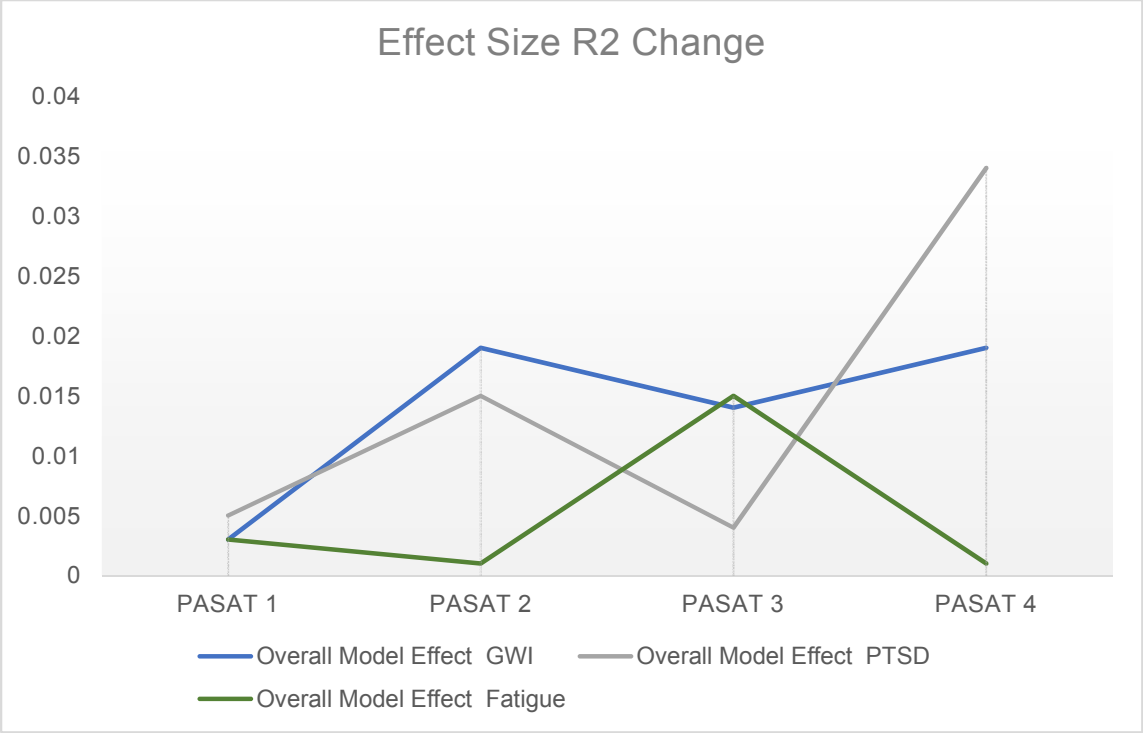

Figure 1. The change in R^2 across all four PASAT trials for GWI, PTSD and Fatigue. Health Condition or GWI appears to be more meaningful in the second and fourth trials, while PTSD only approaches a meaningful effect towards the last trial. Fatigue did not demonstrate a meaningful effect overall.

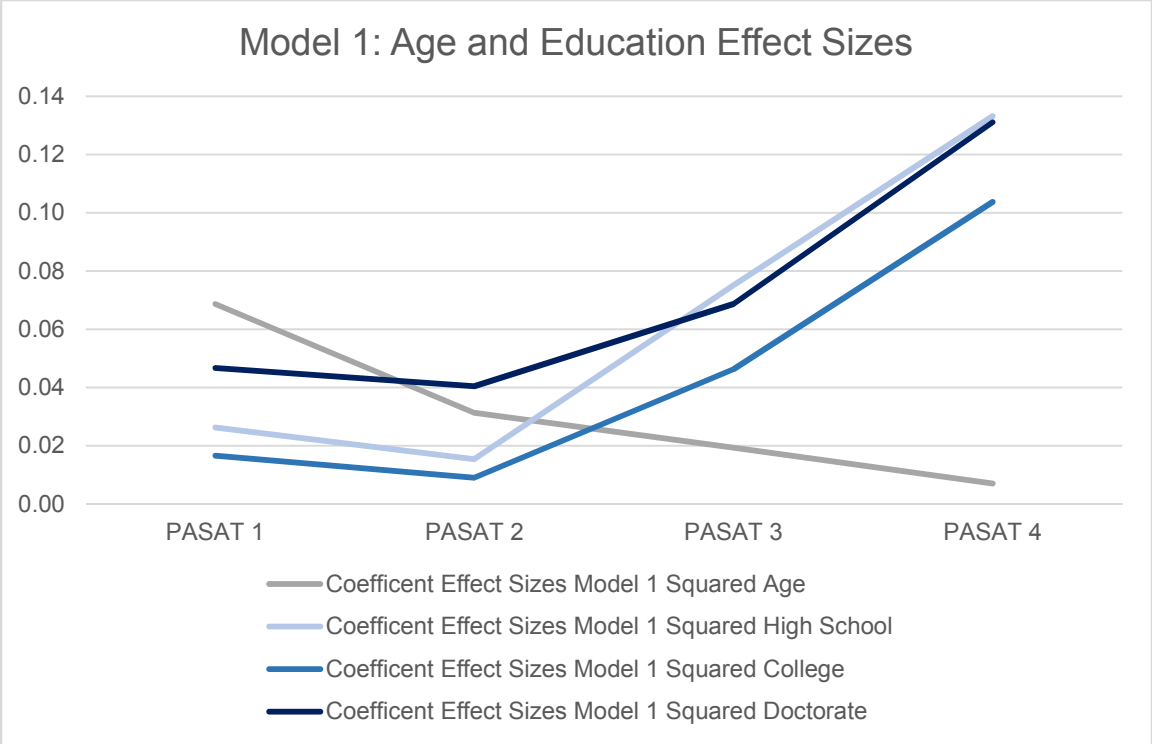

Figure 2. Coefficient effect size as plotted by each trial for Model 1 which included age and education level (high school, college, doctorate). Age showed a meaningful effect until Trial 4, which was the most demanding. Regarding education level, a doctoral level of education demonstrated a meaningful effect across all trials. A high school level of education showed a meaningful effect for all trials except Trial 2. A collegiate level of education was only meaningful within the last two trials.

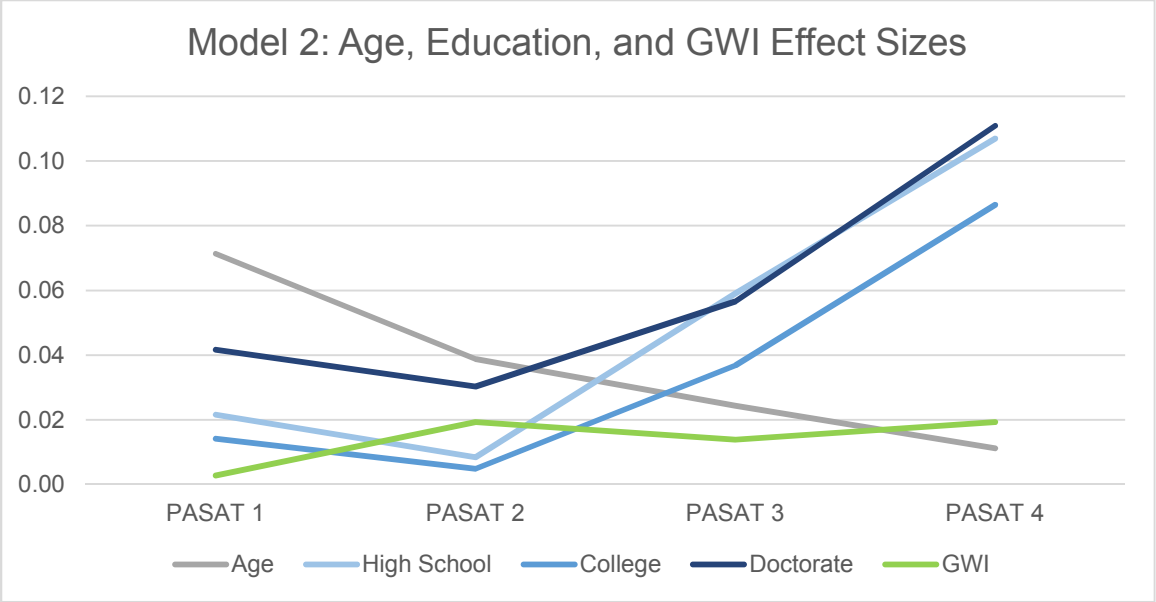

Figure 3. Coefficient effect size as plotted by each trial for Model 2 which included age, education level (high school, college, doctorate), and health condition (GWI or healthy control). As in the first model, age held a meaningful effect until the last trial. Education levels demonstrated the same patterns as in Model One. However, GWI only showed a potential meaningful effect during the second and fourth PASAT Trial.

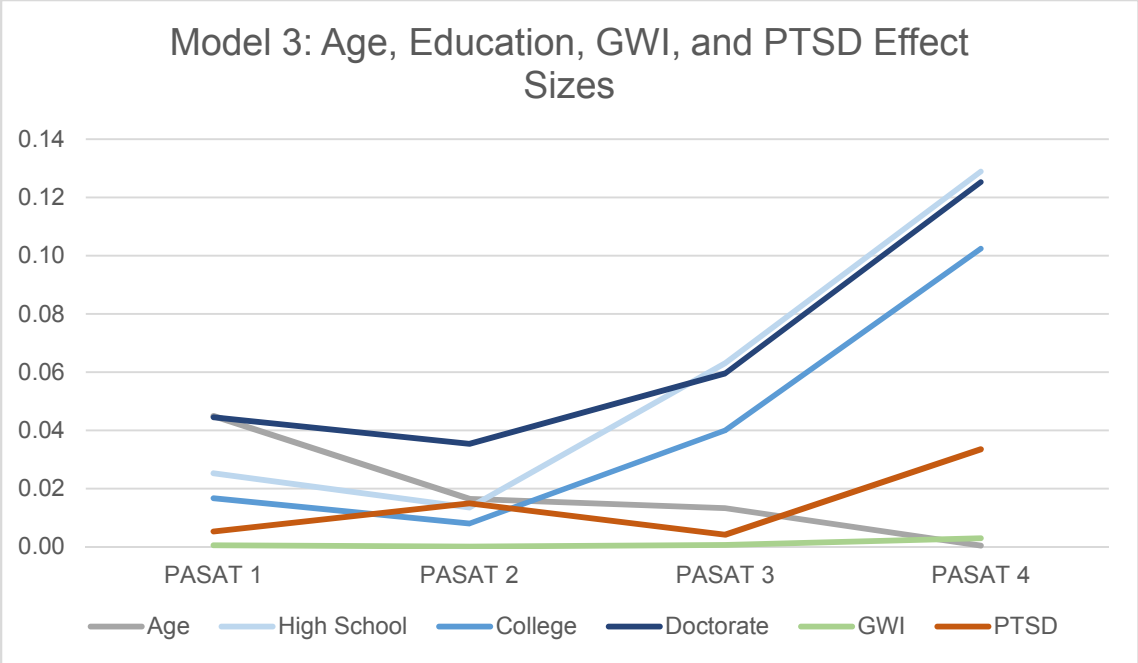

Figure 4. Coefficient effect size as plotted by each trial for Model 3 which included age, education level (high school, college, doctorate), health condition (GWI or healthy control), and PTSD symptom level. Age was only meaningful for the first trial. For education levels, high school was meaningful within all trials except Trial 2 whereas college was only meaningful during the last two trials. Doctoral level of education was meaningful across all trials. Health condition did not demonstrate a meaningful effect. Finally, PTSD only demonstrate a meaningful effect in PASAT Trial 4.

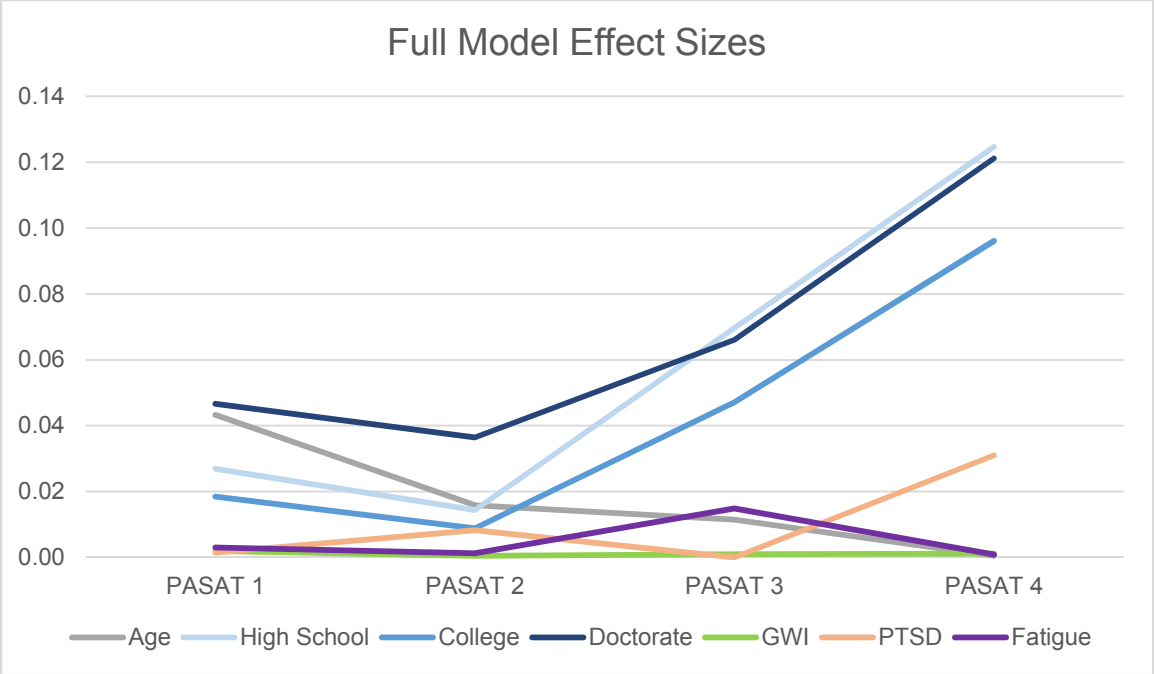

Figure 5. Coefficient effect size as plotted by each trial for the full model comprised of age, education level (high school, college, doctorate), health condition (GWI or healthy control), PTSD symptom level, and fatigue level. As in Model 3, age was only meaningful for the first trial. Education level continued to show the same trends as in Model 3. Health condition continued to not demonstrate a meaningful effect. However, PTSD continued to show a meaningful effect in Trial 4 of the PASAT. Fatigue did not produce any meaningful effects.

Fatigue Results by Condition and Cytokines

Another hierarchical regression model was used on available data (n = 57) to investigate if condition and cytokines (as measured by levels of IL-4 and IL-10) would predict how veterans reported fatigue. Fatigue, as measured by the MFI, was divided between five subscales: General Fatigue, Physical Fatigue, Mental Fatigue, Reduced Motivation, and Reduced Activity. In the second set of hierarchical regression models, all the subscales were analyzed in separate models. Predictor blocks were held constant across models: Block 1 (GWI) and Block 2 (IL-4, IL-10). Tables 11 through 19 present selected statistical information from the analyses.

General Fatigue. Models (n = 57) were designed to first evaluate condition (GWI versus healthy control) and subsequently the levels of cytokines. The overall model for

General Fatigue was significant, $R^2 = .600$, 95% CI [.454, .746], $F(3, 53) = 26.451$, $p < .001$, adjusted $R^2 = .577$. However, the addition of IL-4 and IL-10 in the second predictor block did not lead to a statistically significant incremental increase, $\Delta F(2, 53) = 1.148$, $p = .325$. $\Delta R^2 = 017$, Coefficient semi-partial correlations revealed a positive association with heath condition ($r_{sp} = .763$, 95% CI [.626, .854] $r_{sp}^2 = 0.582$) but not for separate interleukins.

Table 11
MFI General Fatigue

	Model 1		Model 2	
Variable	B	r_{sp}^2	B	r_{sp}^2
Constant	17.559		16.898	
Condition [a]	47.096**	.58	48.092**	.59
IL-4			5.449	.01
IL-10			1.381	.01
R^2	.582**		.600**	
$R^{2\ adj}$	.575**		.577**	
F	76.647**		26.451**	
ΔR^2	.582**		.017	
ΔF	76.647**		1.148	

Note. *p < .05, **p <.001, [a] Case designation (GWI or Healthy Control), B indicates unstandardized coefficients, r_{sp}^2 indicates squared semi-partial correlations

General Fatigue Reanalysis. A reanalysis was run with General Fatigue as the dependent variable on remaining data (n = 55) without outlier identified in the previous analysis. The final model including health condition and both cytokines was significantly associated with General Fatigue, $R^2 = .673$, 95% CI [.545, .801], $F(3, 51) = 35.048$, $p < .001$, adjusted $R^2 = .654$. The addition of IL-4 and IL-10 also showed a small meaningful effect in $\Delta R^2 = .049$. There were no changes in the interpretation of coefficient semi-partial correlations.

Table 12
MFI General Fatigue with and without Outliers

	Model 1		Model 2	
Variable	B	r_{sp}^2	B	r_{sp}^2
Constant	17.559(15.740**)		16.898(13.760**)	
Condition [a]	47.096**(49.289**)	.58(.62)	48.092**(52.792**)	.59(.62)
IL-4			5.449(7.938)	.01(.01)
IL-10			1.381(3.388)	.01(.01)
R^2	.582**(.625**)		.600**(.673**)	
$R^{2\ adj}$	.575**(.618**)		.577**(.654**)	
F	76.647**(88.236**)		26.451**(35.048**)	
ΔR^2	.582**(.625**)		.017(.049*)	
Δ F	76.647**(88.236**)		1.148(3.797*)	

Note. *p < .05, **p <.001,[a] Case designation (GWI or Healthy Control), B indicates unstandardized coefficients, r_{sp}^2 indicates squared semi-partial correlations

Physical Fatigue. Models (n = 56) were designed to first evaluate condition (GWI versus healthy control) and, subsequently, the levels of cytokines. The overall model for Physical Fatigue was significant, $R^2 = .599$, 95% CI [.452, .746], $F(3, 52) = 25.862$, $p < .001$, adjusted $R^2 = .576$. However, the addition of IL-4 and IL-10 in Block 2 did not show a statistically significant incremental value $\Delta F(2, 52) = 2.387$, $p = .102$, $\Delta R^2 = .037$. However, the change did point towards a small effect. Coefficient semi-partial correlations within the full model showed a large effect size associated with health status ($r_{sp} = .765$, 95% CI [.629, .856]; $r_{sp}^2 = 0.585$) indicating that veterans with GWI endorse higher levels of Physical Fatigue over healthy controls; however, IL-4 ($r_{sp} = .094$, 95% CI [-.173, .348]; $r_{sp}^2 = 0.009$) and IL-10 ($r_{sp} = .119$, 95% CI [-.149, .370, .546]; $r_{sp}^2 = 0.014$) did not demonstrate a meaningful effect.

