NeuroImage: Clinical 36 (2022) 103146

Contents lists available at ScienceDirect

NeuroImage: Clinical

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

PTSD symptomatology is selectively associated with impaired sustained attention ability and dorsal attention network synchronization

Travis C. Evans [a,b,*], Marina Rodriguez Alonso [c], Audreyana Jagger-Rickels [a,d], David Rothlein [a,d], Agnieszka Zuberer [a,e,f], John Bernstein [g], Catherine B. Fortier [g,h,i], Jennifer R. Fonda [b,g,h,i], Audri Villalon [j,k], Ricardo Jorge [j,k], William Milberg [g,h,i], Regina McGlinchey [g,h,i], Joseph DeGutis [a,h,i], Michael Esterman [a,b,d,l]

[a] Boston Attention and Learning Lab (BALLAB), VA Boston Healthcare System, USA
[b] Department of Psychiatry, Boston University School of Medicine, USA
[c] Department of Psychology, Boston University, USA
[d] National Center for PTSD, VA Boston Healthcare System, USA
[e] Department of Psychiatry and Psychotherapy, University Hospital Jena, Germany
[f] Department of Psychiatry and Psychotherapy, University of Tübingen, Germany
[g] Translational Research Center for TBI and Stress Disorders (TRACTS), VA Boston Healthcare System, USA
[h] Department of Psychiatry, Harvard Medical School, USA
[i] Geriatric Research, Education, and Clinical Center (GRECC), VA Boston Healthcare System, USA
[j] Translational Research Center for TBI and Stress Disorders (TRACTS), Michael E. DeBakey VA Medical Center, Houston, TX, USA
[k] Beth K. and Stuart C. Yudofsky Division of Neuropsychiatry, Baylor College of Medicine, USA
[l] Neuroimaging Research for Veterans (NeRVe) Center, VA Boston Healthcare System, USA

ARTICLE INFO

Keywords:
PTSD
Sustained attention
fMRI
Neural networks
Cognition

ABSTRACT

Posttraumatic Stress Disorder (PTSD) symptomatology is associated with dysregulated sustained attention, which produces functional impairments. Performance on sustained attention paradigms such as continuous performance tasks are influenced by both the ability to sustain attention and response strategy. However, previous studies have not dissociated PTSD-related associations with sustained attention ability and strategy, which limits characterization of neural circuitry underlying PTSD-related attentional impairments. Therefore, we characterized and replicated PTSD-related associations with sustained attention ability and response strategy in trauma-exposed Veterans, which guided characterization of PTSD-related differences in neural circuit function. In Study 1, PTSD symptoms were selectively associated with reduced sustained attention ability, but not more impulsive response strategies. In Study 2, we utilized task and resting-state fMRI to characterize neural circuitry underlying PTSD-related differences in sustained attention ability. Both PTSD symptomatology and sustained attention ability exhibited converging associations with reduced dorsal attention network (DAN) synchronization to endogeneous attentional fluctuations. Post-hoc time course analyses demonstrated that PTSD symptoms were most accurately characterized by delayed, rather than globally reduced, DAN synchronization to endogenous attentional fluctuations. Together, these findings suggest that PTSD symptomatology may selectively impair sustained attention ability by disrupting proactive engagement of attentional control circuitry.

1. General introduction

Posttraumatic stress disorder (PTSD) develops in approximately 14% of post-9/11 Veterans who served in Operations Iraqi Freedom, Enduring Freedom, and/or New Dawn (Tanielian, Tanielian, & Jaycox, 2008). Broadly defined, PTSD is characterized by symptom clusters including reexperiencing (e.g., trauma-related flashbacks), avoidance (e.g., avoiding trauma-related cues), negative cognitions and mood (e.g., anhedonia), and hyperarousal symptoms (e.g., difficulty concentrating; American Psychiatric Association, 2013). In addition to trauma-related perturbations, a growing body of literature demonstrates that PTSD symptomatology is also associated with more global impairments

* Corresponding author at: VA Boston Healthcare System, 150 S. Huntington Avenue, Boston, MA 02130, USA.
E-mail address: travis.evans@va.gov (T.C. Evans).

https://doi.org/10.1016/j.nicl.2022.103146
Received 1 April 2022; Received in revised form 3 July 2022; Accepted 3 August 2022
Available online 6 August 2022

in sustained attention (for reviews, see Aupperle, Melrose, Stein, & Paulus, 2012; Scott et al., 2015). Although it remains unclear if sustained attention deficits reflect a PTSD risk factor, sequela, or both (Samuelson et al., 2020; Vasterling, Brailey, Constans, & Sutker, 1998), impaired sustained attention produces significant functional impairments and may extend PTSD chronicity (Catarino, Küpper, Werner-Seidler, Dalgleish, & Anderson, 2015; Aupperle et al., 2012; Jagger-Rickels et al., 2022). For example, disrupted cognitive functioning in PTSD is associated with difficulties maintaining employment (Smith, Schnurr, & Rosenheck, 2005). To better understand PTSD-related attentional dysfunction, however, an important first step is to more precisely characterize PTSD-related associations with sustained attention and supporting neural circuitry.

Sustained attention is a core cognitive function that maintains information processing across time, which exhibits moment-to-moment fluctuations depending on factors such as arousal and/or motivation (Shenhav et al., 2017; Sarter, Givens, & Bruno, 2001; Esterman & Rothlein, 2019; Fortenbaugh et al., 2017b). To measure sustained attention dynamics, experimental research often utilizes continuous performance tasks (CPTs) that continuously present stimuli that require

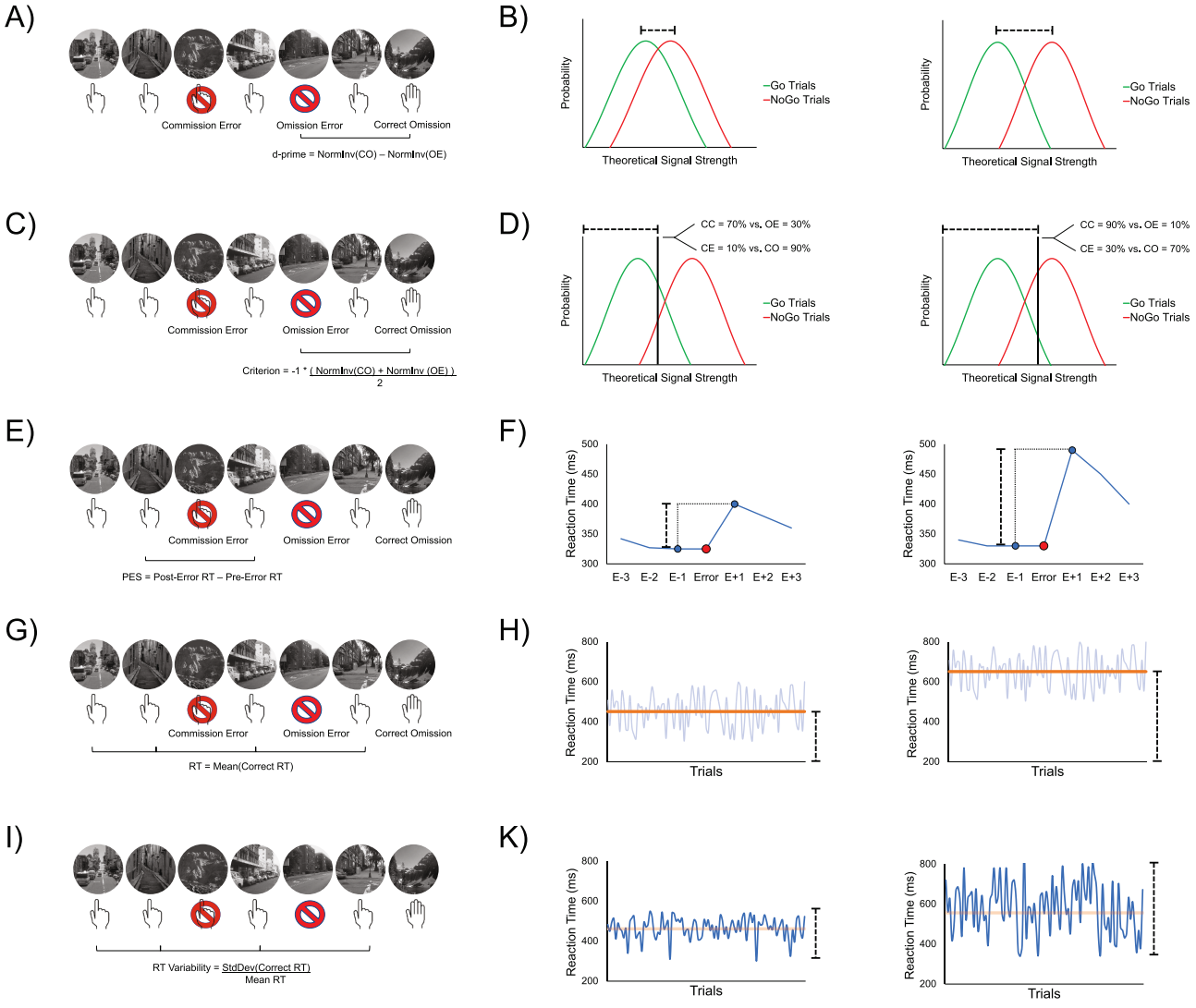

Fig. 1. Gradual Onset Continuous Performance Task (gradCPT) and Sustained Attention Measures. *Legend:* In the gradCPT, participants are instructed to respond to city scenes, but withhold responses to mountain scenes. For city scenes, participants may either correctly initiate a response (correct commission; CC) or incorrectly fail to initiate a response (omission error; OE). For mountain scenes, participants may either correctly inhibit a response (correct omission; CO) or incorrectly initiate a response (commission error; CE). A) To measure overall task accuracy, d-prime is computed as the relative normal inverse cumulative distribution function of "hits" (COs) and "false alarms" (OEs). B) For two hypothetical participants, data distributions of city trials (green lines) and mountain trials (red lines) produce a lower d-prime (left; dashed bracket) or higher d-prime (right; dashed bracket). C) Criterion is computed as the average normal inverse cumulative distribution function of "hits" (COs) and "false alarms" (OEs) and reflects the decision bias to respond or withhold response. D) For two hypothetical participants with the same d-prime, response thresholds (solid black lines) are depicted for a more conservative criterion (left; dashed bracket) or less conservative criterion (right; dashed brackets). E) Post-error slowing (PES) measures how much RT slows following an error (red circles), which is computed as the relative difference between pre-error RTs (blue circle) and post-error RTs (blue circle). F) For two hypothetical participants, post-error slowing is either smaller (left; dashed bracket) or larger (right; dashed bracket). G) Mean RT is computed as the mean (orange line) of correct response RTs to city scenes (blue lines). H) For two hypothetical participants, mean RT is smaller/faster (left; dashed bracket) or larger/slower (right; dashed bracket). I) RT variability is computed as the coefficient of variation, which is measured as the standard deviation of RTs for correct responses to city scenes (blue lines) controlling for overall mean RT (orange lines). K) For two hypothetical participants, RT variability is smaller (left; dashed bracket) or larger (right; dashed bracket).

either initiation of responses ("go" trials) or inhibition of responses ("no-go" trials; for a review, see Langner & Eickhoff, 2013). Consistent with signal detection theory (Marcum, 1960), performance on CPT paradigms can be decomposed into measures that primarily reflect the *ability* to sustain attention or the response *strategy* used to maintain task performance (Fortenbaugh et al., 2015; Riley, Esterman, Fortenbaugh, & DeGutis, 2017; Esterman et al., 2014a). However, it remains unclear if PTSD symptomatology is associated with impaired ability to sustain attention, sub-optimal response strategies, or both factors in CPT paradigms.

Regarding sustained attention *ability*, PTSD symptoms have been associated with reductions in both the accuracy and stability of task performance. For example, some studies demonstrate that PTSD symptoms are associated with weaker response inhibition as measured by more frequent errors on "no-go" trials, whereas other studies demonstrate PTSD symptoms are associated with weaker response initiation as measured by more frequent errors on "go" trials (DeGutis et al., 2015; Swick, Honzel, Larsen, & Ashley, 2013; Swick, Honzel, Larsen, Ashley, & Justus, 2012; Swick, Honzel, & Turken, 2015; Swick & Ashley, 2020; Campbell et al., 2009; Quinones, Gallegos, Lin, & Heffner, 2020; Vasterling et al., 2002). Although seemingly contradictory, these findings suggest that PTSD symptomatology may be most accurately characterized by an impaired ability to dynamically switch *between* response initiation and response inhibition (Aupperle et al., 2012; Dutra, Marx, McGlinchey, DeGutis, & Esterman, 2018). Importantly, the ability to switch between response inhibition and response initiation varies as a function of attention stability. Specifically, reaction time (RT) variability is used to index stable attention states that are more resilient to disruption (lower RT variability) and unstable attention states that are more susceptible to disruption (higher RT variability; Jun & Lee, 2021; Esterman et al., 2014b; Esterman, Noonan, Rosenberg, & DeGutis, 2013). Previous research demonstrates that PTSD symptoms are associated with greater RT variability, which indicates less stable sustained attention (Swick et al., 2013; Swick & Ashley, 2017; Alon, Naim, Pine, Bliese, & Bar-Haim, 2019; Esterman et al., 2019). Together, these findings suggest that PTSD symptomatology is associated with a reduced ability to maintain accurate (lower d-prime) and stable (greater RT variability) task performance on CPT paradigms.

Additionally, PTSD symptomatology may be characterized by more impulsive response *strategies* during CPT paradigms. Broadly, response strategies reflect a trade-off between prioritizing response inhibition (more cautious) or prioritizing response initiation (more impulsive; see Fig. 1). For example, PTSD symptoms are associated with a more impulsive response criterion threshold (i.e., prioritized response initiation), but this association may depend on whether task stimuli are affective or non-affective (Amick et al., 2013; Fortenbaugh et al., 2017a). Also consistent with a more impulsive response strategy, PTSD symptoms are associated with generally faster responses during CPT paradigms (Wu et al., 2010; Swick & Ashley, 2020), which decreases response initiation failures at the cost of increasing response inhibition failures (Fortenbaugh et al., 2015). Although inconsistent across studies, some research suggests that PTSD symptoms are also associated with less post-error slowing (PES) immediately following errors (Clemans, El-Baz, Hollifield, & Sokhadze, 2012; Swick et al., 2015; Evans et al., 2021), which may increase the probability of subsequent errors (for a review, see Danielmeier & Ullsperger, 2011). To summarize, PTSD symptoms may be associated with more impulsive *strategies* when completing CPT paradigms, which aligns with elevated impulsivity associated with PTSD more generally (American Psychiatric Association, 2013).

Given that previous studies have examined sustained attention ability and strategy in isolation, however, it remains unclear if PTSD symptoms are associated with impaired sustained attention ability, more impulsive strategies, or both factors. Specifically, no research has conjointly characterized PTSD-related associations with sustained attention ability and strategy *within* the same study. Due to marked cross-study differences in sample characteristics and CPT parameters, it is also not possible to directly compare PTSD-related associations with sustained attention ability and strategy *between* studies. Regarding sample characteristics, previous research has demonstrated that PTSD-related associations with sustained attention measures may systematically vary as a function of comorbid anxiety and/or depressive symptoms as well as the co-occurrence of traumatic brain injuries (TBIs; Esterman et al., 2019; Swick et al., 2012). Regarding CPT parameters, PTSD-related associations may vary depending on task duration given that sustained attention is increasingly taxed over time (Shenhav et al., 2017; Esterman & Rothlein, 2019) and/or differing response probabilities that titrate demands on inhibitory control (Jun, Remington, Koutstaal, & Jiang, 2019). Thus, it remains unclear if PTSD symptoms are associated with impaired sustained attention ability, more impulsive strategies, or both factors.

Failure to dissociate PTSD-related associations with sustained attention and strategy also has direct bearing on investigating the neural correlates of PTSD-related attentional dysfunction. Neuroimaging research suggests that sustained attention ability and response strategy may be supported by distinct neurocognitive systems. For example, measures of sustained attention ability such as d-prime and RT variability are associated with the dynamic engagement of large-scale cortical networks such as the dorsal attention network (DAN) and default mode network (DMN) to stabilize attentional states (Fortenbaugh, Rothlein, McGlinchey, DeGutis, & Esterman, 2018; Kucyi, Hove, Esterman, Hutchison, & Valera, 2016). In contrast, response strategies are instead predominantly supported by Salience Network (SN) nodes such as the anterior cingulate cortex and anterior insula (Yamashita et al., 2021a; Yamashita et al., 2021c; Ham, Leff, de Boissezon, Joffe, & Sharp, 2013). Therefore, dissociating PTSD-related associations with sustained attention ability and response strategy is an important first step prior to characterizing the neural correlates of such PTSD-related differences.

2. Objectives of the current studies

To address these issues, we conducted two behavioral experiments and one neuroimaging experiment. First, we characterized PTSD-related associations with signal detection-based measures that dissociate sustained attention ability and strategy using same sustained attention paradigm within a large sample of trauma-exposed veterans (Study 1: Discovery Sample). Second, we aimed to directly replicate this pattern of PTSD-related associations in an independent sample of trauma-exposed veterans (Study 1: Replication Sample). In Study 2, we aimed to replicate and extend these behavioral results by using functional magnetic response imaging (fMRI) to characterize the neural correlates of PTSD-related associations with the attention factor(s) identified in Study 1.

3. Study 1

To dissociate PTSD-related associations with sustained attention ability and response strategy, we administered a well-validated gradual onset continuous performance task (gradCPT) to two large samples of post-9/11 veterans (see Table 1; Esterman et al., 2013). Given mixed patterns of PTSD-related associations observed across prior studies, we did not make *a priori* hypotheses regarding selective PTSD-related associations with sustained attention ability or strategy. Instead, we conducted Study 1 to initially characterize PTSD-related associations among these measures in a data-driven manner (Discovery Sample). Next, we attempted to directly replicate these PTSD-related associations in an independent sample of post-9/11 Veterans (Replication Sample). Supporting this two-step approach, the Discovery and Replication samples did not differ in PTSD severity or sustained attention measures (see Table 1 and Results). However, the Discovery and Replication study samples did differ in the composition of self-reported racial identity (see Table 1). Given these sample-related differences in demographic

Table 1
Sample Characteristics and Comparisons.

Measure	Study 1 Discovery ($n = 220$)	Study 1 Replication ($n = 107$)	Study 2 Neuroimaging ($n = 117$)	Sample Difference
Age	36.92 (9.04)	37.73 (7.93)	32.02 (7.97)	$p < 0.001$
Sex (% Male)	90.45%	89.52%	92.17%	$p = 0.79$
Education (Years)	14.60 (2.41)	14.46 (2.01)	14.24 (1.99)	$p = 0.36$
Racial Identity				
% Caucasian	73.18%	47.66%	77.97%	$p < 0.001$
% Black	8.18%	26.17%	8.47%	$p < 0.001$
% Asian	4.55%	0.93%	0.85%	$p = 0.06$
% Native American	0.45%	3.74%	0.00%	$p = 0.01$
% Pacific Islander	0.00%	2.80%	0.85%	$p = 0.04$
% Other/Unknown	13.64%	18.69%	13.26%	$p = 0.31$
PTSD Dx	51.82%	49.06%	60.87%	$p = 0.17$
CAPS Total	46.11 (31.32)	47.75 (27.65)	50.10 (26.66)	$p = 0.49$
DASS-21	31.99 (26.71)	38.02 (27.28)	27.82 (23.40)	$p = 0.02$
Number of Military TBIs	1.07 (1.80)	0.97 (0.96)	0.72 (1.05)	$p = 0.11$

Note: Means and standard deviations for final study samples following all exclusions. Dx: Diagnosis; CAPS: Clinician Administered PTSD Scale (4th Edition); DASS-21: Depression Anxiety and Stress Scale. TBI; Traumatic Brain Injury. To compare sample characteristics across study samples, we utilized ANOVAs for continuous variables (Age, Education, CAPS, and number of number of military TBIs) and Pearson Chi-Square tests for dichotomous variables (Sex, Racial Identities, and PTSD diagnostic status).

characteristics, a direct replication would improve confidence that PTSD-related associations may generalize to more demographically representative samples. Nevertheless, we also conducted post-hoc analyses to rule out the possibility that cross-sample differences in racial identity contributed to PTSD-related associations.