Table 13
MFI Physical Fatigue

	Model 1		Model 2	
Variable	B	r_{sp}^2	B	r_{sp}^2
Constant	13.117		11.763	
Condition [a]	47.227**	.56	49.030**	.59
IL-4			6.212	.01
IL-10			2.676	.01
R^2	.562**		.599**	
$R^{2\ adj}$	.554**		.576**	
F	69.255**		25.862**	
ΔR^2	.562**		.037	
ΔF	69.255**		2.387	

Note. *p < .05, **p <.001, [a] Case designation (GWI or Healthy Control), B indicates unstandardized coefficients, r_{sp}^2 indicates squared semi-partial correlations

Physical Fatigue Reanalysis. A reanalysis also run for Physical Fatigue without outliers on remaining data (n = 54). The final model including health condition and both cytokines was significantly associated with Physical Fatigue, $R^2 = .677$, 95% CI [.549, .805], $F(2, 50) = 34.969$, $p < .001$, adjusted $R^2 = .658$. The addition of IL-4 and IL-10 also showed a small meaningful effect in $\Delta R^2 = .088$. Additionally, coefficient semi-partial correlations changed as IL-10 showed a small positive association without outliers ($r_{sp} = .211$, 95% CI [-.060, .453]; $r_{sp}^2 = 0.04$).

Table 14
MFI Physical Fatigue with and without Outliers

	Model 1		Model 2	
Variable	B	r_{sp}^2	B	r_{sp}^2
Constant	13.117*(11.698*)		11.763(7.704*)	
Condition [a]	47.227**(49.164**)	.56 (.58)	49.030**(55.256**)	.59(.65)
IL-4			6.212(5.607)	.01(.01)
IL-10			2.676(6.555*)	.01(.04)
R^2	.562**(.590**)		.599**(.677**)	
$R^{2\ adj}$	.554**(.582**)		.576**(.658*)	
F	69.255**(74.694**)		25.862**(34.696**)	
ΔR^2	.562**(.590**)		.037(.088*)	
ΔF	69.255**(76.694**)		2.387(6.790*)	

Note. *p < .05, **p <.001,[a] Case designation (GWI or Healthy Control), B indicates unstandardized coefficients, r_{sp}^2 indicates squared semi-partial correlations

Mental Fatigue. The full model (n= 58) was significant, $R^2 = .532$, 95% CI [.372, .692], $F(3, 54) = 20.425$, $p < .001$, adjusted $R^2 = .506$. The addition of interleukins in the

second predictor block did not return significance, Δ F(2, 54) = 1.634, p = .205, Δ R^2= .028. However, there was a small effect. Semi-partial correlations from the full model returned a large effect size concerning health status (r_{sp} = .683, 95% CI [.516, .800]; r_{sp}^2 =0.466) with a positive association between GWI and increased Mental Fatigue scores. Additionally, there was a small and positive effect shown in IL-4 (r_{sp} = .158, 95% CI [-.105, .400]; r_{sp}^2 =0.025). IL-10 (r_{sp} = -.113, 95% CI [-.361, .150]; r_{sp}^2 =0.013) did not demonstrate a meaningful effect.

Table 15
MFI Mental Fatigue

	Model 1		Model 2	
Variable	B	r_{sp}^2	B	r_{sp}^2
Constant	15.476		17.266	
Condition [a]	49.246**	.50	48.201**	.47
IL-4			11.703	.02
IL-10			-2.834	.01
R^2	.503**		.532**	
$R^{2\ adj}$	.494**		.506**	
F	56.725**		20.425**	
Δ R^2	.503**		.028	
Δ F	56.725**		1.634	

Note. *p < .05, **p <.001, [a] Case designation (GWI or Healthy Control), B indicates unstandardized coefficients, r_{sp}^2 indicates squared semi-partial correlations

Mental Fatigue Reanalysis. A reanalysis also run for Mental Fatigue without outliers on remaining data (n = 56). The final model including health condition and both cytokines was significantly associated with Mental Fatigue, R^2 = .567, 95% CI [.412, .722] F(3, 52) = 22.708, p < .001, adjusted R^2 = .524. The addition of IL-4 and IL-10 continued to evidence a small meaningful effect in ΔR^2= .033. Coefficient semi-partial correlation interpretation remained the same.

Table 16
MFI Mental Fatigue with and without Outliers

	Model 1		Model 2	
Variable	B	r_{sp}^2	B	r_{sp}^2
Constant	15.476(14.197)		17.266(15.039)	
Condition [a]	49.246**(51.607**)	.50(.53)	48.201**(51.241**)	.47(.47)
IL-4			11.703(14.613*)	.02(.03)
IL-10			-2.834(-1.940)	.01(.00)
R^2	.503**(.535**)		.532**(.567**)	
$R^{2\ adj}$	.494**(.526**)		.506**(.542**)	
F	56.725**(62.028**)		20.425**(22.708**)	
ΔR^2	.503**(.535**)		.028(.033)	
Δ F	56.725**		1.634(1.053)	

Note. *p < .05, **p <.001, [a] Case designation (GWI or Healthy Control), B indicates unstandardized coefficients, r_{sp}^2 indicates squared semi-partial correlations

Reduced Activity. The full model (n = 56) was significant, R^2 = .491, 95% CI [.322, .660], F(2, 52) = 16.752, p < .001, adjusted R^2 = .462. The second block, with the addition of cytokines, was nonsignificant, Δ F(3, 52) = .104, p = .901, ΔR^2 = .002. Partial correlation analysis showed a large effect size for condition with a positive association (r_{sp} = .700, 95% CI [.536, .813]; r_{sp}^2 =0.49) indicating that veterans with GWI endorse higher levels of reduced activity. No other meaningful effects were identified.

Table 17
MFI Reduced Activity

	Model 1		Model 2	
Variable	B	r_{sp}^2	B	r_{sp}^2
Constant	14.583		13.919	
Condition [a]	39.732**	.49	40.657**	.45
IL-4			-.890	.00
IL-10			1.230	.00
R^2	.489**		.491**	
$R^{2\ adj}$	.480**		.462**	
F	51.765**		16.752**	
ΔR^2	.489**		.002	
Δ F	51.765**		.104	

Note. *p < .05, **p <.001, [a] Case designation (GWI or Healthy Control), B indicates unstandardized coefficients, r_{sp}^2 indicates squared semi-partial correlations

Reduced Activity Reanalysis. A reanalysis was conducted with Reduced Activity without outliers on available data (n = 55). The final model including health condition and both cytokines was significantly associated with Reduced Activity, R^2 =

.542, 95% [.381, .703] F(3, 51) = 20.081, p < .001, adjusted R^2 = .515. The addition of IL-4 and IL-10 continued to not provide any meaningful effect, ΔR^2= .008. The interpretation of coefficient semi-partial correlations did not change.

Table 18
MFI Reduced Activity with and without Outliers

	Model 1		Model 2	
Variable	B	r_{sp}^2	B	r_{sp}^2
Constant	14.583(12.808)		13.919(12.345)	
Condition [a]	39.732**(41.507**)	.49(.53)	40.657**(42.43**)	.45(.49)
IL-4			-.890(3.899)	.00(.00)
IL-10			1.230(.736)	.00(.00)
R^2	.489**(.534**)		.491**(.542**)	
$R^{2\ adj}$	.480**(.525**)		.462**(.515**)	
F	51.765**(60.708**)		16.752**(20.081**)	
ΔR^2	.489**(.534**)		.002(.008)	
Δ F	51.765**(60.708**)		.104(.426)	

Note. *p < .05, **p <.001, [a] Case designation (GWI or Healthy Control), B indicates unstandardized coefficients, r_{sp}^2 indicates squared semi-partial correlations

Reduced Motivation. The final model (n= 57) was statistically significant, R^2 = .502, 95% CI [.336, .668], F(3, 53) = 17.818, p < .001, adjusted R^2 = .474. The addition of the interleukin variables did not return a significant change or had an effect of meaningful magnitude, Δ F(2, 53) = .469, p = .628, ΔR^2= .009. Coefficient analysis revealed a large effect size regarding condition status (r_{sp} = .702, 95% CI [.540, .814]; r_{sp}^2 =0.493) indicating that GWI diagnosis is positively associated with higher levels of Reduced Motivation. No other correlations were notable.

Table 19
MFI Reduced Motivation

	Model 1		Model 2	
Variable	B	r_{sp}^2	B	r_{sp}^2
Constant	11.728		12.892	
Condition [a]	41.466**	.49	40.390**	.45
IL-4			2.055	.00
IL-10			-1.986	.01
R^2	.493**		.502**	
$R^{2\ adj}$	.484**		.474**	
F	53.552**		17.818**	
ΔR^2	.493**		.009	
Δ F	53.552**		.469	

Note. *p < .05, **p <.001, [a] Case designation (GWI or Healthy Control), B indicates unstandardized coefficients, r_{sp}^2 indicates squared semi-partial correlations

Reduced Motivation Reanalysis. The final model (n =55) analyzed without outliers and comprised of condition status followed by cytokines (i.e., IL-10, IL-4) on the prediction of self-report of Reduced Motivation was statistically significant, $R^2 = .550$, 95% CI [.391, .709], $F(3, 51) = 20.789$, $p < .001$, adjusted $R^2 = .524$. The addition of the interleukin variables did not return a significant change or had meaning, $\Delta R^2 = .003$, $F(2, 51) = .192$, $p = .826$. Coefficient analysis revealed a large effect size regarding condition status ($r_{sp} = .707$, 95% CI [.544, .819]; $r_{sp}^2 = 0.50$) which was positively associated with Reduced Motivation. The interleukin variables did not produce a meaningful effect.

Table 20
MFI Reduced Motivation with and without Outliers

	Model 1		Model 2	
Variable	B	r_{sp}^2	B	r_{sp}^2
Constant	11.728(10.416)		12.892(9.745)	
Condition [a]	41.466**(44.181**)	.49(.54)	40.390**(45.248**)	.45(.54)
IL-4			2.055(1.293)	.00(.00)
IL-10			-1.986(1.122)	.01(.00)
R^2	.493**(.547**)		.502**(.550)	
$R^{2\ adj}$	.484**(.538**)		.474**(.524)	
F	53.552**(63.961**)		17.818**(20.789**)	
ΔR^2	.493**(.547**)		.009(.003)	
Δ F	53.552**(63.961**)		.469(.192)	

Note. *p < .05, **p <.001, [a] Case designation (GWI or Healthy Control), B indicates unstandardized coefficients, r_{sp}^2 indicates squared semi-partial correlations

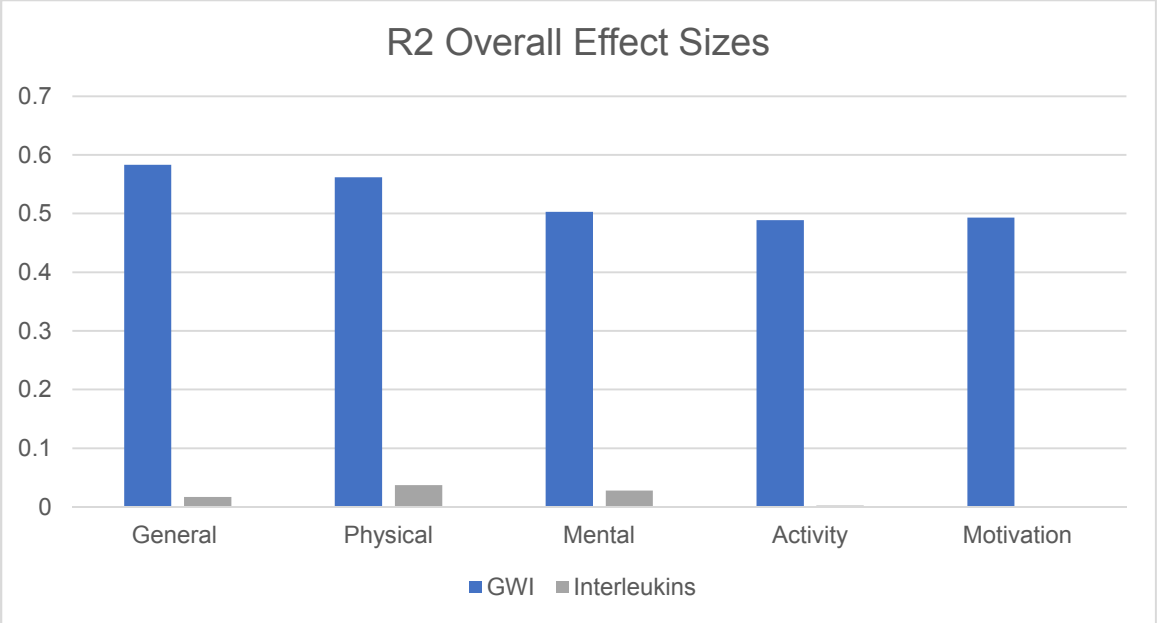

Figure 6. This bar chart demonstrates the R^2 or change as a measure of effect size. While GWI status had a meaningful effect within all fatigue domains, interleukins did not show a meaningful effect.

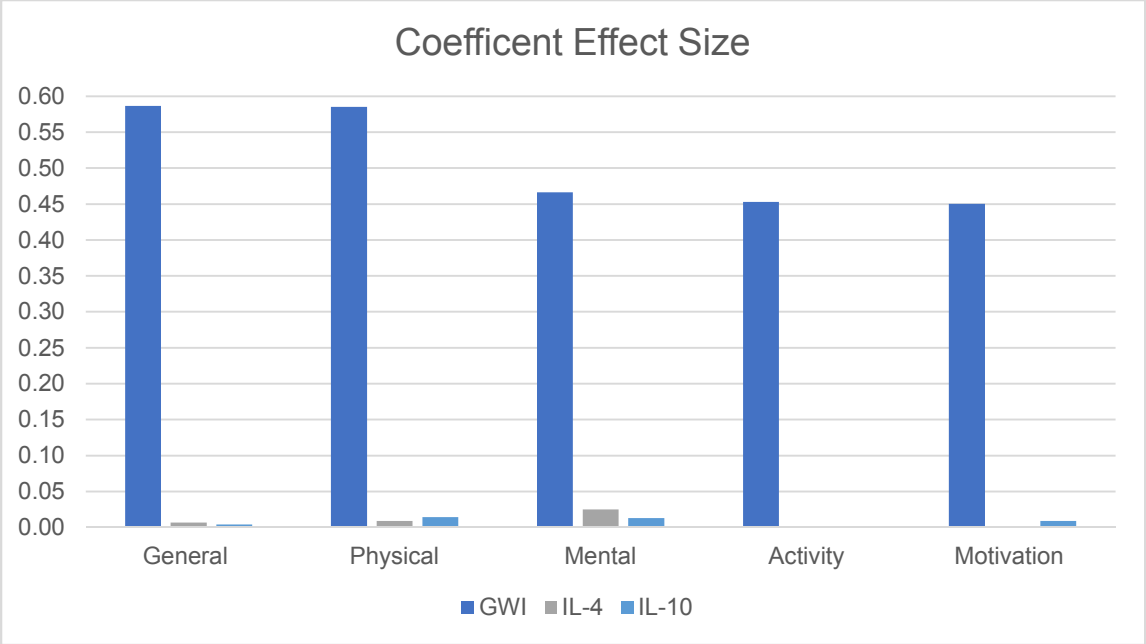

Figure 7. This bar chart demonstrates semi-partial squared effect sizes for each coefficient. As with the overall model, GWI was the most powerful predictor of reporting different areas of fatigue. Cytokines were less influential, with interleukin 4 showing a small but meaningful impact in Mental Fatigue.

Summary of the A Priori Results

Overall, the first analysis of the first hypothesis investigating the impact of GWI versus healthy control, PTSD, and fatigue over age and education on the PASAT, did not demonstrate significant results overall. In general, age and education demonstrated virtually consistent effects on across the PASAT trials. The diagnosis of GWI was approaching a meaningful effect in later trials, particularly Trials 2 and 4. Finally, trauma did demonstrate a meaningful effect within the last trial of the PASAT. However, the addition of fatigue was not contributing to the model in a meaningful way. This finding is consistent with Johnson, Lange, DeLuca, Korn and Natelson (1997) who found that individuals with diagnoses associated with higher levels of fatigue including chronic fatigue syndrome, was not significantly differ in comparison to healthy controls.

Additionally, results for the second analysis testing fatigue levels by health

condition (GWI versus healthy control) and interleukins IL-4 and IL-10 found that GWI status was the most consistent variable associated with higher levels of self-reported fatigue levels. In regard to interleukins, results were inconsistent showing possibly trends towards elevated IL-10 with physical fatigue and elevated IL-4 with increased mental fatigue; therefore, it was consistent with Broderick et al. (2017) that found varied results. Nevertheless, it did not indicate a clear pattern.

To further investigate possible contributions to PASAT scores, the researcher conducted a post analysis for PASAT trials. Results concerning the MFI was more varied and was associated with changes in interleukin 4 (IL-4), interleukin 12 (IL-12), and IL-10. GWI, particularly in models of higher stress, has been associated with changes in pro-inflammatory markers (Broderick et al., 2011; Symlie et al. 2013; Whistler et al., 2009). Additionally, PTSD has been associated with inflammation and inflammatory mediators (Wang & Young, 2016). A correlation between variables of interest and available cytokines was conducted to investigate possible associations with PASAT scores. Correlations returned significance for cytokines with PASAT performance including tumor necrosis factor alpha (TNFα PASAT Trial 3 r = -.377) and interferon gamma (INFγ PASAT Trial 2 r = -.357; PASAT Trial 3 r = -.359; PASAT Trial 4 r = -.342). An additional analysis was run to include interleukin 6 (IL-6: PASAT Trial 3 r = -.37) and interleukin 8 (IL-8: Trial 3 r = -.43; Trial 4 r =-.38). Therefore, the researcher investigated a model that removed fatigue as a variable and adding cytokines within the hierarchical analysis. Therefore, the model was designed to investigate health condition (GWI versus healthy control), cytokines (TNFα, INFγ followed by IL-6 and IL-8) and PTSD symptoms predicted performance on the PASAT while controlling for age and

education.