4. Methods

4.1. Procedure

Veterans were recruited from the Translational Research Center for Traumatic Brain Injury and Stress Disorders (TRACTS). TRACTS is a National Network TBI longitudinal cohort study with sites at the Veterans Affairs Boston Healthcare System (VABHS) and the Veteran Affairs Houston Health System (VAHHS; McGlinchey, Milberg, Fonda, & Fortier, 2017). During a study visit, Veterans completed a battery of psychiatric and neurological measures including the 1) Clinician-Administered PTSD Scale (CAPS-IV), 2) Boston Assessment of TBI-Lifetime (BAT-L), and 3) Depression Anxiety and Stress Scale (DASS-21). Using a cross-sectional design, we examined contemporaneous relationships between PTSD symptoms and sustained attention measures.

All research procedures were conducted in accordance with the Institutional Review Board of Human Studies Research at VABHS or VAHHS. All Veterans provided written consent and were financially compensated for their participation.

4.2. Participants

All study participants were trauma-exposed, post-9/11 Veterans who served as part of Operations Enduring Freedom/Iraqi Freedom/New Dawn (OEF/OIF/OND; see Table 1). In TRACTS, Veterans report a heterogeneous array of traumatic experiences (e.g., combat exposure, sexual assault, etc.), which includes both service-related and service-unrelated traumas. Veterans were sequentially recruited from the larger TRACTS program in Boston (VABHS; Discovery Sample) or Houston (VAHHC; Replication Sample). General exclusion criteria for TRACTS include: (a) history of neurological illness; (b) history of seizures; (c) current diagnosis of psychotic disorders such as Schizophrenia; (d) current suicidal and/or homicidal ideation; (e) failure on a symptom validity measure; or (f) diagnosis of cognitive disorder due to general medical condition. Additionally, Veterans were excluded if they demonstrated a history of moderate or severe traumatic brain injury (TBI). Although rare in the TRACTS cohort, Veterans were not excluded due to reporting trauma-related dissociation or trauma-specific hallucinations.

Based on these exclusion criteria, the initial samples were composed of 220 veterans (VABHS; Discovery Sample) and 115 veterans (VAHHS; Replication Sample), respectively. Consistent with previous gradCPT research, we also excluded veterans who failed to make motor responses for a duration greater than 30 s and/or exhibited an omission error rate $\geq$ 50% (Fortenbaugh et al., 2018). Based on these task-based exclusion criteria, 8 VAHHC veterans were excluded in the Replication sample, which was attributable to reversing response contingencies during the gradCPT (i.e., responding to mountain scenes and withholding responses to city scenes). Compared to non-excluded Veterans, excluded Veterans did not significantly differ in CAPS-IV scores, DASS-21, age, gender, or racial identity (all $ps > 0.09$). However, excluded Veterans did report a significantly greater number of TBIs during their military service compared to non-excluded Veterans ($t(113) = 2.88$, $p = 0.005$). Thus, we cannot rule out the possibility that excluded Veterans reversed response contingencies due to cognitive impairments associated with military TBIs. Following these task-based exclusions, analyses were conducted in a final Discovery Sample of 220 Veterans and a final Replication Sample of 107 Veterans (see Table 1).

4.3. Clinical measures

4.3.1. Clinician-Administered PTSD Scale (CAPS-IV)

PTSD severity was assessed using the CAPS-IV, a semi-structured clinical interview used to assess PTSD symptoms based on DSM-IV criteria (Blake et al., 1995). The CAPS-IV assesses 17 specific PTSD symptoms across 3 symptom clusters (re-experiencing, avoidance and numbing, and hyperarousal). The frequency and intensity of each symptom is assessed on separate 5-point (0–4) rating scales, which are then summed up to a 9-point severity score (0–8). To calculate PTSD symptom severity, symptom scores were summed to produce a total score ranging from 0 to 136. All CAPS-IV interviews were administered by doctoral-level psychologists, which were reviewed and validated at weekly diagnostic consensus meetings that consisted of doctoral-level psychologists and/or psychiatrists.

4.3.2. The Boston assessment of TBI-Lifetime (BAT-L)

The BAT-L is a semi-structured interview that uses a forensic assessment approach to extensively assess TBIs experienced before, during, and after military service (Fortier et al., 2014). TBI diagnoses made using the BAT-L exhibit strong interrater reliability (Cohen's k's > 0.80) and excellent convergence with other TBI diagnostic measures (Fortier et al., 2014). The BAT-L was administered by doctoral-level psychologists and all TBI-related diagnoses were reviewed at aforementioned weekly diagnostic consensus meetings.

4.3.3. The Depression, Anxiety, and Stress Scale (DASS-21)

The DASS-21 is a self-report measure that assesses depression, anxiety, and general stress (Lovibond & Lovibond, 1995). DASS-21 items are rated on a 4-point Likert-type scale, which can be summed to generate a total internalizing symptom score ranging from 0 to 63.

4.4. Behavioral paradigm

4.4.1. gradCPT

In the gradCPT paradigm, participants initiate responses on go trials (city images), but inhibit responses on no-go trials (mountain images; see Fig. 1). Whereas city trials are presented frequently (90% of trials), mountain trials are presented relatively infrequently (10% of trials). Given the rapid presentation of go/no-go stimuli and gradual transition between stimuli, participants must continuously maintain sustained attention and inhibitory control. In total, participants were presented with 300 trials (270 cities and 30 mountains) over the course of 4 min (Riley et al., 2017; Rothlein et al., 2018; Fortenbaugh et al., 2015; Yamashita et al., 2021c).

4.5. Sustained attention measures

4.5.1. Reaction time (RT)

Based on previous research, RTs were calculated relative to the onset of an image using a validated iterative algorithm (Esterman et al., 2013). For example, a 400 ms RT indicates that a response was made when the current stimulus reached 50% opacity and the previous stimulus reached 50% opacity. After unambiguous response assignment, any remaining ambiguous responses (i.e., previous stimulus $>$ 70% coherence or subsequent stimulus $>$ 40% coherence) were assigned using a validated algorithm. Following response assignment, mean RT was computed as the average of all correct response initiations (see Fig. 1).

4.5.2. Coefficient of variation (CV)

The coefficient of variation served as the primary measure of RT variability (Martin & Gray, 1971). To compute CV, the standard deviation of a participant's reaction time distribution is first calculated, which provides a course measure of RT variability. Next, the standard deviation is weighted by the participant's mean RT to ensure that RT variability is independent of overall RT (see Fig. 1).

4.5.3. Sustained attention accuracy (d-prime)

To measure sustained attention accuracy, we utilized a d-prime measure derived from signal detection theory, which integrates information from both types of errors in the gradCPT paradigm (Fortenbaugh et al., 2015). In response to "no-go" stimuli (mountain scenes), participants may either correctly omit a response (correct omissions; COs) or incorrectly commit a response (commission errors; CEs). In response to "go" stimuli (city scenes), participants may either correctly initiate a response (correct commission) or incorrectly omit a response (omission error; OE). To compute d-prime, we calculated *relative* ratio between the normal inverse cumulative distribution function of "hits" (COs) and "false alarms" (OEs; NormInv[COs] – NormInv[OEs]). Using standard procedures, one-half error was added or deducted if participants exhibited 100% or 0% accuracy rates, respectively. Thus, a higher d-prime value indicates greater accuracy in dynamically switching between response inhibition and response initiation (see Fig. 1).

4.5.4. Error-related behavioral adjustments (post-error slowing)

To measure behavioral adjustments following inhibitory control failures, we calculated post-error slowing (PES) using a robust computation approach (Dutilh et al., 2012). In the gradCPT, PES is measured by indexing the trial RT immediately following a commission error relative to the trial RT immediately preceding that commission error (i.e., $RT_{PostCE} - RT_{PreCE}$; see Fig. 1). Using this measure, larger PES values indicate greater behavioral adjustments following errors, which suggests stronger error-related cognitive control (Regev & Meiran, 2014).

4.5.5. Criterion

Participants may employ different thresholds for response initiation, which can be measured by a criterion value derived from signal detection theory (Fortenbaugh et al., 2015). For example, a participant may employ a conservative response threshold characterized by correctly responding less frequently to mountain stimuli (i.e., more COs), but also incorrectly responding less frequently to city stimuli (i.e., more OEs). Conversely, a participant may use a less conservative strategy by correctly pressing more frequently to city stimuli (i.e., fewer OEs), but also incorrectly pressing more frequently to mountain stimuli (i.e., more CEs). In this manner, two participants may exhibit the same d-prime value, but utilize a different response criterion (see Fig. 1). To compute criterion, we calculated the *average* normal inverse cumulative distribution function of "hits" and "false alarms" (-1 * (NormInv[COs] + NormInv[OEs]) / 2).

4.6. Data analytic approach

4.6.1. Primary analyses

In Study 1, our primary analyses used Pearson correlations to characterize linear relationships between PTSD symptoms (CAPS-IV) and sustained attention measures. To establish the degree to which PTSD-related associations could be directly replicated in an independent sample, we conducted identical Pearson correlation analyses in the Discovery and Replication samples. To compute confidence intervals for correlation coefficients, we utilized a bootstrapping approach with 1000 resamples. In both the Discovery and Replication sample, we conducted a total of five Pearson correlations for our primary analyses, which examined linear relationships between PTSD symptoms and each attention measure. Given our aim to independently replicate PTSD-related associations, we did not perform stringent multiple comparison correction. To determine if PTSD-related associations and/or attention measures differed between the Discovery and Replication samples, we conducted a 2 (Sample: Discovery vs Replication) $\times$ continuous (CAPS-IV) ANCOVA.

Additionally, it is possible that distinct PTSD symptom clusters exhibit distinct or potentially opposing associations with attention measures. Thus, we repeated our primary analyses using separate CAPS-IV symptom cluster scores: 1) re-experiencing (CAPS-B), 2) Avoidance/Numbing (CAPS-C), and 3) Hyperarousal (CAPS-D). Overall, we observed similar patterns of PTSD-related associations between symptom cluster scores and attention measures (see Supplemental Information).

All statistical analyses were conducted using SPSS software ver. 24.0 (IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM) andstatistical significance was defined as $p \leq 0.05$ (two-tailed). For all analyses, missing values were excluded using pairwise deletion, which accounted for slightly different degrees of freedom in PES analyses and control analyses using the DASS-21. Specifically, several Veterans made no errors during the gradCPT ($n = 4$), which precluded computation of post-error slowing. Additionally, some Veterans did not complete the DASS-21 ($n = 13$), which precluded including these Veterans in control analyses that used DASS-21 scores as a covariate.

4.6.2. Post-hoc analyses

First, it is possible that the Discovery and Replication samples were not adequately powered to detect smaller PTSD-related associations. To address this issue, we repeated our correlation analyses in a larger sample that combined the Discovery and Replication samples.

Second, we examined if significant PTSD-related associations with attention measures were independent of and/or interacted with either the number of reported military TBIs (BAT-L) or comorbid internalizing symptoms (DASS-21). First, we used Pearson correlations to test the

associations between these covariates and attention measures that exhibited significant PTSD-related associations. Second, we conducted separate multiple regression models examining the relationship between CAPS-IV scores and attention measures while controlling for covariates and interaction effects (e.g., CAPS × DASS-21). For these post-hoc control analyses, CAPS-IV scores and the respective covariate were mean-centered and input as main effects in the first model step and the interaction term between CAPS-IV scores and the respective covariate was entered in the second model step.

5. Results

5.1. Discovery sample

In the Discovery sample, PTSD symptoms were significantly associated with lower d-prime values ($r(218) = -0.14$, $p = 0.03$; 95% CI [-0.28, -0.01], see Fig. 2A). A RM-ANCOVA model demonstrated that PTSD-related associations did not significantly differ between specific error types (CEs vs OEs) as evidenced by a non-significant Error Type × CAPS interaction ($F_{(1,218)} = 0.85$, $p = 0.36$, $\eta_p^2 = 0.00$). Thus, the relationship between PTSD symptoms and d-prime was not driven by a specific type of error.

In contrast, PTSD symptoms were not significantly associated with CV ($r(218) = 0.12$, $p = 0.09$), mean RT ($r(218) = 0.00$, $p = 0.96$), Criterion ($r(218) = -0.03$, $p = 0.68$), or PES ($r(210) = -0.04$, $p = 0.59$).

5.2. Replication sample

In the Replication sample, we directly replicated the significant relationship between PTSD symptoms and lower d-prime values ($r(105) = -0.26$, $p = 0.007$; 95% CI [-0.42, -0.08], see Fig. 2B). Similarly, a RM-ANCOVA model demonstrated that PTSD-related associations did not significantly differ between specific error types (CEs vs OEs) as evidenced by a non-significant Error Type × CAPS interaction ($F_{(1,105)} = 0.65$, $p = 0.42$, $\eta_p^2 = 0.01$).

Also replicating Study 1 results, PTSD symptoms were not significantly associated with CV ($r(105) = 0.15$, $p = 0.14$), mean RT ($r(105) = 0.06$, $p = 0.54$), Criterion ($r(105) = -0.05$, $p = 0.63$), or PES ($r(105) = 0.01$, $p = 0.93$).

5.3. Sample comparisons

To compare attention measures and PTSD-related associations between the Discovery and Replication samples, we conducted a 2 (Sample: Discovery vs Replication) × CAPS ANCOVA For all attention measures, we did not observe a significant Sample × CAPS interaction (all $ps > 0.17$) or main effect of Sample (all $ps > 0.23$). Thus, the Discovery and Replication samples exhibited similar gradCPT task performance as well as similar patterns of PTSD-related associations.[1]

5.4. Post-Hoc analyses

5.4.1. Combined sample

In the combined sample, we observed a significant relationship between PTSD symptoms and lower d-prime values ($r(325) = -0.18$, $p = 0.001$; 95% CI [-0.29, -0.08]). Similarly, a RM-ANCOVA model demonstrated that PTSD-related associations did not significantly differ between specific error types (CEs vs COs) as evidenced by a non-significant Error Type × CAPS interaction ($F_{(1,325)} = 1.52$, $p = 0.22$, $\eta_p^2 = 0.01$). In the combined sample, we also observed a significant association between PTSD symptoms and greater RT variability ($r(325) = 0.13$, $p = 0.02$; 95% CI [0.02, 0.23], see Fig. 2D).

Consistent with sample-specific results, PTSD symptoms in the combined sample were also not associated with mean RT ($r(325) = 0.02$, $p = 0.74$), Criterion ($r(325) = -0.04$, $p = 0.53$), or PES ($r(317) = -0.02$, $p = 0.68$).

5.4.2. Comorbid symptomatology

First, we conducted Pearson correlations examing the relationships between attention measures and the number of military TBIs or comorbid internalizing symptoms. For the number of military TBIs, we observed a significant association with lower d-prime ($r(325) = -0.11$, $p = 0.049$; 95% CI [-0.22, −0.001]), but not with CV ($r(325) = 0.05$, $p = 0.35$), mean RT ($r(325) = -0.01$, $p = 0.81$), Criterion ($r(325) = -0.02$, $p = 0.74$), or PES ($r(317) = 0.02$, $p = 0.78$). For comorbid internalizing symptoms, we did not observe significant associations with d-prime ($r(312) = -0.09$, $p = 0.12$), CV ($r(312) = 0.08$, $p = 0.17$), mean RT ($r(312) = 0.04$, $p = 0.49$), Criterion ($r(312) = -0.03$, $p = 0.60$), or PES ($r(304) = -0.09$, $p = 0.12$).

Second, we examined if PTSD-related associations with d-prime and CV were independent of and/or interacted with number of military TBIs or comorbid internalizing symptoms. PTSD-related associations with d-prime and CV did not interact with either military TBIs (CAPS × BAT-L: both $Fs < 0.64$, both $ps > 0.43$) or comorbid internalizing symptoms (CAPS × DASS-21: both $Fs < 0.52$, both $ps > 0.47$). In these control analyses, we continued to observe significant PTSD-related associations with d-prime after controlling for number of military TBIs ($F_{(1,323)} = 8.61$, $p = 0.004$, $\eta_p^2 = 0.03$) and internalizing symptoms ($F_{(1,310)} = 9.39$, $p = 0.002$, $\eta_p^2 = 0.03$). Somewhat similarly, we also continued to observe significant a PTSD-related association with CV after controlling for number of military TBIs ($F_{(1,323)} = 4.58$, $p = 0.03$, $\eta_p^2 = 0.01$), but not after controlling for internalizing symptoms ($F_{(1,310)} = 2.39$, $p = 0.09$, $\eta_p^2 < 0.01$).

6. Discussion

Across two independent samples of post-9/11 Veterans, PTSD symptoms were reliably associated with lower d-prime on the gradCPT paradigm. In a larger sample combining both the Discovery and Replication samples, PTSD symptoms were also modestly associated with greater RT variability. Together, these findings suggest that PTSD symptoms were associated with a reduced ability to maintain accurate (lower d-prime) and stable (greater RT variability) task performance. In both the independent and combined samples, PTSD symptoms were not reliably associated with a more impulsive response strategy as measured by mean RT, criterion, or PES. Although this pattern of results suggest that PTSD symptomatology is selectively associated with impaired ability to sustain attention, it is important to note that PTSD-related associations exhibited small effect sizes, which is consistent with previous studies (for a review, see Aupperle et al., 2012).

Taken together, our results demonstrate that PTSD symptomatology was selectively associated with impaired sustained attention ability, but not utilization of more impulsive response strategies. However, there are several potential mechanisms that may contribute to PTSD-related associations with impaired sustained attention ability, which cannot be easily disentangled with behavioral measures. For example, PTSD symptomatology may be associated with dysregulation of neural systems that support more effortful attentional control processes and/or more automatic attentional control processes specifically during active demands on sustained attention. Alternatively, PTSD symptomatology may be associated with more global dysregulation of neural systems that is not necessarily specific to sustained attention demands, but subsequently contributes to impaired sustained attention ability. To disentangle these possibilities, Study 2 utilized an 8-minute version of the

[1] Given that the Discovery and Replication samples significantly differed in self-reported racial identity, we also examined PTSD-related associations while controlling for self-reported racial identity. In these control analyses, we continued to observe a significant association between CAPS-IV scores and both d-prime ($F_{(1,325)} = 9.98$, $p = 0.002$) and RT variability ($F_{(1,325)} = 4.52$, $p = 0.03$). Similarly, we continued to observe no PTSD-related associations with mean RT, criterion, or PES (all $Fs < 0.16$, all $ps > 0.69$).