Post-hoc Analyses

Correlation. Correlations were run on all variables of interest including demographic variables, PASAT Trials, MFI scores, and available cytokines on available data to investigate any possible associations cytokines have on PASAT scores (n = 34). Correlations are reported in the appendices.

PASAT Results by Condition, TNFα/INFγ, and PTSD Symptoms

Another hierarchical regression model was utilized to investigate if condition (GWI status), cytokines (i.e., TNFα and/or INFγ), and PTSD symptoms would predict how veterans performed on a measure of working memory and attention (PASAT) over and above demographic factors. Predictor blocks were held constant across models: Block 1 (Age and Education), Block 2(GWI), Block 3 (TNFα, INFγ,) and Block 4 (PTSD symptoms). Tables 22 through 28 present selected statistical information from the analyses.

PASAT Trial 1. Regression models were used on available data (n = 48) to test if GWI status, TNFα and/or INFγ, and PTSD symptoms. The full model for PASAT Trial 1 was nonsignificant, $R^2 = .257$, 95% CI [.089, .425], $F(8, 39) = 1.683$, $p = .134$, adjusted $R^2 = .104$. The first predictor block including age and education had a medium effect and approached significance, $R^2 = .164$, $F(4, 43) = 2.104$, $p = .097$, adjusted $R^2 = .086$. The addition of condition did not contribute significantly by means of incremental variance, $\Delta F(1, 42) = .393$, $p = .534$, $\Delta R^2 = .008$. Next, the addition of cytokines did not produce significant incremental variance but had a small effect, $\Delta F(2, 40) = 2.277$, $p = .116$, $\Delta R^2 = .085$. Finally, the addition of PTSD symptoms did not add incremental variance,

$\Delta F(1, 39) = .028$, $p = .867$, $\Delta R^2 = .001$. In the final model, squared semi-partial correlations showed a negative association and small effect with age ($r_{sp} = -.227$, 95% CI [-.480, .061]; $r_{sp}^2 = 0.05$). Positive associations and a small effect were produced regarding education at the high school level ($r_{sp} = .158$, 95% CI [-.132, .423]; $r_{sp}^2 = 0.02$), collegiate level ($r_{sp} = .148$, 95% CI [-.142, .415]; $r_{sp}^2 = 0.02$), and the doctoral level ($r_{sp} = .224$, 95% CI [-.064, .478]; $r_{sp}^2 = 0.05$). Furthermore, the cytokines also showed a negative association with a small effect size in INFγ ($r_{sp} = -.18$, 95% CI [-.442, .110]; $r_{sp}^2 = 0.03$) and TNFα ($r_{sp} = -.20$, 95% CI [-.458, .089]; $r_{sp}^2 = 0.04$).

Table 21
PASAT Trial 1Post Hoc

	Model 1		Model 2		Model 3		Model 4	
Variable	B	r_{sp}^2	B	r_{sp}^2	B	r_{sp}^2	B	r_{sp}^2
Constant	50.95		54.37		51.28		49.76	
Age	-.66	.07	-.68	.06	-.67	.07	-.64	.05
Edu. Level								
High School	14.6	.02	12.99	.02	15.14	.02	15.64	.02
Collegiate	12.27	.02	11.01	.01	13.87	.02	14.20	.02
Doctoral	20.98	.05	19.55	.04	22.08	.05	22.34	.05
Condition [a]			-2.36	.01	-1.44	.00	-.66	.00
INFγ					-4.35	.04	-4.23	.03
TNFα					-2.37	.04	-2.34	.04
PTSD Level [b]							-.012	.00
R^2	.164		.171		.256		.257	
$R^{2\ adj}$	.086		.073		.126		.104	
F	2.104		1.738		1.968		1.683	
ΔR^2	.164		.008		.085		.001	
ΔF	2.104		.393		2.277		.028	

Note. *p < .05, **p <.001, [a] Case designation (GWI or Healthy Control), [b] PTSD level (PTSD-related symptoms from DTS total); B indicates unstandardized coefficients, r_{sp}^2 indicates squared semi-partial correlations

PASAT Trial 1 Reanalysis without Outliers. Assumption testing of the data revealed two potential outliers which were excluded for the following analysis (n = 46). The analysis interpretation did not change with the full model for PASAT 1 as it remained nonsignificant (see Table 22 for comparison values). However, the effect sizes for model one ($R^2 = .159$) remained a medium effect; model three also remained non-

significant with a small effect ($\Delta R^2 = .091$). Coefficients as reported with the squared semi-partial correlations did not produce a notable change in values and were interpreted in the same manner.

PASAT Trial 1 Reanalysis with Recoding. PASAT data was reanalyzed to include the participant with elementary level education (n =1) by combining his data with other participants with a high school education. There were no major changes to data with the exception of high school education level having a nonmeaningful effect score which was previously a small effect size in both the original data ($r_{sp}^2 = 0.02$) and data without outliers ($r_{sp}^2 = 0.02$).

Table 22
PASAT Trial 1 with and without Outliers Post Hoc

	Model 1		Model 2		Model 3		Model 4	
Variable	B	r_{sp}^2	B	r_{sp}^2	B	r_{sp}^2	B	r_{sp}^2
Constant	50.95		54.37		51.28		49.76	
	(50.58)		(53.84)		(49.46)		(48.4)	
Age	-.66	.07	-.68	.06	-.67	.07	-.64	.05
	(-.65)	(.07)	(-.67)	(.07)	(-.62)	(.06)	(-.6)	(.04)
Education								
High Sch	14.6	.02	12.99	.02	15.14	.02	15.64	.02
	(14.84)	(.02)	(13.13)	(.02)	(15.02)	(.02)	(15.37)	(.02)
College	12.27	.02	11.01	.01	13.87	.02	14.20	.02
	(12.3)	(.02)	(10.96)	(.01)	(14)	(.02)	(14.24)	(.02)
Doctoral	20.98	.05	19.55	.04	22.08	.05	22.34	.05
	(21.01)	(.05)	(19.49)	(.04)	(22.14)	(.05)	(22.33)	(.05)
Cond. [a]			-2.36	.01	-1.44	.00	-.66	.00
			(-2.57)	(.01)	(-1.83)	(.00)	(-1.27)	(.00)
INFγ					-4.35	.04	-4.23	.03
					(-4.75)	(.04)	(-4.65)	(.04)
TNFα					-2.37	.04	-2.34	.04
					(-2.43)	(.04)	(-2.41)	(.04)
PTSD[b]							-.012	.00
							(-.009)	(.00)
R^2	.164		.171		.256		.257	
	(.159)		(.168)		(.259)		(.259)	
$R^{2\ adj}$	.086		.073		.126		.104	
	(.077)		(.064)		(.122)		(.099)	
F	2.104		1.738		1.968		1.683	
	(1.943)		(1.618)		(1.896)		(1.617)	
Δ R^2	.164		.008		.085		.001	
	(.159)		(.009)		(.091)		(.000)	
Δ F	2.104		.393		2.277		.028	
	(1.943)		(.428)		(2.321)		(.013)	

Note. *p < .05, **p <.001, Analysis without outliers within parentheses, [a] Case designation (GWI or Healthy Control), [b] PTSD level (PTSD-related symptoms from DTS total), [c] Fatigue (as designated by MFI General Fatigue); B indicates unstandardized coefficients, r_{sp}^2 indicates squared semi-partial correlations Abbreviations were also used. High Sch = High School, Cond. = Condition.

PASAT Trial 2. The full model (n = 48) for PASAT Trial 2 was nonsignificant, R^2 = .273, 95% CI[.104, .442], F(8, 39) = 1.833, p = .1, adjusted R^2 = .124. The first predictor block with age and education demonstrated a medium effect but was nonsignificant, R^2 = .135, F(4, 43) = 1.679, p = .172, adjusted R^2 = .055. The addition of condition did not produce significant incremental variance, ΔF(1, 42) = 1.361, p = .250, Δ R^2= .027; however, there was a small effect. Next, Block 3 with the addition of cytokines showed a small effect but was also nonsignificant, ΔF(2, 40) = 2.956 p = .064,

ΔR^2= .108. Finally, the addition of PTSD symptoms did not produce incremental variance, $\Delta F(1, 39) = .170$, $p = .682$, ΔR^2= .003. In the final model, squared semi-partial correlations revealed a negative association and small effect in age (r_{sp} = -.162, 95% CI [-.427, .128]; r_{sp}^2 =0.03). Positive associations and a small effect were produced regarding education at the doctoral level (r_{sp} = .197, 95% CI [-.092, .456]; r_{sp}^2 =0.04). All other levels of education did not indicate a meaningful effect. The cytokines showed a negative association with a small effect size in INFγ (r_{sp} = -.169, 95% CI [-.432, .121]; r_{sp}^2 =0.03) and TNFα (r_{sp} = -.246, 95% CI [-.496, .041]; r_{sp}^2 =0.06). GWI and PTSD did not produce meaningful effects.

Table 23
PASAT Trial 2 Post Hoc

	Model 1		Model 2		Model 3		Model 4	
Variable	B	r_{sp}^2	B	r_{sp}^2	B	r_{sp}^2	B	r_{sp}^2
Constant	44.72		50.38		47.51		44.26	
Age	-.44	.04	-.48	.05	-.47	.04	-.4	.03
Edu. Level								
High School	9.16	.01	6.51	.01	8.63	.01	9.7	.01
Collegiate	7.39	.01	5.29	.00	7.99	.01	8.69	.01
Doctoral	16.79	.04	14.42	.03	16.81	.04	17.38	.04
Condition [a]			-3.91	.03	-3.15	.02	-1.48	.00
INFγ					-3.79	.03	-3.52	.03
TNFα					-2.61	.06	-2.55	.06
PTSD Level [b]							-.03	.00
R^2	.135		.162		.270		.273	
$R^{2\ adj}$	.055		.063		.142		.124	
F	1.679		1.627		2.115		1.833	
ΔR^2	.135		.027		.108		.003	
Δ F	1.679		1.361		2.956		.170	

Note. *p < .05, **p <.001, [a] Case designation (GWI or Healthy Control), [b] PTSD level (PTSD-related symptoms from DTS total); B indicates unstandardized coefficients, r_{sp}^2 indicates squared semi-partial correlations

PASAT Trial 2 Reanalysis without Outliers. The overall model of age, education, condition, cytokines, and PTSD symptoms (n = 46) did not significantly predict changes on the second trial of the PASAT when analyzed without outliers, R^2 = .273, 95% CI [.102, .444] $F(8, 37) = 1.739$, $p = .122$, adjusted R^2 = .116. However, the

first model ($R^2 = .135$) with age and education continued to hold a medium effect size overall. In addition, the second model ($\Delta R^2 = .027$) had the same small effect with the addition of health condition. The third model demonstrated a small effect overall ($\Delta R^2 = .103$). The fourth model, with the PTSD as a covariate, was not significant. The interpretations of covariates remained the same.

PASAT Trial 2 Reanalysis with Recoding. Reanalysis with the original data returned a significant effect with Model 3 ($p = .044$) with age, education, health condition, and cytokines, which was previously not significant. Additionally, Model 1 and Model 1 ΔR^2 with age and education had a small effect ($R^2 = .123$) which was previously a medium effect size ($R^2 = .135$). Without outliers, there were similar results in that the Model 3 p value was significant ($p = .055$). Model 1 and Model 1 ΔR^2 had a small effect (.128) rather than medium effect (.142).

Table 24
PASAT Trial 2 with and without Outliers Post Hoc

	Model 1		Model 2		Model 3		Model 4	
Variable	B	r_{sp}^2	B	r_{sp}^2	B	r_{sp}^2	B	r_{sp}^2
Constant	44.72		50.38		47.51		44.26	
	(45.84)		(50.81)		(46.96)		(44.44)	
Age	-.44	.04	-.48	.05	-.47	.04	-.4	.03
	(-.47)	(.04)	(-.49)	(.05)	(-.45)	(.04)	(-.4)	(.03)
Education								
High Sch	9.16	.01	6.51	.01	8.63	.01	9.7	.01
	(9.77)	(.01)	(7.17)	(.01)	(8.93)	(.01)	(9.8)	(.01)
College	7.39	.01	5.29	.00	7.99	.01	8.69	.01
	(7.3)	(.01)	(5.25)	(.00)	(7.95)	(.01)	(8.51)	(.01)
Doctoral	16.79	.04	14.42	.03	16.81	.04	17.38	.04
	(16.7)	(.04)	(14.38)	(.03)	(16.75)	(.04)	(17.21)	(.04)
Cond. [a]			-3.91	.03	-3.15	.02	-1.48	.00
			(-3.93)	(.03)	(-3.37)	(.02)	(-2.03)	(.00)
INFγ					-3.79	.03	-3.52	.03
					(-3.9)	(.04)	(-3.67)	(.03)
TNFα					-2.61	.06	-2.55	.06
					(-2.55)	(.06)	(-2.5)	(.06)
PTSD							-.03	.00
Level [b]							(-.02)	(.00)
R^2	.135		.162		.270		.273	
	(.142)		(.168)		(.271)		(.273)	
$R^{2\ adj}$	.055		.063		.142		.124	
	(.058)		(.064)		(.137)		(.116)	
F	1.679		1.627		2.115		1.833	
	(1.694)		(1.62)		(2.021)		(1.739)	
Δ R^2	.135		.027		.108		.003	
	(.142)		(.027)		(.103)		(.002)	
Δ F	1.679		1.361		2.956		.170	
	(1.694)		(1.275)		(2.685)		(.099)	

Note. *p < .05, **p <.001, Analysis without outliers within parentheses, [a] Case designation (GWI or Healthy Control), [b] PTSD level (PTSD-related symptoms from DTS total), [c] Fatigue (as designated by MFI General Fatigue); B indicates unstandardized coefficients, r_{sp}^2 indicates squared semi-partial correlations Abbreviations were also used. High Sch = High School, Cond. = Condition.

PASAT Trial 3 Analysis. The full model (n = 48) for PASAT Trial 3 was nonsignificant, R^2 = .291, 95% CI [.120, .462], F(8, 39) = 2.004, p = .072, adjusted R^2 = .146. The first predictor block (i.e., age and education) produced a medium effect; however, the model was nonsignificant, R^2 = .146, F(4, 43) = 1.834, p = .140, adjusted R^2 = .066. The addition of condition did not indicate incremental variance, ΔF(1, 42) = 1.288, p = .263, Δ R^2= .025; however, a small effect was observed. The third block with

the addition of cytokines showed a statistically significant increase in variance with a small effect $\Delta F(2, 40) = 3.391$, $p = .044$, $\Delta R^2 = .120$. Finally, the addition of PTSD symptoms did not produce incremental variance, $\Delta F(1, 39) = .001$, $p = .979$, $\Delta R^2 = .000$. Squared semi-partial correlations were interpreted for the full model. Age was negatively associated with scores and had a small effect ($r_{sp} = -.165$, 95% CI [-.429, .125]; $r_{sp}^2 = 0.03$). Positive associations and a small effect were produced regarding education at the high school level ($r_{sp} = .234$, 95% CI [-.054, .486]; $r_{sp}^2 = 0.05$), at the collegiate level ($r_{sp} = .205$, 95% CI [-.084, .462]; $r_{sp}^2 = 0.04$), and at the doctoral level ($r_{sp} = .246$, 95% CI [-.041, .496]; $r_{sp}^2 = 0.04$). The cytokines showed a negative association with scores and a small effect size, INFγ ($r_{sp} = -.149$, 95% CI [-.416, .141]; $r_{sp}^2 = 0.02$) and TNFα ($r_{sp} = -.294$, 95% CI [-.534, -.011]; $r_{sp}^2 = 0.09$). GWI and PTSD continued to not produce meaningful effects.

Table 25
PASAT Trial 3 Post Hoc

	Model 1		Model 2		Model 3		Model 4	
Variable	B	r_{sp}^2	B	r_{sp}^2	B	r_{sp}^2	B	r_{sp}^2
Constant	28.68		33.39		31.11		30.94	
Age	-.33	.03	-.37	.04	-.36	.04	-.35	.03
Edu. Level								
High School	17.85	.06	15.65	.05	17.51	.06	17.57	.05
Collegiate	14.44	.04	12.69	.03	14.89	.04	14.93	.04
Doctoral	18.62	.06	16.64	.05	18.61	.06	18.64	.06
Condition [a]			-3.25	.03	-2.77	.02	-2.68	.01
INFγ					-2.68	.02	-2.67	.02
TNFα					-2.63	.09	-2.63	.09
PTSD Level [b]							-.001	.02
R^2	.146		.171		.291		.291	
$R^{2\ adj}$	.066		.073		.167		.146	
F	1.834		1.735		2.349		2.004	
ΔR^2	.146		.025		.120		.000	
ΔF	1.834		1.288		3.391		.001	

Note. *p < .05, **p <.001, [a] Case designation (GWI or Healthy Control), [b] PTSD level (PTSD-related symptoms from DTS total), [c] Fatigue (as designated by MFI General Fatigue); B indicates unstandardized coefficients, β indicates standardized coefficients, r_{sp}^2 indicates squared semi-partial correlations

PASAT Trial 3 Reanalysis without Outliers. The full model for PASAT Trial 3 (n = 46) remained non-significant without outliers, $R^2 = .306$, 95% CI [.133, .479], F(8, 37) = 2.042, p = .068, adjusted $R^2 = .156$. However, there was a meaningful effect in the first three models as before. The first model had a medium effect size ($R^2 = .151$) with all parameters of the model (i.e., age and level of education) demonstrating a small effect (i.e., at or above .02). The second model also had a small meaningful effect ($\Delta R^2 = .031$) with parameters of a small effect across age, education, and condition. Lastly, the third model retained its small effect ($\Delta R^2 = .123$) as well as all the included coefficients of age, educational level, health condition, and cytokines. The fourth model continued to demonstrate no significant or meaningful effect. Additionally, coefficients did not change in their interpretation.