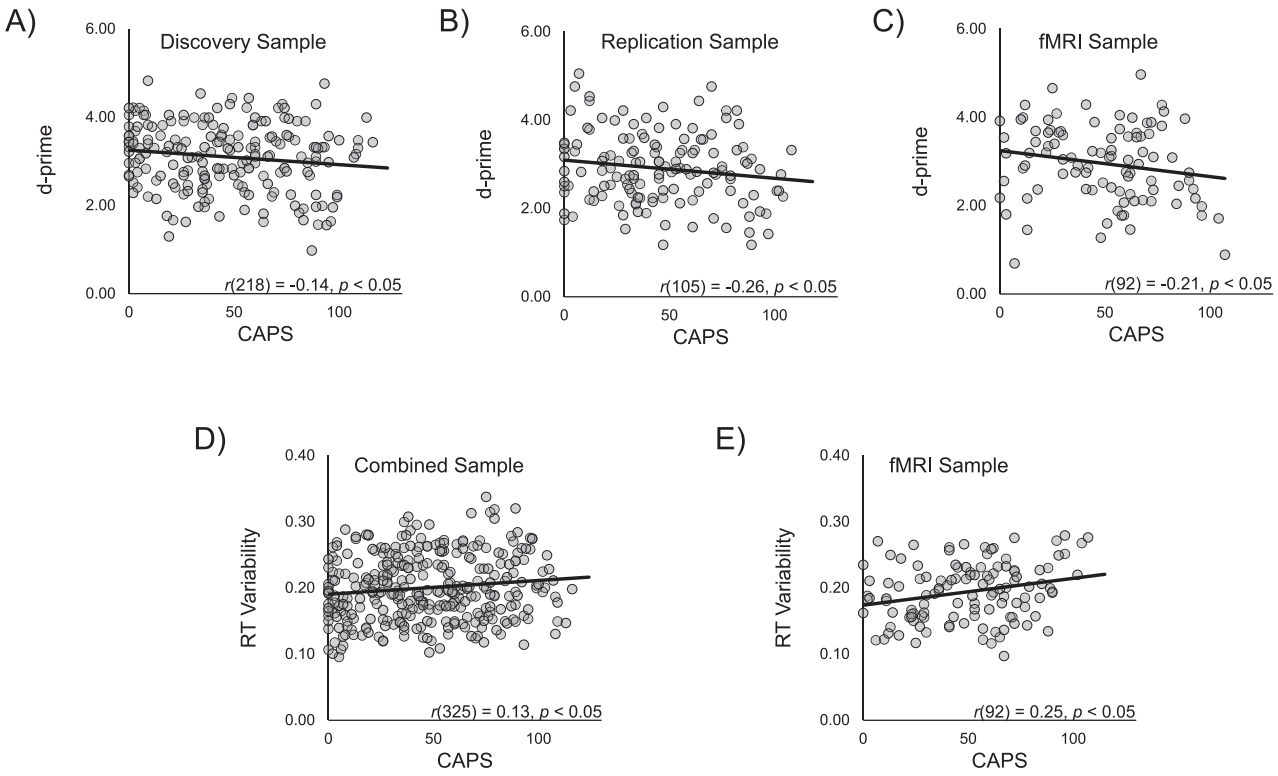

Fig. 2. PTSD Symptoms Are Associated with Measures of Sustained Attention Ability. *Legend:* PTSD symptom severity was significantly associated with lower d-prime values within two independent behavioral samples (A) Discovery Sample, (B) Replication Sample and within an independent fMRI sub-sample: (C) MRI sample. PTSD symptom severity was significantly associated with greater RT variability in the combined Study 1 sample (D) and within an independent fMRI sub-sample (E). **Note:** CAPS = Clinician Administered PTSD Scale (4th Edition).

gradCPT in conjunction with functional magnetic response imaging (fMRI) alongside a passive resting state condition.

7. Study 2

Previous research demonstrates that individual differences in sustained attention ability are associated with the strength of synchronization between neural network activity and attentional fluctuations (brain-behavior synchronization; Esterman & Rothlein, 2019; Kucyi et al., 2016; Fortenbaugh et al., 2018). To measure attentional fluctuations, the gradCPT samples behavioral responses at a relatively high frequency (~1.25 Hz) to capture dynamic attentional states that range from sub-optimal to optimal. Within each subject, trial-by-trial changes in RT variability during the gradCPT are used to generate a variance time course (VTC; see Fig. 3). The VTC captures dynamic changes in RT variability that reliably index attentional fluctuations ranging from sub-optimal attention states (periods of higher RT variability) to more optimal attention states (periods of lower RT variability; Esterman et al., 2013). Moreover, task performance is robustly stronger in more optimal states of sustained attention relative to sub-optimal states (Fortenbaugh et al., 2017b; Esterman et al., 2013). Importantly, these fluctuations in sustained attention are syncrhonized with ongoing neural activation.

In both the gradCPT and other paradigms, neural network activity exhibits reliable synchronization with attentional fluctuations (Esterman et al., 2013; Kucyi et al., 2016; Yamashita et al., 2021a; Yamashita et al., 2021b; Fortenbaugh et al., 2018). Specifically, the Dorsal Attention Network (DAN) exhibits *positive* coupling with the VTC such that dynamic increases in RT variability (less optimal attention) are temporally synchronized with dynamic increases in DAN activity (Fortenbaugh et al., 2018; Kucyi et al., 2016; Esterman et al., 2014b; Esterman & Rothlein, 2019; Yamashita et al., 2021b). Functionally, stronger *positive* DAN synchronization is associated with higher d-prime and/or lower RT variability, which suggests engagement of effortful attentional control processes that facilitate departure from sub-optimal attention states (Fortenbaugh et al., 2018; Yamashita et al., 2021a). Therefore, PTSD-related reductions in *positive* DAN synchronization may impair sustained attention ability by disrupting proactive engagement of more effortful attentional control processes. In contrast, the Default Mode Network (DMN) exhibits *negative* coupling with the VTC such that dynamic decreases in RT variability (more optimal attention) are temporally synchronized with dynamic increases in DMN activity (Kucyi et al., 2016; Esterman et al., 2013). Functionally, stronger *negative* DMN synchronization is associated with higher d-prime and/or lower RT variability, which suggests engagement of more automatic attentional control processes that maintain optimal attention states (Fortenbaugh et al., 2018; Yamashita et al., 2021a). Therefore, PTSD-related reductions in *negative* DMN synchronization may impair sustained attention ability by disrupting maintenance of automatic attentional control processes during optimal attention states. Thus, PTSD-related disruption of DAN and/or DMN synchronization with attentional fluctuations may contribute to impairments in sustained attention ability.

Alternatively, recent neurobiological models propose that PTSD is characterized by more global patterns of dysfunction within a triple-network system comprised of the salience network (SN), frontoparietal control network (FPCN), and DMN (Akiki, Averill, & Abdallah, 2017). Briefly, PTSD has been associated with *intra*network hyperconnectivity within the SN, which may contribute to SN-FPCN and SN-DMN *inter*-network hyperconnectivity (for a review, see Akiki et al., 2017). Due in part to SN hyperconnectivity, PTSD is putatively associated with intra-network *hypo*connectivity within the FPCN and DMN as well as inter-network FPCN-DMN *hyper*connectivity (for a review, see Akiki et al., 2017). Importantly, these models propose that PTSD symptoms are associated with dysregulated intrinsic network connectivity even during