PASAT Trial 3 Reanalysis with Recoding. Model 1 R^2, Model 1 ΔR^2, Model 2 R^2 returned a small effect (Model 1 $R^2/\Delta R^2 = .084$, Model 2 $R^2 = .125$) which was interpreted as a medium effect beforehand (Model 1 $R^2/\Delta R^2 = .146$, Model 2 $R^2 = .171$). Furthermore, Model 3 R^2 and Model 4 R^2 returned a medium effect (Model 3 $R^2 = .234$, Model 4 $R^2 = .237$) which was previously a large effect size (Model 3 $R^2 = .291$, Model 4 $R^2 = .291$). For the final model semi-partial correlates, reanalysis showed differences in high school level of education (non-significant, previously $r_{sp}^2 = .05$), doctoral level of education (non-significant, previously $r_{sp}^2 = .06$), health condition ($r_{sp}^2 = .02$, previously non-significant), and PTSD symptoms (non-significant, previously $r_{sp}^2 = .02$).

Analysis without outliers produced similar results in that Model 1 R^2, Model 1 ΔR^2, returned a small effect (Model 1 $R^2/\Delta R^2 = .084$) which previously a medium effect (.151). Additionally, Model 3 R^2 and Model 4 R^2 had medium effect sizes (Model 3 R^2 =

.247, Model 4 R^2 = .252) which was previously large (Model 3 R^2 = .306, Model 4 R^2 = .306). Lastly, semi-partial correlation effect sizes revealed changes in high school educational levels (non-significant, previously r_{sp}^2 = .05), doctoral education levels (non-significant, previously r_{sp}^2 = .06), and health condition (r_{sp}^2 = .03, previously non-significant).

Table 26
PASAT Trial 3 with and without Outliers Post Hoc

	Model 1		Model 2		Model 3		Model 4	
Variable	B	r_{sp}^2	B	r_{sp}^2	B	r_{sp}^2	B	r_{sp}^2
Constant	28.68		33.39		31.11		30.94	
	(27.91)		(32.55)		(29.25)		(30.21)	
Age	-.33	.03	-.37	.04	-.36	.04	-.35	.03
	(-.32)	(.03)	(-.34)	(.03)	(-.31)	(.03)	(-.33)	(.02)
Education								
High Sch	17.85	.06	15.65	.05	17.51	.06	17.57	.05
	(18.57)	(.07)	(16.14)	(.05)	(17.75)	(.06)	(17.44)	(.05)
College	14.44	.04	12.69	.03	14.89	.04	14.93	.04
	(14.5)	(.04)	(12.59)	(.03)	(14.94)	(.04)	(14.72)	(.04)
Doctoral	18.62	.06	16.64	.05	18.61	.06	18.64	.06
	(18.68)	(.07)	(16.51)	(.05)	(18.58)	(.06)	(18.41)	(.06)
Cond. [a]			-3.25	.03	-2.77	.02	-2.68	.01
			(-3.66)	(.03)	(-3.28)	(.02)	(-3.79)	(.01)
INFγ					-2.68	.02	-2.67	.02
					(-3.07)	(.03)	(-3.16)	(.03)
TNFα					-2.63	.09	-2.63	.09
					(-2.6)	(.09)	(-2.61)	(.09)
PTSD							-.001	.00
Level [b]							(.008)	(.00)
R^2	.146		.171		.291		.291	
	(.151)		(.182)		(.306)		(.306)	
$R^{2\ adj}$	.066		.073		.167		.146	
	(.068)		(.080)		(.178)		(.156)	
F	1.834		1.735		2.349		2.004	
	(1.823)		(1.785)		(2.392)		(2.042)	
Δ R^2	.146		.025		.120		.000	
	(.151)		(.031)		(.123)		(.000)	
Δ F	1.834		1.288		3.391		.001	
	(1.823)		(1.539)		(2.392)		(.020)	

Note. *p < .05, **p <.001, Analysis without outliers within parentheses, [a] Case designation (GWI or Healthy Control), [b] PTSD level (PTSD-related symptoms from DTS total), [c] Fatigue (as designated by MFI General Fatigue); B indicates unstandardized coefficients, r_{sp}^2 indicates squared semi-partial correlations Abbreviations were also used. High Sch = High School, Cond. = Condition.

PASAT Trial 4 Analysis. The full model (n = 48) for PASAT Trial 4 was significant, R^2 = .333, 95% CI [.161, .505], F(8, 39) = 2.437, p = .03, adjusted R^2 = .197.

The first predictor block including age and education produced a medium effect and was nonsignificant, $R^2 = .181$, $F(4, 43) = 2.376$, $p = .067$, adjusted $R^2 = .105$. The addition of condition did not produce statistically significant incremental variance, $\Delta F(1, 42) = 1.278$, $p = .265$, $\Delta R^2 = .024$; however, it did produce a small effect. The third block with the addition of cytokines was significant and had a small effect $\Delta F(2, 40) = 3.237$, $p = .05$, $\Delta R^2 = .111$. Finally, the addition of PTSD symptoms did not produce incremental variance, $\Delta F(1, 39) = 1.019$, $p = .319$, $\Delta R^2 = .017$. Squared semi-partial correlations were interpreted within the full model. Age did not produce a meaningful effect. Positive associations and a small effect were produced regarding education at the collegiate level ($r_{sp} = .323$, 95% CI [.043, .556]; $r_{sp}^2 = 0.10$); there were positive associations with a medium effect at the high school level ($r_{sp} = .358$, 95% CI [.082, .583]; $r_{sp}^2 = 0.13$), and at the doctoral level ($r_{sp} = .358$, 95% CI [.082, .583]; $r_{sp}^2 = 0.13$). The interleukin TNFα ($r_{sp} = -.294$, 95% CI [-.498, .038]; $r_{sp}^2 = 0.09$) was negatively associated with scores with a small effect. INFγ and GWI were not interpreted as meaningful. However, PTSD symptoms showed a small effect ($r_{sp} = -.132$ 95% CI [-.401, .158]; $r_{sp}^2 = 0.02$).

Table 27
PASAT Trial 4 Post Hoc

	Model 1		Model 2		Model 3		Model 4	
Variable	B	r_{sp}^2	B	r_{sp}^2	B	r_{sp}^2	B	r_{sp}^2
Constant	10.8		14.76		13.39		7.75	
Age	-.19	.01	-.21	.02	-.21	.02	-.1	.00
Edu. Level								
High School	21.76	.12	19.91	.10	21.29	.11	23.16	.13
Collegiate	19.1	.10	17.63	.08	19.02	.09	20.25	.10
Doctoral	22.73	.13	21.08	.11	22.36	.12	23.36	.13
Condition [a]			-2.73	.02	-2.63	.02	.28	.00
INFγ					-1.1	.01	-.63	.00
TNFα					-2.42	.10	-2.31	.09
PTSD Level [b]							-.05	.02
R^2	.181		.205		.316		.333	
$R^{2\ adj}$	.105		.111		.196		.197	
F	2.376		2.168		2.639		2.437	
Δ R^2	.181		.024		.111		.017	
Δ F	2.376		1.278		3.237		1.019	

Note. *p < .05, **p <.001, [a] Case designation (GWI or Healthy Control), [b] PTSD level (PTSD-related symptoms from DTS total), [c] Fatigue (as designated by MFI General Fatigue); B indicates unstandardized coefficients, r_{sp}^2 indicates squared semi-partial correlations

PASAT Trial 4 Reanalysis without Outliers. The same analysis was conducted without identified outliers (n = 46). The full model on the fourth trial remained significant, $R^2 = .334$, 95% CI [.161, 507], $F(8, 37) = 2.319$, $p = .04$, adjusted $R^2 = .190$ with a medium effect size. The addition of condition to the model was not statistically significant but had a small effect (Δ $R^2 = .023$). However, the addition of cytokines was not significant (i.e., TNFα and INFγ) with an increase in R^2 of .103, $F(2, 38) = 2.861$, $p = .07$ with a small effect. On the last model with the inclusion of PTSD symptoms, the model was significant, but PTSD did not lead to a significant increase of R(Δ $R^2 = .015$) or a meaningful effect. Within the final model, the only parameters that changed were in the first model. There was a medium positive effect in education at the high school level and age demonstrated a small effect (see Table 28).

PASAT Trial 4 Reanalysis with Recoding. Model 1 R^2, Model 1 ΔR^2, Model 2 R^2, had a small effect (Model 1 $R^2/\Delta R^2 = .057$, Model 2 $R^2 = .105$) which was previously interpreted as a medium effect size (Model 1$R^2/\Delta R^2 = .181$, Model 2 $R^2 = .205$). Model 3 R^2 and Model 4 R^2 returned medium effect sizes (Model 3 $R^2 = .202$, Model 4 $R^2 = .205$) which previously had large effect sizes (Model 3 $R^2 = .316$, Model 4 $R^2 = .333$). For the final model semi-partial correlates, reanalysis showed differences in age ($r_{sp}^2 = .02$, previously non-significant), high school level of education (non-significant, previously $r_{sp}^2 = .13$), doctoral level of education (non-significant, previously $r_{sp}^2 = .13$), and PTSD symptoms (non-significant, previously $r_{sp}^2 = .02$).

When analyzed without outliers, there were similar results in that Model 1 R^2, Model 1 ΔR^2, and Model 2 R^2 were interpreted as a small effect (Model 1 $R^2/\Delta R^2 = .065$, Model 2 $R^2 = .111$) which were previously a medium effect (Model 1$R^2/\Delta R^2 = .193$, Model 2 $R^2 = .216$). Model 3 R^2 and Model 4 R^2 revealed a medium effect (Model 3 $R^2 = .202$, Model 4 $R^2 = .205$) from a previously large effect size (Model 3 $R^2 = .319$, Model 4 $R^2 = .334$). For the final model semi-partial correlates, reanalysis showed differences in age ($r_{sp}^2 = .02$, previously non-significant), high school level of education (non-significant, previously $r_{sp}^2 = .13$), doctoral level of education (non-significant, previously $r_{sp}^2 = .13$), and PTSD symptoms (non-significant, previously $r_{sp}^2 = .02$).

Table 28
PASAT Trial 4 with and without Outliers Post Hoc

	Model 1		Model 2		Model 3		Model 4	
Variable	B	r_{sp}^2	B	r_{sp}^2	B	r_{sp}^2	B	r_{sp}^2
Constant	10.8		14.76		13.39		7.75	
	(11.8)		(15.23)		(13.42)		(8.21)	
Age	-.19	.01	-.21	.02	-.21	.02	-.1	.00
	(-.21)	(.02)	(-.22)	(.02)	(-.21)	(.00)	(-.1)	(.00)
Education								
High Sch	21.76	.12	19.91	.10	21.29	.11	23.16	.13
	(22.23)	(.13)	(20.44)	(.10)	(21.56)	(.12)	(23.26)	(.13)
College	19.1	.10	17.63	.08	19.02	.09	20.25	.10
	(19.01)	(.10)	(17.6)	(.08)	(18.96)	(.09)	(20.12)	(.10)
Doctoral	22.73	.13	21.08	.11	22.36	.12	23.36	.13
	(22.65)	(.13)	(21.05)	(.11)	(22.29)	(.12)	(23.24)	(.13)
Cond. [a]			-2.73	.02	-2.63	.02	.28	.00
			(-2.71)	(.02)	(-2.7)	(.02)	(.06)	(.00)
INFγ					-1.1	.01	-.63	.00
					(-1.1)	(.01)	(-.63)	(.00)
TNFα					-2.42	.10	-2.31	.09
					(-2.36)	(.09)	(2.3)	(.09)
PTSD							-.05	.02
Level [b]							(-.04)	(.02)
R^2	.181		.205		.316		.333	
	(.193)		(.216)		(.319)		(.334)	
$R^{2\ adj}$	.105		.111		.196		.197	
	(.115)		(.118)		(.193)		(.190)	
F	2.376		2.168		2.639		2.437	
	(2.458)		(2.208)		(2.542)		(2.319)	
Δ R^2	.181		.024		.111		.017	
	(.193)		(.023)		(.103)		(.015)	
Δ F	2.376		1.278		3.237		1.019	
	(2.46)		(1.17)		(2.86)		(.836)	

Note. *p < .05, **p <.001, Analysis without outliers within parentheses, [a] Case designation (GWI or Healthy Control), [b] PTSD level (PTSD-related symptoms from DTS total), [c] Fatigue (as designated by MFI General Fatigue); B indicates unstandardized coefficients, r_{sp}^2 indicates squared semi-partial correlations Abbreviations were also used. High Sch = High School, Cond. = Condition.

PASAT Results by Condition, TNFα/INFγ/IL-6/IL-8, and PTSD Symptoms

Another hierarchical regression model was utilized to investigate if condition (GWI status), cytokines (i.e., TNFα, INFγ, IL-6, and IL-8), and PTSD symptoms would predict how veterans performed on a measure of working memory and attention (PASAT) over and above demographic factors. Predictor blocks were held constant

across models: Block 1 (Age and Education), Block 2(GWI), Block 3 (TNFα, INFγ, IL-6, and IL-8) and Block 4 (PTSD symptoms). Tables 29 through 36 present selected statistical information from the analyses.

PASAT Trial 1. Regression models were used on available data (n = 44) to test if GWI status, TNFα, INFγ, IL-6, and IL-8 and PTSD symptoms had an impact on attention and working memory. The full model for PASAT Trial 1 was nonsignificant, $R^2 = .279$, 95% CI [.121, .437], $F(10, 33) = 1.277$, $p = .283$, adjusted $R^2 = .06$. The first predictor block including age and education returned a medium effect, $R^2 = .161$, $F(4, 39) = 1.877$, $p = .134$, adjusted $R^2 = .075$. The addition of health condition did not contribute significantly by means of incremental variance, $\Delta F(1, 38) = .281$, $p = .599$, $\Delta R^2 = .006$. The addition of cytokines did not produce significant incremental variance but had a small effect, $\Delta F(4, 34) = 1.311$, $p = .286$, $\Delta R^2 = .279$. Finally, the addition of PTSD symptoms did not add incremental variance, $\Delta F(1, 33) = .006$, $p = .937$, $\Delta R^2 = .00$. In the final model, squared semi-partial correlations showed a negative association and small effect with age ($r_{sp} = -.220$, 95% CI [-.485, .082]; $r_{sp}^2 = 0.05$). Positive associations and a small effect were produced regarding education at the high school level ($r_{sp} = .166$, 95% CI [-.138, .441]; $r_{sp}^2 = 0.03$), collegiate level ($r_{sp} = .159$, 95% CI [-.145, .435]; $r_{sp}^2 = 0.03$), and the doctoral level ($r_{sp} = .247$, 95% CI [=-.054, .507]; $r_{sp}^2 = 0.06$). Furthermore, some cytokines also demonstrated a small effect size including INFγ ($r_{sp} = -.163$, 95% CI [-.439, .141]; $r_{sp}^2 = 0.03$) and TNFα ($r_{sp} = -.194$, 95% CI [-.464, .109]; $r_{sp}^2 = 0.04$). The variables IL-6, IL-8, and PTSD symptom level did not produce meaningful effects.

Table 29
PASAT Trial 1 Added Cytokines

	Model 1		Model 2		Model 3		Model 4	
Variable	B	r_{sp}^2	B	r_{sp}^2	B	r_{sp}^2	B	r_{sp}^2
Constant	48.03		51.4		47.7		48.46	
Age	-.6	.06	-.62	.06	-.61	.06	-.62	.05
Edu. Level								
High School	15.23	.03	13.77	.02	16.54	.03	16.32	.03
Collegiate	13.22	.02	12.03	.02	15.23	.03	15.04	.03
Doctoral	22.82	.06	21.25	.05	24.7	.06	24.64	.06
Condition [a]			-2.18	.01	-1.62	.00	-2.04	.00
INFγ					-4.27	.03	-4.32	.03
TNFα					-3.08	.04	-3.08	.04
IL-6					1.14	.01	1.15	.01
IL-8					-1.08	.00	-1.13	.00
PTSD Level [b]							.007	.00
R^2	.161		.168		.279		.279	
$R^{2\ adj}$	.075		.058		.088		.060	
F	1.877		1.530		1.461		1.277	
Δ R^2	.161		.006		.111		.000	
Δ F	1.877		.281		1.311		.006	

Note. *p < .05, **p <.001, [a] Case designation (GWI or Healthy Control), [b] PTSD level (PTSD-related symptoms from DTS total); B indicates unstandardized coefficients, r_{sp}^2 indicates squared semi-partial correlations

PASAT Trial 1 Reanalysis without Outliers. Assumption testing of the data revealed two potential outliers which were excluded for the following analysis (n = 43). The analysis interpretation did not change with the full model for PASAT 1 as it remained nonsignificant (see Table 30 for comparison values). Additionally, model and squared semi-partial correlation effect sizes did not produce a notable change in values and were interpreted in the same manner.

PASAT Trial 1 Reanalysis with Recoding. PASAT data was reanalyzed to include the participant with elementary level education (n =1) by combining his data with other participants with a high school education. In terms of R^2 effect size, Model 3 and Model 4 showed a difference as it was medium (Model 3: .249, Model 4: .251) whereas it was previously large (Model 3: .279, Model 4: .279). In terms of semi-partial correlation effect sizes, there was a change across all models in high school as it was non-meaningful

and previously produced small effect sizes (Model 1: .03, Model 2: .02, Model 3: .03, Model 4: .03) .

When analyzed without outliers, there were similar results in that the R^2 effect size was medium (Model 3: .248, Model 4: .251) instead of large (Model 3: .278, Model 4: .27) and the semi-partial correlation effect size in the full model showed that high school was now non-meaningful instead of small (.03) .