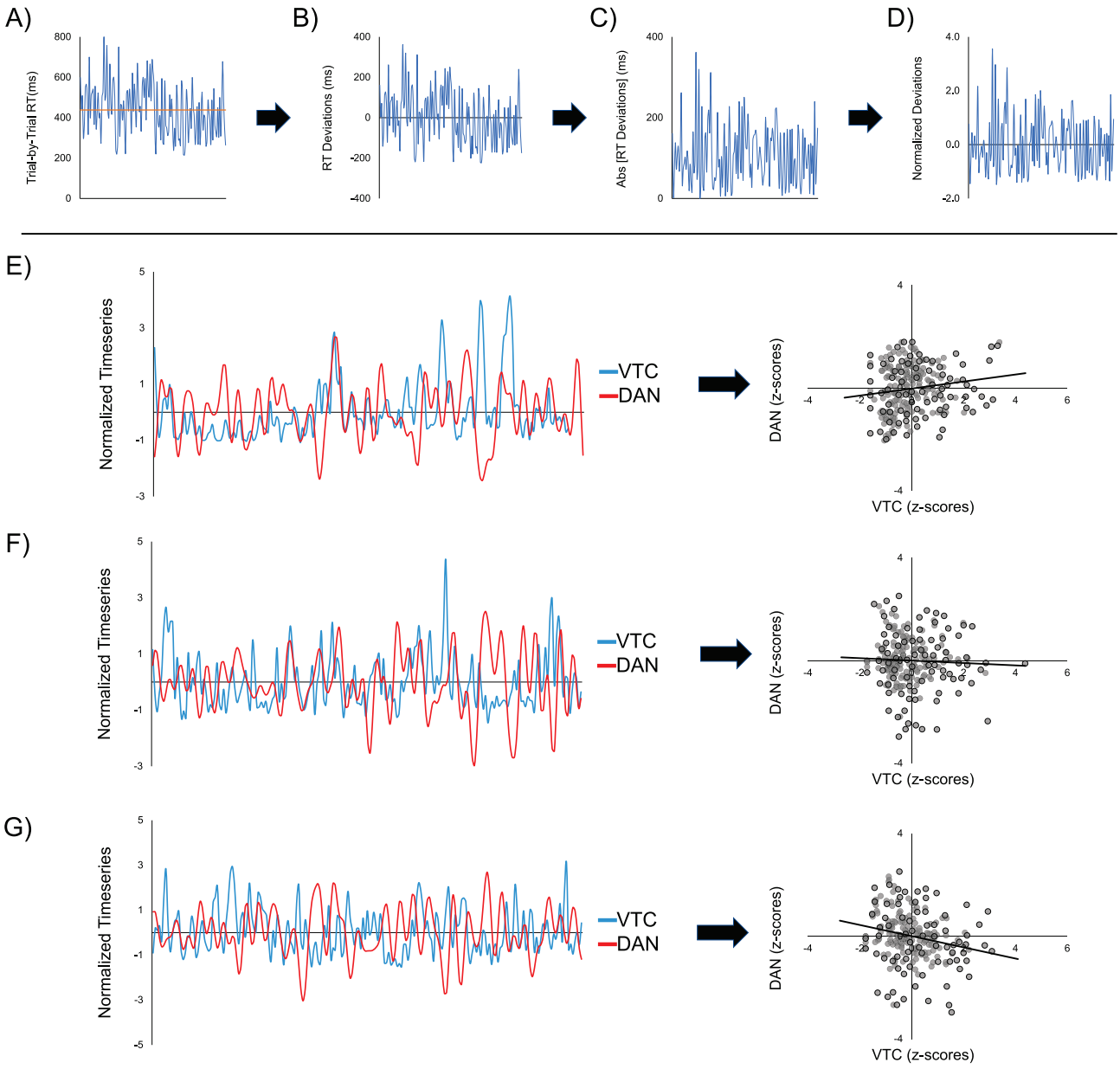

Fig. 3. Computing Variance Time Course and Neural Network Synchronization. *Legend:* To characterize brain-behavior synchronization, we computed the correlation between neural network timeseries and the variance time course (VTC) for each participant. (Top Row) Data processing steps to compute a VTC for a hypothetical participant. (A) The raw reaction time (RT) timeseries was linearly interpolated to account for missing RTs. (B) The interpolated RT timeseries was mean centered to quantify trial-by-trial changes. (C) The absolute magnitude of trial-by-trial RT changes was computed to quantify an absolute RT deviation timeseries. D) The absolute RT deviation timeseries was normalized using a z-transformation to standardize VTCs across participants. (Bottom Row) For illustration purposes, the normalized dorsal attention network (DAN) timeseries and normalized VTC are presented for three representative participants that demonstrated either (E) positive DAN-VTC synchronization, (F) near-zero DAN-VTC synchronization, or (G) negative DAN-VTC synchronization.

passive resting-state conditions that do not recruit task-related processes such as demands on sustained attention (for a review, see Ross & Cisler, 2020). In sum, PTSD symptomatology may be associated with more global dysregulation of triple-network system functional connectivity, which also subsequently impairs sustained attention ability during active demands on sustained attention.

Based on the results of Study 1, we hypothesized that PTSD symptoms would again exhibit selective associations with reduced sustained attention ability, but not more impulsive response strategies. Additionally, we primarily hypothesized that PTSD-related impairments in sustained attention ability would be associated with reduced synchronization between DAN and/or DMN activity and endogenous attentional fluctuations during the gradCPT. Alternatively, PTSD-related reduced sustained attention ability could be attributable to more global pattern of functional connectivity dysfunction within and between a triple network system comprised of the SN, FPCN, and DMN (Akiki et al., 2017). To adjudicate between these hypotheses in a third sample of post-9/11 Veterans, we characterized associations between PTSD symptoms, sustained attention ability, network-based synchronization, and functional connectivity during both active demands on sustained attention (gradCPT) and a passive resting state condition.

8. Methods

8.1. Procedure

All procedures were identical to Study 1 with the exception that Veterans completed an 8-minute version of the gradCPT during fMRI scanning as well as two resting-state fMRI scans. Identical to Study 1, cross-sectional analyses examined contemporaneous relationships among PTSD symptoms, sustained attention measures, and neural measures.

Although we made *a priori* hypotheses regarding PTSD-related associations in Study 2, these hypotheses were not pre-registered prior to data collection or conducting data analyses. All research procedures were conducted in accordance with the Institutional Review Board of Human Studies Research at VABHS or VAHHC. All veterans provided written consent and were financially compensated for their participation.

8.2. Participants

Following the same exclusion criteria outlined in Study 1, the initial sample was comprised of 143 trauma-exposed, post-9/11 veterans (see Table 1 for sample characteristics). Similar to Study 1, all veterans were sequentially recruited from the TRACTS program and reported a heterogeneous array of traumatic experiences.

As in Study 1, we also excluded 4 veterans who failed to make motor responses for a duration greater than 30 s and/or exhibited an omission error rate $\geq$ 50% (Fortenbaugh et al., 2018). Additionally, 22 veterans were excluded due to excessive motion during the task scan and/or resting-state scans (see fMRI Quality Control). Following these exclusions, analyses were conducted in a final fMRI Sample of 117 veterans (see Table 1 for sample characteristics and sample comparisons).

Notably, fMRI data during the gradCPT overlapped with data reported in a previous study (Fortenbaugh et al., 2018). However, this previous study did not examine PTSD-related differences and did not analyze resting-state fMRI data. Additionally, 23 veterans overlapped with the behavioral sample reported in Study 1. To ensure that behavioral results replicated in an independent sample, we exclusively conducted behavioral analyses in the 94 veterans who did not overlap with the sample reported Study 1. All other analyses were conducted in the full sample of 117 veterans.

8.3. fMRI data collection

Neuroimaging data was obtained at the Neuroimaging Research for Veterans (NeRVE) on a 3 T Siemens MAGNETOM Trio System. Two anatomical magnetization prepared rapid gradient-echo (MP-RAGE) structural scans were obtained using a 12-channel head coil. The parameters used for these scans are the following: repetition time (TR) = 2350 ms, echo time (TE) = 3.32 ms, flip angle = 7°, acquisition matrix = 256 × 256 × 176, voxel size = 1 mm^3, resolution = 3.0 × 3.0, and slice thickness = 3.75 mm. To improve the signal to noise ratio, both structural images were averaged and subsequently processed using FreeSurfer software. Task fMRI data was collected using a 32-channel head coil and one whole-brain echo-planar T2*- weighted sequence (TR = 2000 ms, TE = 30 ms, flip angle = 90°, 248 volumes, acquisition matrix = 64 × 64, in-plane resolution = 3.0 × 3.0 mm^2, and slice thickness = 3.75 mm. For resting-state fMRI data, Veterans completed two 6-minute T2* weighted fMRI (TR = 3000 ms, TE = 30 ms, flip angle = 90°, and slice size = 3.0 × 3.0 × 3.7 mm for a total of 38 slices).

8.4. fMRI data preprocessing

To facilitate direct comparisons between task and resting-state measures, we utilized nearly identical pre-processing procedures for both task-state and resting-state scan data. Shared pre-processing steps between resting-state and task scans were carried out using AFNI and in-house MATLAB scripts, which included slice-time correction, motion correction (6-parameter rigid body least-squares alignment), despiking, spatial smoothing (6-mm FWHM Gaussian kernel), identification of volumes in which 20% or more voxels were identified as timeseries outliers, automated co-registration of functional and anatomical data, and normalization to MNI space. Based on automated segmentation, the mean time series of white matter tracts and CSF were also included as nuisance regressors in first-level models. Finally, motion censoring was performed on TRs that exceeded framewise displacement of > 0.3 mm as well as the preceding TR.

8.5. fMRI quality control

To ensure fMRI data quality, we excluded data from Veterans with excessive motion during the task scan and/or resting-state scans. Specifically, Veterans who exhibited excessive motion (>0.3 mm framewise displacement) within 20% or more TRs during either the task scan and/or resting-state scans were excluded from all analyses (n = 22).

8.6. Neural network parcellation

To define neural networks of interest, we utilized a standardized neural network parcellation validated in previous research (Yeo et al., 2011; Schaefer et al., 2018). Specifically, we implemented a 200-node parcellation of seven canonical neural networks. Based on our *a priori* hypotheses, the current study utilized timeseries data from nodes assigned to the DAN (27 nodes), SN (22 nodes), FPCN (30 nodes), and DMN (47 nodes).

8.7. Data analytic approach

8.7.1. First-level fMRI models

Following pre-processing steps, functional data were analyzed using a general linear model (GLM). For both resting-state and task data, first-level models included nuisance regressors comprised of 12 motion parameters (6 rigid body and temporal derivatives), mean white matter and CSF time series, and polynomial trends to account for linear and non-linear scanner drift. Additionally, outlier and excessive motion TRs were censored and excluded from subsequent analyses. Exclusively for the task scan, we modeled task event regressors to residualize event-related activation from the time series (Esterman et al., 2013).

8.7.2. VTC computation

To measure trial-to-trial fluctuations in sustained attention, we employed several processing steps to compute a VTC for each participant (see Fig. 3). First, trials without RTs (COs and OEs) are linearly interpolated using surrounding trial RTs to create a continuous timeseries. Second, trial-by-trial changes in RT are computed relative to a participant's mean RT to produce a timeseries of RT variability. Third, the absolute value of trial-by-trial RT fluctuations is computed such that larger values represent greater deviations from a participant's mean RT in either direction (i.e., larger deviation scores indicate relatively slower *or* faster responses). Fourth, the deviation score timeseries is z-transformed, which produces a normalized VTC that is standardized across participants. Thus, the VTC indexes dynamic fluctuations in sustained attention that are orthogonal to both overall RT and the overall magnitude of RT variability. Importantly, this normalization procedure ensures that individual differences in task-related neural synchronization are independent of individual differences in RT variability magnitude (Esterman et al., 2013).

8.7.3. Task-related synchronization

To measure task-related synchronization, the VTC timeseries for each participant is correlated with each participant's neural network

timeseries (see Fig. 3). To compute a single, composite neural network timeseries, we averaged all nodal timeseries within a given network. For example, the composite DAN timeseries was computed by averaging the mean timeseries from nodes within the standardized DAN parcellation. Next, to account for differences in sampling rate between the VTC (1.25 Hz) and fMRI timeseries (0.5 Hz), the VTC was downsampled to 0.5 Hz using bilinear interpolation. Following VTC downsampling, censored time points in the fMRI timeseries were similarly censored in the VTC to minimize the influence of motion on brain-behavior synchronization. To account for hemodynamic response delay, the VTC timeseries for each participant was then temporally shifted by 6 seconds (3 TRs). After correlating the shifted VTC timeseries with a composite neural network timeseries, the resulting correlation coefficients were transformed using a Fisher r-to-z transformation for subsequent analyses. Finally, we used Pearson correlations to test the associations of brain-behavior synchronization with PTSD symptoms and d-prime.