Table 30
PASAT Trial 1 Added Cytokines with and without Outliers

	Model 1		Model 2		Model 3		Model 4	
Variable	B	r_{sp}^2	B	r_{sp}^2	B	r_{sp}^2	B	r_{sp}^2
Constant	48.03		51.4		47.7		48.46	
	(47.91)		(51.1)		(46.15)		(47.13)	
Age	-.6	.06	-.62	.06	-.61	.06	-.62	.05
	(-.59)	(.06)	(-.61)	(.06)	(-.57)	(.05)	(-.59)	(.04)
Edu. Level								
High	15.23	.03	13.77	.02	16.54	.03	16.32	.03
School	(15.22)	(.03)	(13.67)	(.02)	(16.63)	(.03)	(16.33)	(.03)
Collegiate	13.22	.02	12.03	.02	15.23	.03	15.04	.03
	(13.23)	(.02)	(12.02)	(.02)	(15.48)	(.03)	(15.24)	(.03)
Doctoral	22.82	.06	21.25	.05	24.7	.06	24.64	.06
	(22.83)	(.06)	(21.23)	(.05)	(24.81)	(.06)	(24.74)	(.06)
Condition [a]			-2.18	.01	-1.62	.00	-2.04	.00
			(-2.26)	(.01)	(-1.53)	(.00)	(-2.09)	(.00)
INFγ					-4.27	.03	-4.32	.03
					(-4.23)	(.03)	(-4.3)	(.03)
TNFα					-3.08	.04	-3.08	.04
					(-2.52)	(.02)	(-2.5)	(.02)
IL-6					1.14	.01	1.15	.01
					(.69)	(.00)	(.7)	(.00)
IL-8					-1.08	.00	-1.13	.00
					(-1.52)	(.01)	(-1.59)	(.01)
PTSD							.007	.00
Level [b]							(.01)	(.00)
R^2	.161		.168		.279		.279	
	(.158)		(.164)		(.278)		(.279)	
$R^{2\ adj}$	.075		.058		.088		.060	
	(.069)		(.051)		(.081)		(.053)	
F	1.877		1.530		1.461		1.277	
	(1.778)		(1.453)		(1.414)		(1.236)	
Δ R^2	.161		.006		.111		.000	
	(.158)		(.006)		(.114)		(.000)	
Δ F	1.877		.281		1.311		.006	
	(1.778)		(.288)		(1.305)		(.011)	

Note. *p < .05, **p <.001, Analysis without outliers within parentheses, [a] Case designation (GWI or Healthy Control), [b] PTSD level (PTSD-related symptoms from DTS total), [c] Fatigue (as designated by MFI General Fatigue); B indicates unstandardized coefficients, r_{sp}^2 indicates squared semi-partial correlations Abbreviations were also used. High Sch = High School, Cond. = Condition.

PASAT Trial 2. The full model (n = 44) for PASAT Trial 2 was nonsignificant, $R^2 = .317$, 95% CI[.157, .477], $F(10, 33) = 1.532$, $p = .172$, adjusted $R^2 = .110$. The first predictor block (age and education) demonstrated a medium effect but was nonsignificant, $R^2 = .143$, $F(4, 39) = 1.633$, $p = .185$, adjusted $R^2 = .056$. The second

block (health condition) did not return significant incremental variance, $\Delta F(1, 38) = 1.218$, $p = .277$, $\Delta R^2 = .027$; however, there was a small effect. Next, Block 3 with the addition of cytokines showed a medium effect but was also nonsignificant, $\Delta F(4, 34) = 1.822$, $p = .146$, $\Delta R^2 = .146$. Finally, the addition of PTSD symptoms did not produce incremental variance, $\Delta F(1, 33) = .024$, $p = .877$, $\Delta R^2 = .001$. In the final model, squared semi-partial correlations revealed a negative association and small effect in age ($r_{sp} = -.172$, 95% CI [-.446, .132]; $r_{sp}^2 = 0.03$). Positive associations and a small effect were produced regarding education at the high school level ($r_{sp} = .125$, 95% CI [-.179, .407]; $r_{sp}^2 = 0.02$), and doctoral level ($r_{sp} = .225$, 95% CI [-.077, .489]; $r_{sp}^2 = 0.05$). All other levels of education did not indicate a meaningful effect. The cytokines showed a negative association with a small effect size in INFγ ($r_{sp} = -.127$, 95% CI [-.408, .177]; $r_{sp}^2 = 0.02$), TNFα ($r_{sp} = -.148$, 95% CI [-.426, .156]; $r_{sp}^2 = 0.02$) and IL-8($r_{sp} = -.158$, 95% CI [-.434, .146]; $r_{sp}^2 = 0.02$). The variables for IL-6, GWI and PTSD did not produce meaningful effects.

Table 31
PASAT Trial 2 Added Cytokines

	Model 1		Model 2		Model 3		Model 4	
Variable	B	r_{sp}^2	B	r_{sp}^2	B	r_{sp}^2	B	r_{sp}^2
Constant	41.69		47.91		43.64		44.93	
Age	-.38	.03	-.42	.04	-.41	.04	-.44	.03
Edu. Level								
High School	9.97	.01	7.27	.01	11.25	.02	10.87	.02
Collegiate	8	.01	5.8	.01	9.23	.01	8.92	.01
Doctoral	18.81	.05	15.92	.03	20.04	.05	19.94	.05
Condition [a]			-4.01	.03	-2.66	.01	-3.38	.01
INFγ					-2.89	.02	-3	.02
TNFα					-2.08	.02	-2.08	.02
IL-6					.726	.01	.75	.01
IL-8					-2.45	.03	-2.54	.03
PTSD Level [b]							.01	.00
R^2	.143		.170		.317		.317	
$R^{2\ adj}$	.056		.061		.136		.110	
F	1.633		1.557		1.75		1.532	
Δ R^2	.143		.027		.146		.001	
Δ F	1.633		1.218		1.822		.024	

Note. *p < .05, **p <.001, [a] Case designation (GWI or Healthy Control), [b] PTSD level (PTSD-related symptoms from DTS total); B indicates unstandardized coefficients, r_{sp}^2 indicates squared semi-partial correlations

PASAT Trial 2 Reanalysis without Outliers. The analysis interpretation did not change with the full model for PASAT 2 as it remained nonsignificant (see Table 32). Additionally, model effect sizes did not produce a notable change in values and were interpreted in the same manner. However, the semi-partial correlation effect size for TNFα was non-meaningful whereas it was previously a small effect (.02).

PASAT Trial 2 Reanalysis with Recoding. PASAT data reanalysis showed no difference in significance or effect sizes in data without outliers. When analyzed without outliers, analysis change in that the semi-partial squared effect size showed a difference in high school which was previously a small effect (.02) and now non-meaningful. Additionally, the effect size for condition in both Model 3 and Model 4 showed a small effect size (.02) which was previously non-meaningful.

Table 32
PASAT Trial 2 Added Cytokines with and without Outliers

	Model 1		Model 2		Model 3		Model 4	
Variable	B	r_{sp}^2	B	r_{sp}^2	B	r_{sp}^2	B	r_{sp}^2
Constant	41.69		47.91		43.64		44.93	
	(43.41)		(48.73)		(42.12)		(43.61)	
Age	-.38	.03	-.42	.04	-.41	.04	-.44	.03
	(-.41)	(.03)	(-.45)	(.04)	(-.38)	(.03)	(-.41)	(.03)
Edu. Level								
High	9.97	.01	7.27	.01	11.25	.02	10.87	.02
School	(10.11)	(.01)	(7.53)	(.01)	(11.33)	(.02)	(10.89)	(.02)
Collegiate	8	.01	5.8	.01	9.23	.01	8.92	.01
	(7.85)	(.01)	(5.83)	(.01)	(9.48)	(.01)	(9.11)	(.01)
Doctoral	18.81	.05	15.92	.03	20.04	.05	19.94	.05
	(18.64)	(.05)	(16)	(.03)	(20.15)	(.05)	(20.03)	(.05)
Condition [a]			-4.01	.03	-2.66	.01	-3.38	.01
			(-3.78)	(.02)	(-2.58)	(.01)	(-3.43)	(.01)
INFγ					-2.89	.02	-3	.02
					(-2.86)	(.02)	(-2.97)	(.02)
TNFα					-2.08	.02	-2.08	.02
					(-1.52)	(.01)	(-1.51)	(.01)
IL-6					.726	.01	.75	.01
					(.282)	(.00)	(.30)	(.00)
IL-8					-2.45	.03	-2.54	.03
					(-2.88)	(.03)	(-3)	(.03)
PTSD							.01	.00
Level [b]							(.01)	(.00)
R^2	.143		.170		.317		.317	
	(.149)		(.172)		(.319)		(.32)	
$R^{2\ adj}$	.056		.061		.136		.110	
	(.06)		(.06)		(133)		(.107)	
F	1.633		1.557		1.75		1.532	
	(1.665)		(1.538)		(1.717)		(1.504)	
Δ R^2	.143		.027		.146		.001	
	(.149)		(.023)		(.147)		(.001)	
Δ F	1.633		1.218		1.822		.024	
	(1.665)		(1.025)		(1.779)		(.033)	

Note. *p < .05, **p <.001, Analysis without outliers within parentheses, [a] Case designation (GWI or Healthy Control), [b] PTSD level (PTSD-related symptoms from DTS total), [c] Fatigue (as designated by MFI General Fatigue); B indicates unstandardized coefficients, r_{sp}^2 indicates squared semi-partial correlations Abbreviations were also used. High Sch = High School, Cond. = Condition.

PASAT Trial 3 Analysis. The full model (n = 44) for PASAT Trial 3 was nonsignificant, R^2 = .323, 95% CI [.163, .483], F(10, 33) = 1.572, p = .159, adjusted R^2 = .117. The first predictor block (i.e., age and education) returned a medium effect but was also nonsignificant, R^2 = .156, F(4, 39) = 1.805, p = .147, adjusted R^2 = .070. The second predictor block (i.e., health condition) did not demonstrate incremental variance, ΔF(1,

38) = 1.386, p = .246, Δ R^2= .030, but produced a small effect. The third predictor block (i.e., cytokines) was noncontributory to incremental variance but produced a medium effect ΔF(4, 34) = 1.668, p = .180, Δ R^2= .134. Finally, the fourth predictor block (i.e., PTSD symptoms) did not produce incremental variance, ΔF(1, 33) = .156, p = .695, Δ R^2= .003. Squared semi-partial correlations were interpreted for the full model. Age was negatively associated with scores and had a small effect (r_{sp} = -.73, 95% CI [-.844, -.553]; r_{sp}^2 =0.03). Positive associations and a small effect were produced regarding education at the high school level (r_{sp} = .226, 95% CI [-.076, .490]; r_{sp}^2 =0.05), at the collegiate level (r_{sp} = .198, 95% CI [-.105, .467]; r_{sp}^2 =0.04), and at the doctoral level (r_{sp} = .25, 95% CI [-.051, .509]; r_{sp}^2 =0.06). The correlation for health condition also had a small effect, (r_{sp} = -.146, 95% CI [-.424, .158]; r_{sp}^2 =0.02). The cytokines were in the negative direction and demonstrated small effect sizes, INFγ (r_{sp} = -.184, 95% CI [-.456, .119]; r_{sp}^2 =0.03), and TNFα (r_{sp} = -.265, 95% CI [-.521, .035]; r_{sp}^2 =0.07). Interleukins IL-6 and IL-8 as well as PTSD symptoms did not produce meaningful effects.

Table 33
PASAT Trial 3 Added Cytokines

	Model 1		Model 2		Model 3		Model 4	
Variable	B	r_{sp}^2	B	r_{sp}^2	B	r_{sp}^2	B	r_{sp}^2
Constant	26.48		32.14		29.82		32.63	
Age	-.29	.02	-.33	.03	-.32	.03	-.38	.03
Edu. Level								
High School	18.72	.07	16.27	.05	17.79	.06	16.97	.05
Collegiate	14.6	.04	12.61	.03	15.00	.04	14.32	.04
Doctoral	19.88	.07	17.25	.05	19.32	.06	19.10	.06
Condition [a]			-3.65	.03	-3.61	.02	-5.17	.02
INFγ					-3.54	.03	-3.74	.03
TNFα					-3.21	.07	-3.21	.07
IL-6					.622	.01	.683	.01
IL-8					.173	.00	-.016	.00
PTSD Level [b]							.026	.00
R^2	.156		.186		.319		.323	
$R^{2\ adj}$	.070		.079		.139		.117	
F	1.805		1.735		1.773		1.572	
Δ R^2	.156		.030		.134		.003	
Δ F	1.81		1.386		1.668		.156	

Note. *p < .05, **p <.001,[a] Case designation (GWI or Healthy Control), [b] PTSD level (PTSD-related symptoms from DTS total), [c] Fatigue (as designated by MFI General Fatigue); B indicates unstandardized coefficients, β indicates standardized coefficients, r_{sp}^2 indicates squared semi-partial correlations

PASAT Trial 3 Reanalysis without Outliers. The analysis interpretation did not change with the full model as it was nonsignificant (see Table 34). Additionally, model and squared semi-partial correlation effect sizes did not return a notable change.

PASAT Trial 3 Reanalysis with Recoding. The reanalysis of the PASAT data with outliers showed no difference in significance. In regard to model effect sizes, the first model showed a small effect size (.087) which was previously a medium effect size (.156). Semi-partial correlation effect sizes for the full model also showed that high school was now non-meaningful (previously a small effect = .05), that TNFα was non-meaningful and previously a small effect =.07)., and that IL-8 had a small effect (.02) which was previously non-meaningful. Analysis of the data without outliers also showed that the first model was now a small effect (R^2 =.084) which was previously non-meaningful. Lastly, semi-partial correlation effect sizes of the final model revealed

changes in high school educational level (non-significant, previously $r_{sp}^2 = .05$).

Table 34
PASAT Trial 3 Added Cytokines with and without Outliers

	Model 1		Model 2		Model 3		Model 4	
Variable	B	r_{sp}^2	B	r_{sp}^2	B	r_{sp}^2	B	r_{sp}^2
Constant	26.48		32.14		29.82		32.63	
	(26.68)		(31.92)		(29.02)		(31.87)	
Age	-.29	.02	-.33	.03	-.32	.03	-.38	.03
	(-.29)	(.02)	(-.32)	(.03)	(-.30)	(.02)	(-.36)	(.03)
Edu. Level								
High School	18.72	.07	16.27	.05	17.79	.06	16.97	.05
	(18.74)	(.07)	(16.2)	(.05)	(17.84)	(.06)	(16.98)	(.05)
Collegiate	14.6	.04	12.61	.03	15.00	.04	14.32	.04
	(14.59)	(.04)	(12.6)	(.03)	(15.13)	(.04)	(14.43)	(.04)
Doctoral	19.88	.07	17.25	.05	19.32	.06	19.10	.06
	(19.86)	(.07)	(17.23)	(.05)	(19.38)	(.06)	(19.16)	(.06)
Condition [a]			-3.65	.03	-3.61	.02	-5.17	.02
			(-3.72)	(.03)	(-3.57)	(.03)	(-5.19)	(.02)
INFγ					-3.54	.03	-3.74	.03
					(-3.52)	(.03)	(-3.73)	(.03)
TNFα					-3.21	.07	-3.21	.07
					(-2.92)	(.04)	(-2.88)	(.04)
IL-6					.622	.01	.683	.01
					(.3)	(.00)	(.425)	(.00)
IL-8					.173	.00	-.016	.00
					(-.05)	(.00)	(-.278)	(.00)
PTSD Level [b]							.026	.00
							(.027)	(.00)
R^2	.156		.186		.319		.323	
	(.153)		(.183)		(.318)		(.322)	
$R^{2\ adj}$	.070		.079		.139		.117	
	(.064)		(.073)		(.133)		(.110)	
F	1.805		1.735		1.773		1.572	
	(1.722)		(1.662)		(1.713)		(1.519)	
Δ R^2	.156		.030		.134		.003	
	(.153)		(.03)		(.135)		(.004)	
Δ F	1.81		1.386		1.668		.156	
	(1.722)		(1.358)		(1.634)		(.166)	

Note. *p < .05, **p <.001, Analysis without outliers within parentheses, [a] Case designation (GWI or Healthy Control), [b] PTSD level (PTSD-related symptoms from DTS total), [c] Fatigue (as designated by MFI General Fatigue); B indicates unstandardized coefficients, r_{sp}^2 indicates squared semi-partial correlations Abbreviations were also used. High Sch = High School, Cond. = Condition.

PASAT Trial 4 Analysis. The full model (n = 44) for PASAT Trial 4 was nonsignificant, $R^2 = .351$, 95% CI [.191, .511], $F(10, 33) = 1.783$, $p = .103$, adjusted $R^2 = .154$. The first predictor block including age and education produced a medium effect and was significant, $R^2 = .216$, $F(4, 39) = 2.685$, $p = .045$, adjusted $R^2 = .136$. The addition of

condition did not produce statistically significant incremental variance, $\Delta F(1, 38) = 1.384$, $p = .247$, $\Delta R^2 = .028$; however, it did produce a small effect. The third block with the addition of cytokines was nonsignificant and had a small effect $\Delta F(4, 34) = 1.384$, $p = .260$, $\Delta R^2 = .106$. Finally, the addition of PTSD symptoms did not produce incremental variance, $\Delta F(1, 33) = .068$, $p = .796$, $\Delta R^2 = .001$. Squared semi-partial correlations were interpreted within the full model. Age did not produce a meaningful effect. Positive associations and a small effect were produced regarding education at the collegiate level ($r_{sp} = .308$, 95% CI [.012, .554]; $r_{sp}^2 = 0.10$); there were positive associations with a medium effect at the high school level ($r_{sp} = .346$, 95% CI [.055, .583]; $r_{sp}^2 = 0.12$), and at the doctoral level ($r_{sp} = .365$, 95% CI [.076, .597]; $r_{sp}^2 = 0.13$). The interleukin TNFα ($r_{sp} = -.211$, 95% CI [-.092, .478]; $r_{sp}^2 = 0.04$) was negatively associated with scores with a small effect. INFγ, GWI, IL-6, IL-8, and PTSD were not interpreted as meaningful.