8.7.4. Task state and resting state functional connectivity

To characterize intranetwork and internetwork functional connectivity of the SN, FPCN, and DMN, we performed the following methods separately for fMRI timeseries obtained during task state (gradCPT) and resting state. First, fMRI timeseries data was parcellated into 200 nodes within a standardized seven-network atlas (Yeo et al., 2011; Schaefer et al., 2018). Second, we averaged the timeseries from all voxels within each node to compute a mean nodal timeseries. Third, each mean nodal timeseries was pairwise correlated with the mean nodal timeseries of all other nodes within the same network (intra-network connectivity) or within a different network (inter-network connectivity). For example, to compute SN intra-network connectivity (22 nodes), the mean nodal timeseries for a given SN node was pairwise correlated with each of the mean nodal timeseries of the other 21 SN nodes. Fourth, correlation coefficients for each nodal pair were Fisher-z transformed, grouped according to network assignment, and averaged either within a network (intra-network) or between networks (inter-network). For the task and resting state conditions, we separately computed 3 intra-network functional connectivity estimates (SN, FPCN, and DMN) and 3 inter-network functional connectivity estimates (SN-FPCN, SN-DMN, and FPCN-DMN). In total, this procedure produced a total of 6 functional connectivity estimates during task state and 6 functional connectivity estimates during resting state.

To ensure that functional connectivity results were comparable to task-related synchronization results, our primary analyses did not perform any additional preprocessing steps prior to computing intra-network and inter-network connectivity. However, functional connectivity estimates during resting-state are often computed after removing putatively non-neuronal signal variance via bandpass filtering or global signal regression (GSR). Therefore,to rule out the possibility that results were specific to pre-processing protocols, we also conducted functional connectivity analyses after performing either bandpass filtering (0.01 Hz – 0.10 Hz) or GSR.

8.8. Data analytic strategy

8.8.1. Behavioral analyses

As in Study 1, we used Pearson correlations to characterize linear relationships between PTSD symptoms and sustained attention measures. As noted previously, we restricted behavioral analyses to the independent sample of 94 veterans who did not overlap with Study 1 to provide an additional independent replication of behavioral results. Like Study 1, we also repeated our primary analyses using separate CAPS-IV symptom cluster scores: 1) re-experiencing (CAPS-B), 2) Avoidance/Numbing (CAPS-C), and 3) Hyperarousal (CAPS-D). Overall, we observed similar associations across symptom cluster scores and attention measures (see Supplemental Information).

8.8.2. Neural analyses

Given that we utilized network-based metrics of brain-behavior synchronization (DAN and DMN) or triple network connectivity (SN, FPCN, and DMN), we did not employ nominal or cluster extent threshold commonly used in voxel-wise analyses. Instead, all neural analyses employed Pearson correlations to characterize PTSD-related associations with a composite, network-based metric of brain-behavior synchronization or functional connectivity for each network. First, our primary analyses characterized PTSD-related associations with brain-behavior synchronization (DAN and DMN). Additionally, we also characterized PTSD-related associations with task state and resting state functional connectivity (SN, FPCN, and DMN). For neural network measures that exhibited significant PTSD-related associations, we also subsequently examined associations with d-prime and RT variability using Pearson correlations.

9. Results

9.1. Behavioral

Replicating Study 1, we observed a significant relationship between PTSD symptoms and lower d-prime values ($r(92) = -0.21$, $p = 0.045$; 95% CI [-0.44, 0.03], see Fig. 2C). Similarly, PTSD-related associations did not significantly differ between specific error types (CEs vs OEs) as evidenced by a non-significant Error Type × CAPS interaction ($F_{(1,92)} = 1.04$, $p = 0.31$, $\eta_p^2 = 0.01$).

Replicating the results obtained using the larger, combined sample in Study 1, we also observed a significant relationship between PTSD symptoms and greater RT variability ($r(92) = 0.25$, $p = 0.02$; 95% CI [0.03, 0.43], see Fig. 2E).

Replicating both samples in Study 1, PTSD symptoms were not associated with mean RT ($r(92) = 0.11$, $p = 0.30$), Criterion ($r(92) = 0.01$, $p = 0.96$), or PES ($r(90) = 0.06$, $p = 0.60$).

9.2. Task-related synchronization

As hypothesized, PTSD symptoms were significantly associated with weaker positive DAN synchronization ($r(116) = -0.19$, $p = 0.04$; 95% CI [-0.36, −0.01], see Fig. 4A). Inconsistent with our hypotheses, however, PTSD symptoms were not associated with weaker negative DMN synchronization ($r(116) = -0.11$, $p = 0.22$).

Moreover, we observed a significant relationship between greater positive DAN synchronization and higher d-prime ($r(116) = 0.24$, $p = 0.01$; 95% CI [0.07, 0.40]). Similarly, we also observed a significant relationship between greater positive DAN synchronization and lower CV ($r(116) = -0.24$, $p = 0.008$; 95% CI [-0.41, −0.08], see Fig. 4C). Thus, reduced positive DAN synchronization was associated with both greater PTSD symptoms and more impaired sustained attention ability (d-prime and CV).

9.2.1. Time course of PTSD-Related differences in DAN synchronization

Given the role of the DAN in preparatory recruitment of attentional control processes, we conducted a post-hoc analysis to more precisely characterize PTSD-related differences in DAN synchronization. Specifically, PTSD symptoms may be associated with either *global* reductions in DAN synchronization or *delayed* DAN synchronization. In the case of global reductions in DAN synchronization, PTSD symptoms would be associated with a similar reduction in DAN synchronization across time (i.e., before, during, and after attentional fluctuations). For delayed DAN synchronization, however, PTSD symptoms would be characterized by reduced DAN synchronization during early time points (i.e., before attentional fluctuations), but not later time points (after attentional fluctuations).

In our primary analyses, we temporally shifted each subject's VTC by 3 TRs (6 s) to approximate the canonical hemodynamic delay in response to attention fluctuations. As such, shifting the VTC by <3 TRs

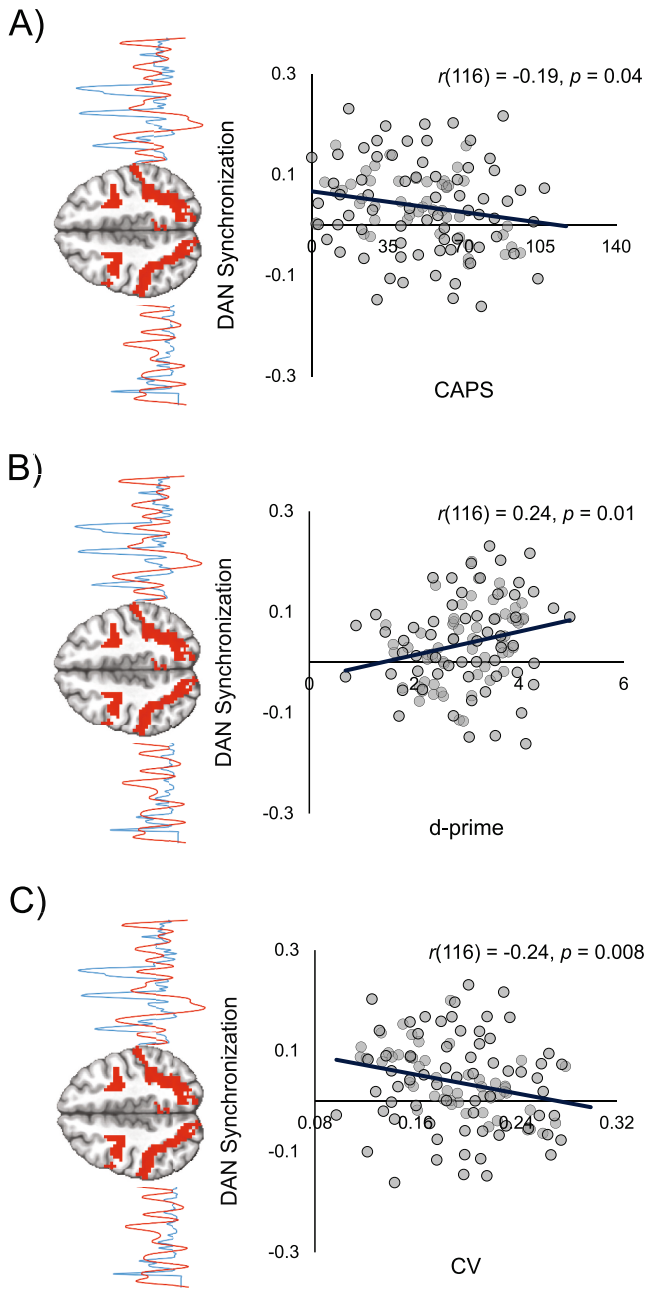

Fig. 4. PTSD Symptomatology and Sustained Attention Ability Measures Are Associated with Dorsal Attention Network Synchronization. *Legend:* Reduced Dorsal Attention Network (DAN) synchronization with attentional fluctuations was associated with (A) greater posttraumatic stress disorder (PTSD) symptomatology, (B) lower sustained attention accuracy as measured by d-prime, and (C) lower sustained attention stability as measured by the coefficient of variation (CV) of reaction time.

(i.e., 0 TRs, 1 TRs, and 2 TRs) would approximate DAN synchronization *before* attentional fluctuations. Conversely, shifting the VTC by >3 TRs (i.e., 4 TRs, 5 TRs, and 6 TRs) would approximate DAN synchronization *after* attentional fluctuations. In total, we measured DAN synchronization at 7 levels of VTC lag, which included 3 "pre-stimulus" lags (0 TR, 1 TR, and 2 TR) and 3 "post-stimulus" lags (4 TR, 5 TR, and 6 TR) that were centered around a canonical hemodynamic lag of 6 s (3 TR). DAN synchronization estimates were next submitted to a 7 (Lag: 0 TRs – 6 TRs) × CAPS RM-ANCOVA with Greenhouse-Geisser corrections for violations of sphericity.