Table 35
PASAT Trial 4 Added Cytokines

	Model 1		Model 2		Model 3		Model 4	
Variable	B	r_{sp}^2	B	r_{sp}^2	B	r_{sp}^2	B	r_{sp}^2
Constant	9.44		14.1		12.38		10.83	
Age	-.16	.01	-.19	.01	-.19	.01	-.15	.01
Edu. Level								
High School	22.28	.13	20.21	.11	21.73	.12	22.18	.12
Collegiate	18.57	.10	16.92	.08	18.67	.09	19.05	.10
Doctoral	24.29	.15	22.13	.12	23.71	.13	23.83	.13
Condition [a]			-3.01	.03	-2.74	.02	-1.87	.00
INFγ					-1.53	.01	-1.42	.01
TNFα					-2.19	.05	-2.19	.05
IL-6					.08	.00	.04	.00
IL-8					-.22	.00	-.12	.00
PTSD Level [b]							-.01	.00
R^2	.216		.243		.349		.351	
$R^{2\ adj}$	.1366		.144		.177		.154	
F	2.69*		2.45*		2.03		1.78	
Δ R^2	.216*		.028		.106		.001	
Δ F	2.69*		1.38		1.38		.068	

Note. *p < .05, **p <.001, [a] Case designation (GWI or Healthy Control), [b] PTSD level (PTSD-related symptoms from DTS total), [c] Fatigue (as designated by MFI General Fatigue); B indicates unstandardized coefficients, r_{sp}^2 indicates squared semi-partial correlations

PASAT Trial 4 Reanalysis without Outliers. The analysis interpretation did not change with the full model for PASAT 4 as it remained significant (see Table 36). Additionally, model effect sizes did not produce a notable change in values and were interpreted in the same manner. However, the semi-partial correlation effect size for age in Model 2 had a small effect (.02), when it was previously non-meaningful.

PASAT Trial 4 Reanalysis with Recoding. There was a change in statistical significance as Model 1 and Model 2 were now non-significant, which previously had a p value at or below .05. Model 1 R^2, Model 1 Δ R^2 had a small effect (Model 1 R^2/Δ R^2 = .082) which was previously interpreted as a medium effect size (Model 1R^2/ Δ R^2 = .216). Model 3 R^2 and Model 4 R^2 returned medium effect sizes (Model 3 R^2 = .230, Model 4 R^2 = .231) which previously had a large effect sizes (Model 3 R^2 = .349, Model 4 R^2 = .351). For the final model semi-partial correlates, reanalysis showed differences in high

school level of education (non-significant, previously $r_{sp}^2 = .12$), doctoral level of education (small effect = .03, previously $r_{sp}^2 = .13$), and health condition (small effect = .03, previously non-meaningful).

When analyzed without outliers, there were similar results in that Model 1 R^2, and Model 1 ΔR^2 were interpreted as a small effect (Model 1 $R^2/\Delta R^2 = .089$) which were previously a medium effect (Model $1R^2/\Delta R^2 = 225$). Model 3 R^2 and Model 4 R^2 revealed a medium effect (Model 3 $R^2 = .23$, Model 4 $R^2 = .23$) from a previously large effect size (Model 3 $R^2 = .349$, Model 4 $R^2 = .35$). For the final model semi-partial correlates, reanalysis showed differences in age ($r_{sp}^2 = .03$, previously non-significant), high school level of education (non-significant, previously $r_{sp}^2 = .12$), doctoral level of education (small effect = .03, previously $r_{sp}^2 = .13$), and health condition ($r_{sp}^2 = .03$, previously non-significant).

Table 36
PASAT Trial 4 Added Cytokines with and without Outliers

	Model 1		Model 2		Model 3		Model 4	
Variable	B	r_{sp}^2	B	r_{sp}^2	B	r_{sp}^2	B	r_{sp}^2
Constant	9.44		14.1		12.38		10.83	
	(10.94)		(14.86)		(12.79)		(11.22)	
Age	-.16	.01	-.19	.01	-.19	.01	-.15	.01
	(-.19)	(.01)	(-.21)	(.02)	(-.2)	(.01)	(-.16)	(.01)
Edu. Level								
High	22.28	.13	20.21	.11	21.73	.12	22.18	.12
School	(22.35)	(.14)	(20.45)	(.11)	(21.7)	(.12)	(22.17)	(.12)
Collegiate	18.57	.10	16.92	.08	18.67	.09	19.05	.10
	(18.44)	(.09)	(16.95)	(.08)	(18.61)	(.09)	(19)	(.09)
Doctoral	24.29	.15	22.13	.12	23.71	.13	23.83	.13
	(24.14)	(.15)	(22.18)	(.12)	(23.68)	(.13)	(23.8)	(.13)
Condition [a]			-3.01	.03	-2.74	.02	-1.87	.00
			(-2.79)	(.02)	(-2.75)	(.02)	(-1.85)	(.00)
INFγ					-1.53	.01	-1.42	.01
					(-1.54)	(.01)	(-1.43)	(.01)
TNFα					-2.19	.05	-2.19	.05
					(-2.34)	(.03)	(-2.36)	(.04)
IL-6					.08	.00	.04	.00
					(.2)	(.00)	(.18)	(.00)
IL-8					-.22	.00	-.12	.00
					(-.10)	(.00)	(.02)	(.00)
PTSD							-.01	.00
Level [b]							(-.02)	(.00)
R^2	.216		.243		.349		.351	
	(.225)		(.248)		(.349)		(.35)	
$R^{2\ adj}$	.136		.144		.177		.154	
	(.143)		(.146)		(.171)		(.147)	
F	2.698*		2.45*		2.03		1.78	
	(2.75)*		(2.435*)		(1.965)		(1.73)	
Δ R^2	.216*		.028		.106		.001	
	(.225*)		(.023)		(.101)		(.001)	
Δ F	2.69*		1.38		1.38		.068	
	(2.75*)		(2.435*)		(.072)		(.072)	

Note. *p < .05, **p <.001, Analysis without outliers within parentheses, [a] Case designation (GWI or Healthy Control), [b] PTSD level (PTSD-related symptoms from DTS total), [c] Fatigue (as designated by MFI General Fatigue); B indicates unstandardized coefficients, r_{sp}^2 indicates squared semi-partial correlations Abbreviations were also used. High Sch = High School, Cond. = Condition.

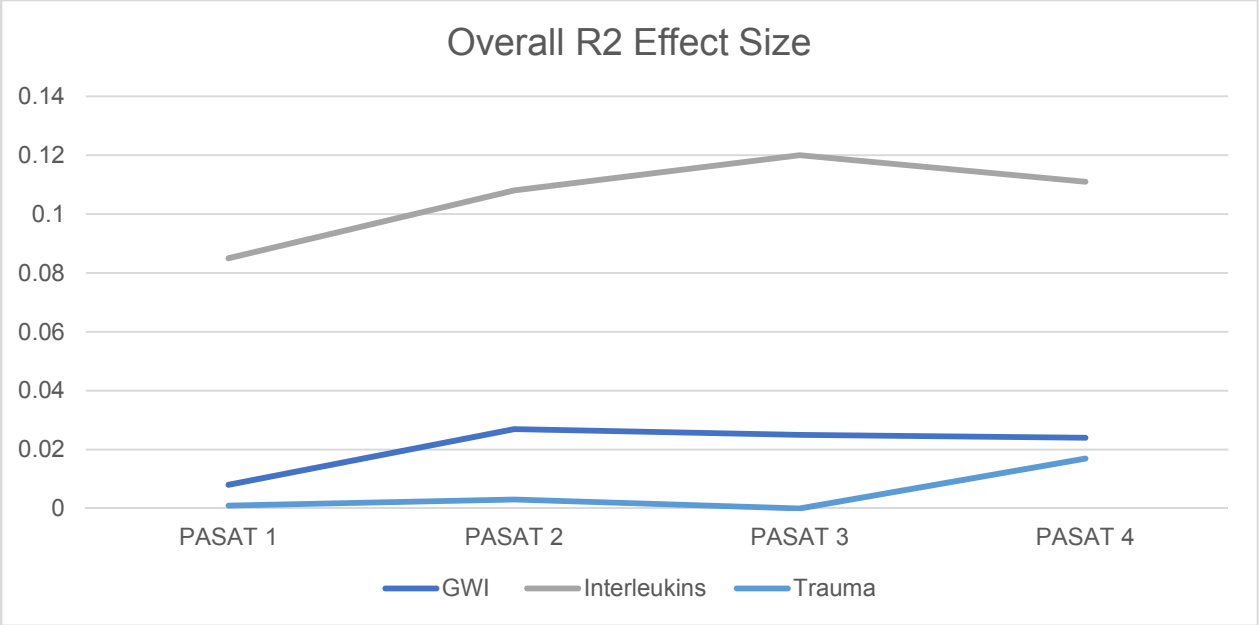

Figure 8. The change in R^2 across all four PASAT trials for GWI, Cytokines and Trauma (PTSD). This graph shows that cytokines had the highest effect across trials. GWI also had a meaningful effect in Trial 2, 3, and 4. However, PTSD was only meaningful in the last trial.

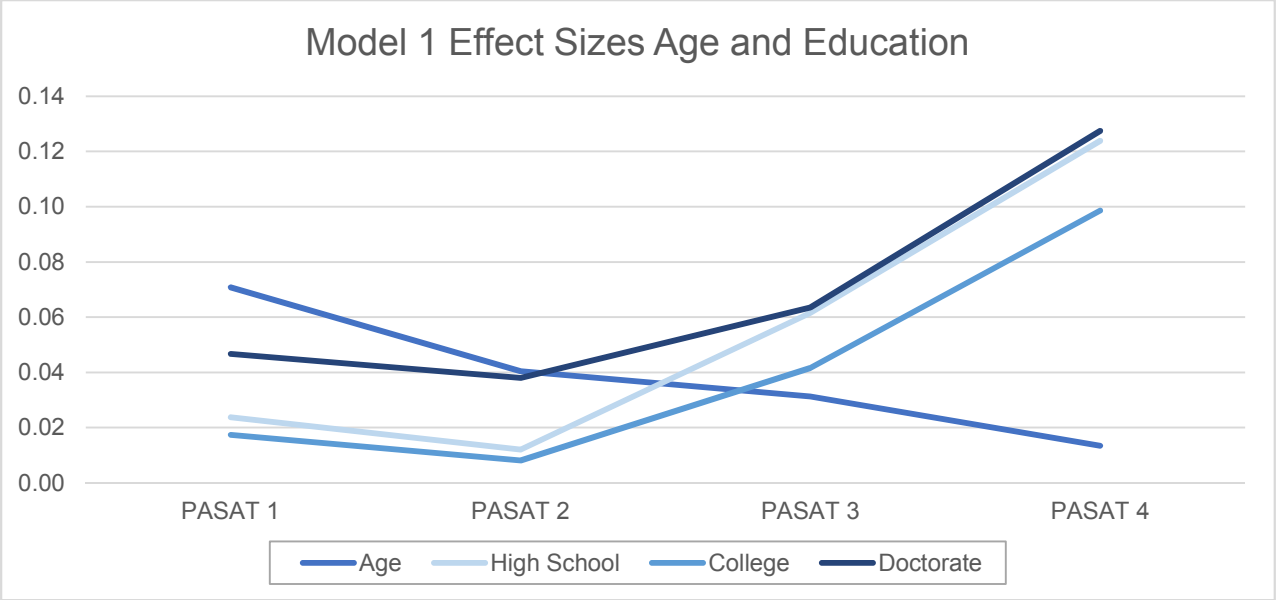

Figure 9. Coefficient effect size as plotted by each trial for Model 1 which included age and education level (high school, college, doctorate). Age showed a meaningful effect until Trial 4. For education, a doctoral level of education demonstrated a meaningful effect across all trials. A high school level of education showed a meaningful effect for all trials except Trial 2. A collegiate level of education was only meaningful within the last two trials.

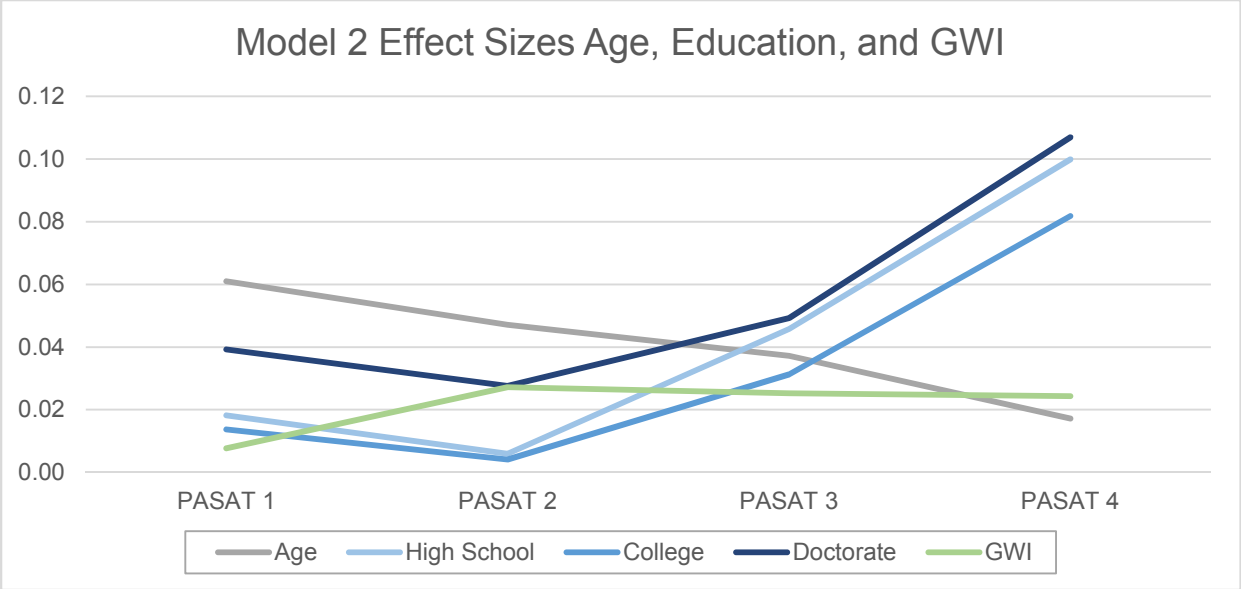

Figure 10. Coefficient effect size as plotted by each trial for Model 2 which included age, education level (high school, college, doctorate), and health condition (GWI or healthy control). Age and education levels held virtually the same pattern as the first model. GWI demonstrated a meaningful effect for Trial 2, 3, and 4.

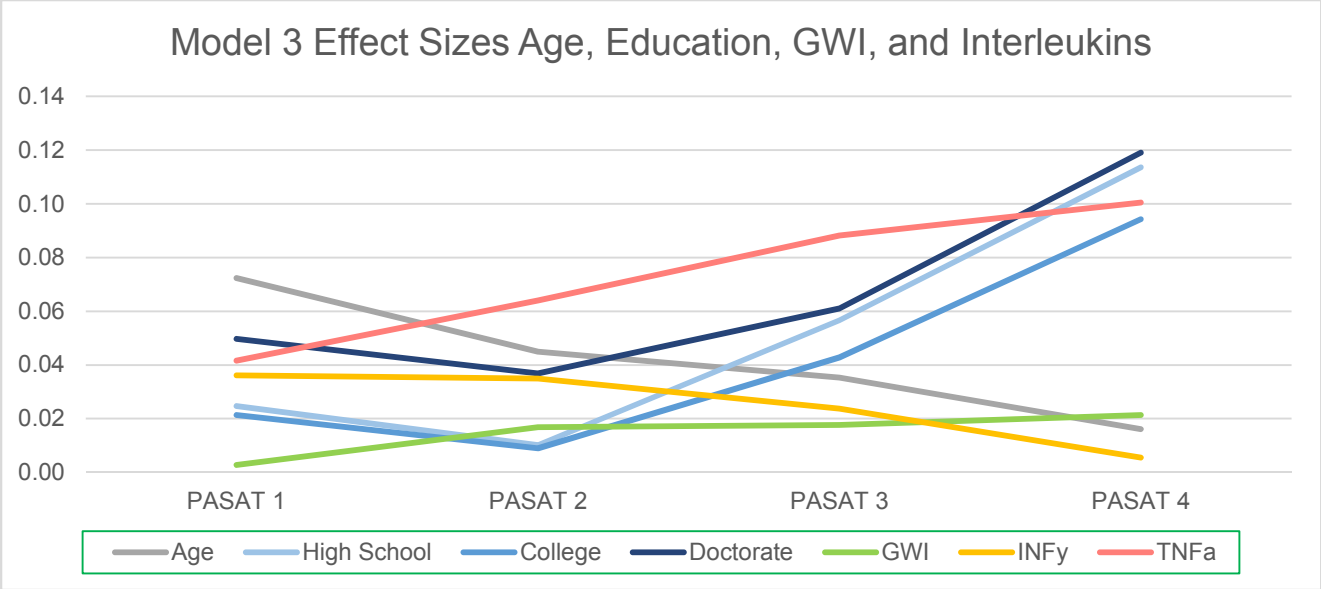

Figure 11. Coefficient effect size as plotted by each trial for Model 3 which included age, education level (high school, college, doctorate), health condition (GWI or healthy control), and cytokines INFγ and TNFα. Age and doctoral level of education retained the same pattern. The high school level of education showed meaningful impacts on Trial 1, 3, 4 in addition to a collegiate level of education. GWI was only meaningful in the last PASAT trial. One of the stronger predictors was TNFα which was meaningful across trials. However, INFγ showed a different pattern as it decreased in effect size with a non-meaningful effect in the last trial.

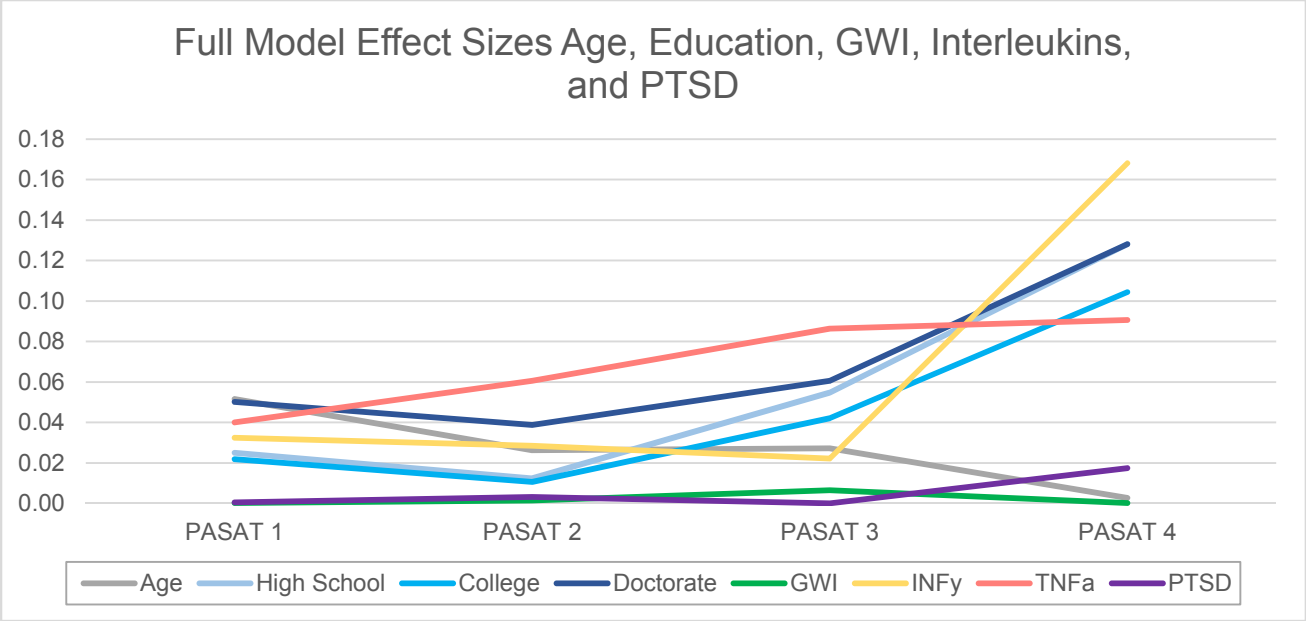

Figure 12. Coefficient effect size as plotted by each trial for Model 4 which included age, education level (high school, college, doctorate), health condition (GWI or healthy control), cytokines INFγ and TNFα, and PTSD level. Age and education level retained the same pattern as Model 3. GWI did not demonstrate a meaningful effect. TNFα remained a strong predictor across trials. Additionally, INFγ was significant across all trials with the highest effect in the last trial.

Chapter V: Discussion

The present study was designed to investigate GWI, a debilitating and poorly understood condition, and its impact on cognition, a common symptom endorsed by diagnosed veterans (Smith et al., 2012; Yee et. al., 2016). Research investigating GWI is limited; as such, research investigating neuropsychological performance in GWI is understandably sparse, especially when considering how aspects such as trauma and fatigue, may also confound the relationship between GWI and cognitive functioning. Initially, this study had two primary goals. The first goal was to investigate the unique contribution of GWI, PTSD symptoms, and fatigue towards performance across four trials of a measure of working memory and attention while controlling for age and education level. Secondly, the investigator aimed to analyze how GWI and levels of targeted interleukins, IL-4 and IL-10, impacted reported levels of fatigue across five domains: General Fatigue, Physical Fatigue, Mental Fatigue, Reduced Activity, and Reduced Motivation. Given the lack of meaningful results within the second analysis, the researcher tested a post-hoc hypothesis that investigated how GWI, pro-inflammatory cytokines correlated with PASAT, and PTSD symptoms contributed to performance on the attention and working memory measure while controlling for age and educational level. All of these hypotheses were tested with a set of hierarchical regression analyses, detailed further.

Primary Outcomes

The first goal of this current study was to examine how GWI, PTSD, and fatigue impacted the amount of correct answers on a measure of working memory and attention (i.e., PASAT). It was hypothesized that GWI diagnosis would account for the most

variance (after accounting for age and education) followed by PTSD symptoms and fatigue. Therefore, GWI status would overall be the primary factor that contributed to worse scores on the PASAT, with trauma being the second most relevant factor followed by fatigue.

Primary Outcome First Hypothesis. Regarding demographic factors, the GWI and healthy control group did not differ significantly on age or educational demographic factors. Additionally, the GWI and healthy control group were roughly consistent regarding the dispersion of different age ranges, race, ethnicity, and educational levels. Analysis of the full model (Model 4) with age and education, GWI status, PTSD symptoms, and fatigue did not return any statistical significance as defined by an alpha level at or below .05. Additionally, no hierarchical models prior to the full model (Model 1, Model 2, and Model 3) demonstrated statistical significance. These results are likely attributable to the underpowered sample size; therefore, effect sizes for the overall models and coefficients were calculated to estimate a clinical effect. For the first trial of PASAT, the only model that showed a meaningful effect (R^2 = .178) was the first model with age and education, showing that increase in age was generally associated with poorer scores on the PASAT and education overall was associated with higher scores. The second trial of PASAT, with a slight increase in task demands, again showed that the model with age and education was the only model that met the threshold of clinical significance (R^2 = .136) with age associated with worse scores and education (i.e., high school and doctorate) associated with higher scores. However, the second model approached a meaningful effect (ΔR^2 = .019) with GWI status associated with poorer performance over and above age and education. Even with increased task demands in the

third trial of the PASAT, only age and education remained significant predictors, demonstrating the same trends as previous trials in Model 1 (R^2 = .161). The most interesting findings were seen in the last trial of the PASAT, Trial 4, which is the most difficult trial with the highest task demands. The first model demonstrated a meaningful effect (R^2 = .184).; however, education accounted for the meaningful variance, with age no longer associated with score performance. The second model, which added GWI, demonstrated an effect approaching a meaningful score (ΔR^2 = .019), with GWI demonstrating a small effect and negatively impacting scores. However, the third model was clinically significant (ΔR^2 = .034) and GWI as a predictor was no longer meaningful once PTSD symptoms were added to the model.

Therefore, these results did not support the hypothesis that GWI status would account for the most variance once controlling for age and education. At best, when GWI is added to the model, it approaches significance and parameters show a possible small effect size. However, the only other model that met the threshold outside of age and education models included GWI and PTSD with PTSD accounting for the meaningful variance. Therefore, GWI may only be somewhat meaningful when psychological variables are not accounted for via the analyses.

Of note, these analyses were performed again without identified outliers. The interpretation of the data virtually remained the same with a few exceptions. Within the PASAT Trial 3, the second model approached significance, but did not meet the threshold, indicating a possible small effect associated with a GWI diagnosis. Additionally, in the fourth trial of the PASAT, the first model with age and education met statistical significance (R^2 = .198, p = .054). However, the interpretation via effect sizes

remained the same with PTSD accounting for more variance over GWI once added to the model.

The PASAT data was also reanalyzed using recoded education data in which the elementary school participant (n = 1) was included in the high school level education group. The interpretation of the data with outliers changed as high school level of education now had a non-meaningful semi-partial correlation effect size in the final model of PASAT Trial 1. Additionally, PASAT Trial 2 results were interpreted differently as the R^2 effect size showed a small effect in Model 1 (.12) and Model 2 (.026). PASAT Trial 3 returned different scores as the R^2 effect size in Model 1 (.086), Model 2 (.116), Model 3 (.116) and Model 4 (.124) was interpreted as small. Furthermore, the incremental R^2 effect size for Model 2 was now a small effect size (.03). Lastly, for semi-partial correlation effect sizes of the final model, age had a small effect whereas high school and doctoral level of education was now non-meaningful. Finally, PASAT Trial 4 returned different R^2 effect sizes for Model 1 (.051), Model 2 (.1), Model 3 (.11) and Model 4 (.11) which were interpreted as small effect sizes. As in Trial 3, the incremental R^2 effect size for Model 2 was now a small effect (.05). Lastly, the semi-partial correlations did not return a meaningful effect for high school education, doctoral education, or PTSD symptoms.

These results are inconsistent with the more rigorous literature regarding GWI and neuropsychological problems, pointing towards a problem in attention (Januelwicz et al., 2017; Sullivan et al., 2018) in those with GWI. However, these studies included multiple measures of attention; therefore, these results may differ based on the limitation of having one neuropsychological measure of attention. Studies that utilized the PASAT

(David et al., 2002; Toomey et al., 2009; Wallin et al., 2009; White et al., 2001) did not find significant or effect sizes that were meaningful (Wallin et al., 2009) once accounting for multiple comparisons (White et al., 2001). Additionally, some studies found significance, but once psychological effects were accounted for, the relationship was no longer significant (Lange et al., 2001; Lindem et al., 2003). Therefore, the PASAT may be measurement that is sensitive to psychological issues, making it difficult to partial out biological correlates of poor attention in GWI.

Primary Outcome Second Hypothesis. The secondary aim of this investigation was to test if health condition and interleukins were linked to the fatigue factor, anticipating that fatigue was also a significant contributor to poor cognitive outcomes. Although fatigue was not a significant factor for the PASAT, analysis on all five domains of the MFI (i.e., General Fatigue, Physical Fatigue, Mental Fatigue, Reduced Fatigue, and Reduced Activity were carried out. The first variable tested was health condition, GWI versus healthy controls, followed by interleukins. Interleukins were identified via previous research as IL-4 and IL-10 were associated with MFI results (Broderick et al., 2013). Results across all five domains showed a major effect in health condition. Veterans diagnosed with GWI were more likely than their healthy counterparts to endorse higher levels of General Fatigue ($R^2 = .582$, $p < .001$), Physical Fatigue ($R^2 = .562$, $p < .001$), Mental Fatigue ($R^2 = .503$, $p < .001$), Reduced Activity ($R^2 = .489$, $p < .001$), and Reduced Motivation ($R^2 = .489$, $p < .001$). The addition of interleukins overall did not significantly add to the model outside of a small effect of IL-4 that pointed towards higher levels of this interleukin begin associated with higher levels of Mental Fatigue.

Of note, these analyses were ran without outliers identified in the dataset. Without

outliers, interleukins initially showed a small meaningful effect, $\Delta R^2 = .049$; however, IL-4 and IL-10 alone did not produce meaningful results. However, Physical Health showed a small meaningful effect in the interleukin module, with IL-10 elevations being associated with higher levels of Physical Fatigue. Overall, the only difference in interpretation was the possible association between higher IL-10 and higher levels of Physical Fatigue.

The finding that Mental Fatigue (i.e., poor concentration, difficulty focusing) was associated with IL-4 is unique. The relationship underlying this connection remains unclear as IL-4 is not as well studied as other cytokines in relation to psychological variables. IL-4 is known to be involved in a Th2 immune response (anti-inflammatory responses). However, IL-4 is also associated with allergies, autoimmunity, and cancer (Craddock et al., 2015). In regard to GWI, IL-4 has been elevated in veterans deployed to the Gulf War and may have an impact on immune activation (Skowera et al., 2004). Additionally, IL-4 has been elevated in chronic fatigue syndrome, indicating a possible etiology (Montoya et al., 2017; Fletcher et al., 2009). However, it remains unclear how IL-4 contributes to mentally based fatigue, and no precedent has been established in literature linking higher levels of IL-4 to issues with poor concentration and focus. However, researchers have hypothesized that pro-inflammatory cytokines as well as cytokine imbalance has a role in mood disorders including ADHD. One study demonstrated that children with comorbid ADHD and asthma (i.e., a disorder associated with IL-4 levels) had higher risk of developing a major depressive disorder or a bipolar disorder (Chen et al., 2013). Additionally, cerebral spinal fluid analysis of ADHD patients has shown reduced levels of IL-4 (Verlaet, Noriega, Hermans, & Savelkoul,

2014). However, another study investigating early-onset schizophrenia demonstrated that higher levels of IL-4 were associated with the negative symptoms of schizophrenia, known to be associated with more cognitive deficits. Therefore, the literature remains unclear about the specific role IL-4 has in cognitive behavior, which is understandable given the complexity of the issues as well as the sensitivity to the immune systems in shifts in interleukins (Simsek et al., 2016).

The association between elevated IL-10 and elevated Physical Fatigue has minor support in research literature. Some studies support this possible finding as IL-10 has been elevated in those with chronic fatigue syndrome, a "sister" diagnosis to GWI as it also is characterized by fatigue levels (Brenu et al., 2011, Nakamura et al., 2010, Natelson et al., 2005). A systematic literature review investigating CFS and immune levels showed that interleukin-10 genetic expression was also significantly higher and associated to post-exertional malaise (Nijs et al., 2014). However, it is unclear how IL-10 is specific to fatigue in a physical sense outside of this current finding.

Primary Outcome Post-Hoc Analysis. The PASAT data model was re-analyzed, removing fatigue as a variable, as fatigue measures did not contribute significantly, and the literature did not support the use of the PASAT in fatigue-like syndromes (Johnson et al. 1997). Additionally, pro-inflammatory cytokines correlated with the PASAT were added to investigate an immunological trend in attention and working memory. Analysis was conducted through a hierarchical regression model with the first model controlling for age and education, the second model adding health condition (GWI versus healthy controls), the third model adding notable proinflammatory cytokines (i.e., TNFα and INFγ), and the final model adding PTSD symptoms. The final model that included all the

variables only showed significance within the last trial of the PASAT, with the last added variable of PTSD not demonstrating a significant change. Therefore, effect sizes were used to determine meaningful significance given that the sample size likely contributed to reduced power. Lastly, the investigator was primary interested in the original data; therefore, the difference in results based on the absence of outliers or recoded education data is detailed in Tables 22, 24, 26, and 28 and specified results section.

Effects sizes, as determined by ΔR^2 was used to determine if added variables contributed meaningfully to the model after controlling for age and education. The most striking finding across the models was that the addition of cytokines overall contributed to significant change in all four trials of the PASAT (Trial 1 $\Delta R^2 = .085$; Trial 2 $\Delta R^2 = .108$; Trial 3 $\Delta R^2 = .120$; Trial 4 $\Delta R^2 = .111$). Additionally, cytokines appeared to play more of a role in PASAT performance in harder trials (i.e., Trial 3 and 4). Health condition, or GWI status, which was hypothesized to be the most significant contributor appeared to have a small impact on PASAT Trials 2 through 4 (Trial 1 $\Delta R^2 = .008$; Trial 2 $\Delta R^2 = .027$; Trial 3 $\Delta R^2 = .025$; Trial 4 $\Delta R^2 = .024$). However, PTSD symptoms did not contribute meaningfully to any PASAT trials.

To investigate specific contributions, overall effect sizes in conjunction with coefficient effect sizes were also investigated for each PASAT trial. For the first PASAT trial, the first model that included only age and education demonstrated a meaningful effect ($R^2 = 164$) with age negatively associated with PASAT performance and education positively associated with PASAT performance. The only other model with a meaningful effect for the first trial was Model 3 with age, education, GWI status, and cytokines ($\Delta R^2 = .085$). It was demonstrated that both TNFα and INFγ had a small and negative impact,

indicating that higher levels of these pro-inflammatory cytokines were indicative of worse performance on the first trial of the PASAT.

Analyses of the second PASAT trial, showed that Model 1 with age and education, Model 2 with age, education, and health status, and Model 3 with age, education, health status, and cytokines demonstrated a meaningful effect. As stipulated before, increased age was linked to worse PASAT performance; however, only education at the doctoral level was associated with higher scores. Model 2 had the same results in regard to age and education level; however, those with GWI were more likely to perform worse on the second trial of the PASAT. With the addition of the cytokines, age, education, and GWI status demonstrated the same patterns. Both TNFα and INFγ continued to have a small and negative impact on PASAT Trial 2 performance.

For the third PASAT trial, an overall meaningful effect was also seen in Model 1, Model 2, and Model 3. However, Model 3 was also statistically significant, with cytokines leading to a ΔR^2 of .120, $\Delta F(2, 40) = 3.391$, $p = .044$, and an overall model significance of $F(7, 40) = 2.349$, $p = .042$. For Model 1, the age coefficient had a small negative impact on PASAT scores while all education level coefficients demonstrated a positive impact. For Model 2, age and education coefficients held the same effect while GWI contributed negatively to PASAT scores on a small scale. For Model 3, the coefficients for age, education, and GWI continued to demonstrate the same pattern; however, the addition of both TNFα and INFγ showed a small and negative impact on PASAT performance.

For the last and hardest PASAT Trial, Model 1, 2, and 3 demonstrated a meaningful effect overall. For Model 1, age was not meaningful while education

continued to be associated with higher PASAT Trial 4 scores. Of note, doctoral education had a medium level impact while high school and college levels had a small impact. For Model 2, age was shown to have a small negative impact, whereas all education levels had a small positive impact on PASAT scores. GWI, as an added variable, showed a small negative impact as well. For Model 3, there was statistical significance alongside a meaningful effect for the addition of cytokines with a ΔR^2 of .111, $\Delta F (2, 40) = 3.391$, $p = .05$, and an overall model significance of $F(7, 40) = 2.639$, $p = .024$. All other coefficients (i.e., age, education, and GWI) retained the direction and level of impact on the PASAT. However, only TNFα showed a meaningful effect. Of note, the last model did have overall statistical significance even though the effect was not interpreted as meaningful ($\Delta R^2 = .017$). Nevertheless, when investigating the individual coefficients, PTSD showed a small meaningful effect. Additionally, age and GWI no longer had a negative impact on scores. Education levels ranged from small to medium and contributed to higher PASAT scores. TNFα and INFy showed a meaningful effect.

Given these results, GWI status had a small but meaningful effect particularly with later trials of the PASAT. Therefore, the post-hoc analysis somewhat supports the hypothesis that GWI status contributes to performance on a test of working memory and attention; however, these results are interpreted very conservatively given it was conducted as a post-hoc analysis. These results are more in line with literature pointing towards issues with attention in individuals with GWI (Januelwicz et al., 2017; Sullivan et al., 2018). Additionally, as the PASAT is a challenging task with further demands with each subsequent trial, the contribution of GWI within Trial 2, 3, and 4 follow patterns in physical exertion in which more symptoms and more cytokine expression is observed

under a challenge (Broderick et al., 2011). Additionally, GWI status remained significant within the later trials even with the addition of PTSD in the model demonstrating that this pattern may not be solely attributable to issues related to psychological distress. However, GWI was not the most significant contributor the model, revealing the difficulty in diagnosing GWI given its multifactorial and heterogenous nature in regard to symptom expression. Therefore, the role of cytokines, or a more objective measure of immunological dysfunction, was investigated and found to be more meaningful.

Based on these results, there is tentative evidence that cytokines TNFα and INFγ may point towards an underlying process of poorer performance in sustained attention and working memory. Considering GWI, irregular levels of TNFα have been observed in GWI veterans more often than not across investigations. Multiple studies have shown that there is suppressed activity of TNF receptors and higher responsiveness in those with GWI (Broderick et al., 2011; Broderick et al., 2013; Khaiboullina et al., 2015; Whistler et al., 2009). However, Everson et al. (2002) did not find differences in TNFα when comparing those veterans who were healthy with veterans that were symptomatic. Differences in these studies may be attributed to methodological differences as Everson et al. (2002) did not investigate GWI as defined by Fukuda et al. (1998) and tested levels of cytokine at rest. The aforementioned studies had a clear definition of GWI and also the majority of studies investigated cytokines levels at various timepoints (i.e., at rest, exertion). Regarding PTSD, there are inconsistent results regarding TNFα levels and associated PTSD symptoms. Himmerich et al. (2016) found that treatment of PTSD was associated with increased production of TNFα. However, the majority of studies, as explored in a biomarker metanalysis, determined that with increased levels of TNFα were

higher PTSD symptoms (Passos et al., 2015). Regarding the cognitive impact of TNFα, there is evidence that higher levels of TNFα in the hippocampus may impact long-term potentiation which impacts the ability to learn and remember information (Belarbi et al., 2012; McAfoose & Baune, 2008). Therefore, increased levels may have an impact on an individual's ability to use their working memory to learn and retain numbers.

Given that interleukin levels did not change when PTSD was added to the model, it appears that GWI may be more linked to TNFα, which remained a meaningful effect for the PASAT overall. However, this is a tentative interpretation as the cause of the interleukin's change (i.e. GWI or PTSD) was investigated via trends over group differences which would more clearly differentiate patterns.

In regard to INFγ, studies point towards higher levels in GWI. Elevated INFγ has been associated with veterans with multisymptom illness in vitro after controlling for age, sex, and vaccination status (Skowera et al., 2004) as well as in GWI subjects overall (Khaiboullina et al., 2015). In studies with an exercise paradigm, higher levels of INFγ in GWI cases has been associated with higher stimulation during the exercise challenge (Broderick et al., 2011) in addition to all time points (Whistler et al., 2009; Smylie et al., 2013). In regard to PTSD, metanalysis supported that PTSD symptoms were also associated with higher levels of INFγ in comparison to healthy controls. Furthermore, this pattern indicates a shift towards Th1 or a proinflammatory response given the higher levels of INFγ (Zhou et al., 2014). Unfortunately, there has not been extensive research investigating potential issues with working memory or attention and differing INFγ levels. However, higher levels of INFγ have been observed in patients with ADHD (Oades et al., 2010), which may have a contributing factor to difficulties with measures

of attention and working memory.

The final analysis was conducted to include IL-6 and IL-8 in the same model for the post hoc analysis. Therefore, the hierarchical regression model was designed to have the first model with predictors of age and education, the second model with the health condition predictor, the third model with the TNFα, INFγ, IL-6, and IL-8 predictors , and the fourth model with the PTSD symptoms predictors. Given the similarity of the models, the primary focus of the discussion will be on the added interleukins or changes in the model. Additionally, the investigator focused on the original data with data reported without outliers or recoded as detailed in Tables 30, 32, 34, and 36 and specified results section.

There were minimal changes when adding the interleukins IL-6 and IL-8. There were no changes in the PASAT Trial 1 model, and semi-partial correlation effect sizes showed that Il-6 and IL-8 were non-meaningful. In regard to PASAT Trial 2, the only change was seen in the semi-partial correlation effect sizes in which high school education was now interpreted as small (.02), rather than non-significant. Lastly, the semi-partial correlation effect sizes for IL6 was non-meaningful and the IL-8 interleukin was interpreted as small. PASAT Trial 3 interpretation was changed as health condition and PTSD symptoms were interpreted as small via their semi-partial correlation effect sizes. However, IL-6 and IL-8 were non-meaningful in the final model. Lastly, the PASAT Trial 4 returned significance for the first Model ($p = .045$) which was previously non-significant. Additionally, semi-partial correlation effects sizes showed that IL-6 and IL-8 were non-meaningful.

Limitations. Several limitations are noteworthy given the interpretation of these

results. The most striking limitation is the small sample size especially considering the multiple analyses conducted. Therefore, effect sizes were utilized over an alpha level criterion as the study was likely underpowered and interpretation would have a higher risk for Type 2 errors. Additionally, the small sample size and use of measures limited the ability to truly investigate the differences between individuals with PTSD. The only measure of PTSD was a screening measure (i.e., DTS), which is not sufficient for a formal diagnosis, and therefore the score was used as a range of PTSD symptom severity. Additionally, this limited the available analyses for PTSD and GWI as a formal diagnosis of PTSD would have lent itself to a group analysis. Therefore, this study cannot formally declare the etiology of cytokines given its association with GWI and PTSD. Another notable limitation is the use of one measure of attention and working memory. Additional differential measures of attention and working memory would have been beneficial to investigate if a similar trend was observed in both measures, especially given that neuropsychological measures can detect different trends solely on the method or task design. The PASAT also had notable limitations for this particular participant group being that age effects are seen after age 50 (Roman et al., 1991) , there is high correlation with educational attainment (Stuss et al., 1987), there is a small normative sample (n = 80) from New Zealand (Gronwall & Wrightson, 1974), and there are notable practice effects (Gronwall, 1977). Another limitation is that interleukin measures included in the analysis were only at rest, as that was the only time the PASAT was administered. Therefore, the researcher is unable to make inferences based on what immunological markers would have been impacted during a stimulated hyperimmune response. Additionally, cytokines are very sensitive to changes regarding the time of day, physical

exertion, gender, and other cytokines or hormones. The researcher attempted to control for these factors by including only men in her analysis and cytokines were interpreted at rest. However, it may have been beneficial to investigate the connection between cortisol given the connection between the HPA axis and cytokines (Craddock et al., 2014).

Strengths. Strengths of the study include the control of heavily influential factors and the investigation of a more objective measure of immunological function over heterogenous diagnostic categories for GWI. Specifically, age and education level were controlled for in each analysis especially given that these are known to impact PASAT functioning. Additionally, several studies of GWI are limited in that toxin exposure is based on self-report of toxin exposure or plume analysis which rely on retrospective techniques. The inclusion of cytokines in the analysis enabled the investigator to observe immunological deficits at the time of test administration and therefore, was able to demonstrate consistent patterns of dysfunction despite the large gap of time between the Gulf War and the study. The impact of GWI and cytokines also remained significant even with the inclusion of PTSD severity, which helped support the argument towards an underlying biological process over a purely somatic or psychological one.

The use of the PASAT also had several strengths it that it was a measure with high consistency (Cronbach's alpha = .90; Crawford, Obansawini, & Allan, 1998) and reliability (r = .83-.96; Sjogren, Thomsen, & Olsen, 2000). Additionally, the measure showed good convergent validity (Deary, Langan, Hepburn, & Frier, 1991; Gronwall & Wrightson, 1981; Sherman, Strauss, & Spellacy, 1997; Schachinger, Cox, Linder, Brody, & Keller, 2003) and construct validity (Larrabee & Curtiss, 1995). Lastly, this measure was also thought to be sensitive to fatigue; the personal experiences of this examiner

found many individuals exhibit signs of fatigue towards the last two trials of the task. However, Johnson et al. (1997) found that there were no fatigue effects even with four re-administrations of the task.

Future Directions. This study points towards potential attention or working memory difficulties in veterans with GWI and PTSD symptoms alongside imbalanced levels of certain cytokines. Results of this study would be bolstered with the use of more validated measures of attention and working memory. Additionally, it would be helpful to investigate a cytokine profile with a full neuropsychological battery to better understand the full profile of neuropsychological deficits associated with GWI and PTSD. Furthermore, it remains unclear what aspects of immunological dysfunction are linked to neuropsychological deficits. Repetition of these analyses can show a clearer pattern of biomarkers associated with cognitive symptoms in GWI and PTSD and point towards a specific etiology to better assist diagnosis and treatment.

Another suggestion for future research is the use of more validated measures of PTSD such as the CAPS when investigating neuropsychological performance in conjunction with immunological markers. These investigations would further clarify what cytokines contribute uniquely to GWI and PTSD and its individual influence on cognitive measures, which would further benefit neuropsychologists examining a patient with potential GWI symptoms.

Conclusions

In general, the results are somewhat consistent with prior literature pointing towards problems with attention and working memory (i.e., learning) in GWI. These results show that GWI may contribute to attention and working memory as determined by

one measure; however, the utility of the GWI diagnosis is questionable once other variables are added, especially interleukin. However, these results also did not support the literature that pointed towards a specific psychological etiology in GWI as PTSD as a factor did not appear to meaningfully contribute to the task performance except during the last and hardest trial. Therefore, PTSD symptoms may only play a factor during higher task demands regarding attention and working memory. Overall, this study was able to contribute to the literature of GWI showing the role of cytokines across trials of a working and memory task, in conjunction with a GWI and PTSD diagnosis.

Of note, how cytokines are activated and what role they play in attention and working memory remains to be seen in this study. As GWI and PTSD both are associated with overactive body states, these cytokines could be linked to either condition. Therefore, more rigorous attention to PTSD as a diagnosis is imperative to elucidate these patterns when investigating cytokine levels. This research should also be conducted with awareness that cytokines are sensitive to so many other aspects including gender of the participant, time of day, and level of exertion.

Finally, this study showed a pattern using only one measure of attention and working memory and would have benefitted from a full neuropsychological battery. However, the study did show that cytokines were associated with changes in performance, which gives credence to the study of cytokines in neuropsychological batteries especially in conditions known to impact neurological systems. Additionally, a pattern towards a certain immunological pattern does lend a more biological lean towards GWI and PTSD, which may open more treatment and diagnostic avenues for future practitioners and considerations for those testing the cognitive and biological components

of our veterans.

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Appendix A

Abbreviations

Abbreviation List

Beck Anxiety Inventory	BAI
Beck Depression Inventory	BDI
Brief Symptom Interview	BSI
California Verbal Learning Test	CVLT
Camden Recognition Memory Tests	CRMT
Chemical or Biological Warfare	CBW
Chronic Fatigue Syndrome	CFS
Chronic Multi-Symptom Illness	CMI
Clinical-Administered PTSD Scale	CAPS
Cognitive Failures Questionnaire	CFQ
Combat Exposure Scale	CES
Continuous Performance Test	CPT
Cornell Index	CI
Davidson Trauma Scale	DTS
Expanded Health Symptom Checklist	HSC
Enzyme-Linked Immunosorbents Assay-Based Test	ELISA
Gulf War Illness	GWI
Gulf War Syndrome	GWS
Gulf War Veterans	GWVs
Institutional Review Board	IRB
Interleukin 4	IL-4
Interleukin 10	IL-10

Interleukin 12	IL-12
Life Experience Scale	LES
Major Depressive Disorder	MDD
Medical Outcome Study Short-Form	SF-36
Minnesota Multiphasic Personality Disorder- Second Edition	MMPI-2
Mississippi Combat-Related PTSD Scale	MCRP
Multidimensional Fatigue Inventory	MFI
National Adult Reading Test	NART
Oregon Dual Task Procedure	ODTP
Paced Auditory Serial Addition Test	PASAT
Penn Inventory for PTSD	PIP
Personality Assessment Inventory	PAI
Positive Affect/Negative Schedule	PANS
Post-Traumatic Stress Disorder	PTSD
Post Traumatic Stress Disorder Checklist	PCL
Profile of Mood States	POMS
Pyridostigmine Bromide	PB
Rey Auditory Verbal Learning Test	RAVLT
Rey-Osterrieth Complex Figure Test	ROCF
State-Trait Anger Expression Inventory	STAEI
State-Trait Anxiety Inventory	STAI
Structural Clinical Interview for DSM	SCID
Substance Abuse Subtle Screening Inventory	SASSI

Sustained Attention to Response Task	SART
Symptom Checklist-90-Revised	SCL-90-R
Test of Memory Malingering	TOMM
Trail Making Test	TMT
Weschler Adult Intelligence Scale-Revised	WAIS-R
Weschler Adult Intelligence Scale- Third Edition	WAIS-III
Weschler Memory Scale-Revised	WMS-R
Wisconsin Card Sorting Test	WCST

Appendix B:
Tables

Table 37
Correlations Part 1

	Con	Age	HS	Col	Doc	TrSx	PT1	PT2	PT3	PT4	IL1a	IL1b	IL2	IL4	IL5	IL6	IL8	IL10	IL12	IL13	IL15	IL17	IL23	IFNy
Con	1																							
Age	.1	1																						
HS	-.1	-.3	1																					
Col	.2	.1	-.7	1																				
Doc	-.2	.2	-.3	-.4	1																			
TrSx	.8*	.3	-.2	.3	-.2	1																		
PT1	-.2	-.2	.1	-.2	.3	-.2	1																	
PT2	-.3	-.2	.1	-.2	.3	-.3	.9	1																
PT3	-.2	-.3	.3	-.3	.2	-.3	.8	.9	1															
PT4	-.3	-.2	.3	-.3	.2	-.3	.7	.7	.9	1														
IL1a	.1	.1	-.0	.1	-.1	.1	-.1	-.2	-.2	-.2	1													
IL1b	.1	.1	-.2	.1	.1	.2	-.1	-.2	-.2	-.3	.4	1												
IL2	-.1	.2	-.1	.2	-.1	-.1	-.2	-.2	-.2	-.1	.0	.0	1											
IL4	-.2	.0	.1	.0	-.1	-.1	.1	.1	.1	.1	.0	-.1	.8	1										
IL5	.0	.1	-.2	.2	-.1	.1	-.3	-.3	-.3	-.2	.7*	.3	.6	.6	1									
IL6	.1	.2	-.2	.3	-.1	.1	-.3	-.3	-.4	-.3	.7	.3	.6	.5	1	1								
IL8	.3	-.0	-.0	-.1	.1	.3	-.3	-.4	-.4	-.3	.4	.5*	.3	.1	.5	.5	1							
IL10	-.4	.3	.0	.1	-.1	-.3	-.2	-.1	-.1	-.0	.3	.3	.7	.6	.5	.5	.1	1						
IL12	-.1	-.0	-.1	.2	-.1	-.2	-.0	.0	-.0	.1	-.0	-.0	.6	.7	.4	.3	.0	.5	1					
IL13	.0	.1	-.1	.2	-.1	.1	-.2	-.3	-.3	-.2	.4	.2	.9	.7	.9	.9	.5	.6	.5	1				
IL15	-.1	.1	-.1	.1	.0	-.0	-.2	-.3	-.3	-.3	.6	.7	.2	.1	.5	.5	.7	.4	.2	.4	1			
IL17	-.2	.2	-.1	.2	-.0	-.1	-.3	-.3	-.2	-.1	.1	-.0	.7	.5	.6	.6	.1	.5	.3	.7	.1	1		
IL23	-.1	.0	-.3	.2	.0	-.2	-.1	-.0	-.1	-.0	-.1	.0	.7	.5	.5	.5	-.0	.4	.7	.6	.1	.6	1	
IFNy	-.0	.0	-.1	.0	.2	.1	-.3	-.4	-.4	-.3*	.3	.5	.3	.1	.5	.5	.8	.3	.2	.5	.8	.1	.1	1
TNFa	.0	.1	-.1	.1	.0	.1	-.3	-.3	-.4	-.3	.8	.7	.2	.1	.7	.7	.7	.4	.1	.5	.9	.2	.1	.8

Note: *Bolded indicated significant values. Con = Condition, HS = High School, Col = College, Doc = Doctorate, TrSx = PTSD Symptoms, PT1 = PASAT Trial 1, PT2 = PASAT Trial 2, PT3 = PASAT Trial 3, PT4 = PASAT Trial 4, IL1a = Interleukin 1a, IL1b = Interleukin 1b, IL2 = Interleukin 2, IL4 = Interleukin 4, IL5 = Interleukin 5, IL6 = Interleukin 6, IL8 = Interleukin 8, IL10 = Interleukin 10, IL12 = Interleukin 12, IL13 = Interleukin 13, IL15 = Interleukin 15, IL17 = Interleukin 17, IL23 = Interleukin 23, IFNy = Interferon gamma, TNFa = Tumor necrosis factor alpha

Table 38
Literature Review Summary

First Author (Year)	N	Age	Education	GWI?	Primary Significant Outcomes
Axelrod (1997)	44	33.3	13.5	No	Grooved Pegboard, Stroop, MMPI
Sillanpaa (1997)	49	33.59	13.47	No	Regression Model of Affective Symptoms
Proctor (2003)	215	38.8	Not Reported	No	POMS
White (2001)	240	D = 53.8, ND = 41.0	D = 13.7 ND = 13.7	No	POMS, CPT
David (2002)	341	See reference	See reference	Yes	MPS
Wallin (2009)	41	GWI = 34.5 HC = 30.4	See reference	Yes	PAI, SF-36
Hom (1997)	46	GWI = 47.81 HC = 47.95	GWI mean = 11.92 HC mean = 12.50	Yes	HII, FSIQ, Weschler VI, Perceptual-Motor Intelligence, CT, TMT (Trails B), Motor Tests, WAIS-V, WAIS- Comprehension, PAI
Anger (1999)	101	Cases = 32.6 Controls = 30.6	Cases = 13.5 Controls = 13.8	Yes	Psych, ODTP, Symbol Digit, Simple Reaction Time, Digit Span
Lange (2001)	87	Healthy = 34.3 GWI = 35.5	Not reported	Yes	PASAT, Category Test, NES SRT Category Test
Proctor (2006)	140	See reference	See reference	No	PP, Block Designs
Janulewicz (2017)	14	Not reported	Not reported	No	Block Designs, Digit Span, TMT, CVLT, CP,
Vasterling (1998)	43	Healthy = 35.3 PTSD = 36.3	Healthy = 14.6 PTSD = 13.8	No	Arithmetic, CPT, RAVLT, Continuous Visual Memory Test
Lindem (2003)	240	GW = 34.9 Germany = 41.0	GW = 13.9 Germany = 13.7	No	WAIS-R Information, CPT, FTT, PP, CVLT, WMS Visual Reproduction, POMS
Sullivan (2003)	260	GW-D= 35.6 Non-GW-D = 30.8	GW-D = 13.4 Non-GW-D = 13.9	No	Digit Span, Block Design, Visual Reproduction, ROCF, POMS, TOMM, WCST
Sullivan (2018)	159	See reference	See reference	Yes	CPT, ROCF