Consistent with dynamic PTSD-related differences in DAN synchronization, we observed a significant Lag × CAPS interaction ($F_{(2.91, 334.88)} = 3.86$, $p = 0.01$, $\eta_p^2 = 0.03$). Across earlier and canonical lags (0 TRs – 3 TRs), PTSD symptoms were associated with reduced DAN synchronization (all *r*s > -0.19, all *p*s < 0.04; see Fig. 5). Across later lags (4 TRs – 6 TRs), however, PTSD symptoms were not associated with reduced DAN synchronization (all *r*s < |0.12|, all *p*s > 0.18; see Fig. 5).

10. Task and resting state functional connectivity

Contrary to triple network hypotheses, we did not observe significant associations between PTSD symptoms and functional connectivity during either task or resting state conditions. During the task condition, PTSD symptoms were not associated with functional connectivity *within* networks (all *r*s < |0.02|, all *p*s > 0.80) or *between* networks (all *r*s < |0.08|, all *p*s > 0.40). During the resting state condition, PTSD symptoms were similarly not associated with functional connectivity *within* networks (all *r*s < |0.10|, all *p*s > 0.29) or *between* networks (all *r*s < |0.09|, all *p*s > 0.36).

Secondary analyses confirmed that PTSD symptoms were not associated with functional connectivity during the task condition after applying bandpass filtering (all *r*s < |0.09|, all *p*s > 0.33) or global signal regression (all *r*s < |0.16|, all *p*s > 0.09). Similarly, PTSD symptoms were not associated with functional connectivity during resting state conditions after applying bandpass filtering (all *r*s < |0.03|, all *p*s > 0.74) or global signal regression (all *r*s < |0.17|, all *p*s > 0.07).

11. Discussion

Using an 8-minute version of the gradCPT, we replicated our previous findings that PTSD symptoms were associated with measures of sustained attention ability (d-prime and CV), but not measures of response strategy (mean RT, criterion, and PES). Extending the results of Study 1, we observed that PTSD symptoms were associated with reduced positive DAN synchronization during the gradCPT. Demonstrating a functional relationship, reduced positive DAN synchronization was also associated with impaired sustained attention ability (lower d-prime and greater CV). Additionally, post-hoc analyses demonstrated that PTSD symptoms were characterized by *delayed* DAN synchronization, rather than global deficits in DAN synchronization.

In contrast to triple network hypotheses, however we did not observe any significant PTSD-related differences in intra-network or inter-network functional connectivity during the task or resting state conditions. Given that similar results were observed after applying bandpass filtering or global signal regression, however, it is unlikely that a failure to observe PTSD-related associations can be attributed to differences in pre-processing. Instead, the lack of PTSD-related associations with functional connectivity estimates is consistent with the heterogeneous pattern of PTSD-related differences observed across studies. For example, studies variably demonstrate that PTSD symptoms are associated with *hyper*connectivity, *hypo*connectivity, or no differences in connectivity within the SN (Koch et al., 2016; Neria, 2021). Thus, it is possible that PTSD-related differences in functional connectivity vary widely as a function of sample characteristics (e.g., type of trauma exposure), neurobiological factors (e.g., executive dysfunction), or more complex interactions among specific PTSD symptom clusters (Etkin et al., 2019; Esterman et al., 2020; Sheynin et al., 2020; Jagger-Rickels et al., 2021; Tursich et al., 2015).

12. General discussion

Across three independent samples of post-9/11 Veterans, we observed and replicated that PTSD symptoms were selectively associated with impaired sustained attention ability (d-prime and CV), but not

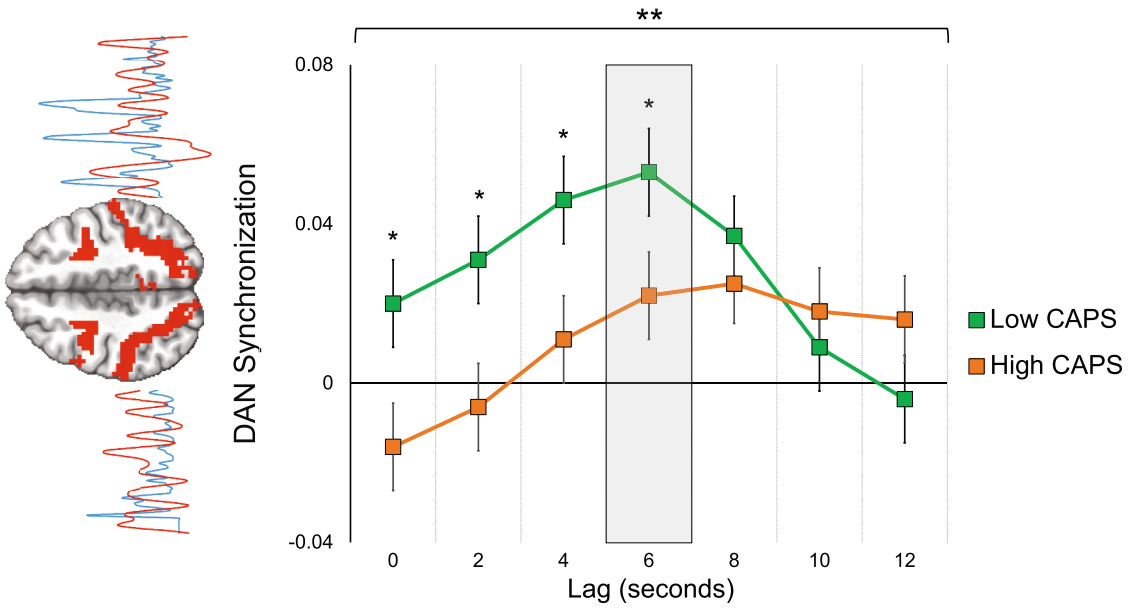

Fig. 5. Time Course of PTSD-Related Differences in Dorsal Attention Network Synchronization. *Legend:* PTSD-related differences in dorsal attention network (DAN) synchronization with the variance time course (VTC) are presented across multiple levels of temporal shift. Given an assumed 3 TR hemodynamic lag, temporal shifts shorter than 3 TRs (0 TRs, 1 TRs, and 2 TRs) approximated DAN synchronization *before* VTC fluctuations occurred, whereas lags longer than 3 TRs (4 TRs, 5 TRs, and 6 TRs) approximated DAN synchronization *after* VTC fluctuations occurred. * $p \leq 0.05$; ** $p \leq 0.01$ Note: For display purposes, DAN-VTC coupling estimates are depicted using simple slope intercepts estimated at high (+1SD; Orange) and low (-1SD; Green) PTSD symptom severity.

response strategy (RT, criterion, and PES). In Study 2, PTSD symptoms were associated with delayed synchronization between DAN activity and attentional fluctuations measured during the gradCPT paradigm. Consistent with previous PTSD research (Aupperle et al., 2012), however, PTSD-related deficits in both sustained attention ability and DAN synchronization were relatively small in magnitude. Nevertheless, these results collectively suggest that PTSD symptomatology may impair sustained attention ability by reducing dynamic recruitment of attentional control processes.

At the behavioral level, PTSD symptoms were selectively associated with reduced sustained attention ability, but not more impulsive response strategies. To date, this issue was not previously addressable due to marked cross-study differences in sample and/or task characteristics. By using the same gradCPT paradigm to measure both sustained attention ability and strategy, however, we were able to more directly dissociate PTSD-related associations among these sustained attention factors. Using this approach, we demonstrated that PTSD symptoms were selectively associated with lower d-prime and greater RT variability, which suggests impairments in sustained attention ability. In contrast, PTSD symptoms were not associated with mean RT, criterion, or PES, which is inconsistent with a more impulsive response strategy. Thus, PTSD symptomatology is primarily characterized by impairments in the ability to maintain accurate (d-prime) and stable (RT variability) attentional states.

At the neural level, we proposed two sets of alternative hypotheses regarding the neural correlates of PTSD-related impairments in sustained attention ability. Based on previous studies using the gradCPT paradigm, we primarily proposed that PTSD symptoms may impair sustained attention ability via reduced synchronization between attentional fluctuations and neural network activity. In short, these hypotheses predicted that PTSD symptomatology would be associated with reduced task-related synchronization of the DAN and/or DMN with endogenous attentional fluctuations. Alternatively, a recently proposed triple-network model proposes that PTSD symptomology may exert a more global influence on functional connectivity within and between the SN, FPCN, and DMN, which occurs independent of sustained attention demands (Akiki et al., 2017). Based on this triple-network model, we alternatively considered that PTSD symptoms may be associated with more global disruption of network functional connectivity during both active task demands and passive resting state conditions.

Among these putative neurobiological mechanisms, our results are most consistent with selective PTSD-related deficits in synchronization between DAN activity and endogenous attentional fluctuations, rather than more global deficits in functional connectivity. Specifically, PTSD symptoms were associated with weaker dynamic increases in DAN activation as a function of less stable attention states. Demonstrating functional relevance to sustained attention ability, reduced DAN synchronization was also associated with lower d-prime and higher CV. As such, PTSD symptomatology may impair the proactive recruitment of top-down attentional control processes as attentional states become unstable. Consistent with this interpretation, time course analyses demonstrated that PTSD symptoms were most accurately characterized by *delayed* synchronization between DAN activation and attentional fluctuations, rather than more global reductions in task-related DAN synchronization. Specifically, PTSD symptoms were associated with weaker DAN synchronization both prior and in response to attentional fluctuations, but PTSD symptoms were not associated with weaker DAN synchronization following attentional fluctuations. Within this time course, however, it is important to note that DAN activity was no longer synchronized with attentional fluctuations during the final two time points using a 10 s lag or 12 s lag. Based on this result, it is not possible to rule out the possibility that the lack of PTSD-related differences at these final two time points reflects a more general decline in DAN synchronization that precludes detection of any PTSD-related associations. Taken together, however, this converging pattern of results suggests that DAN synchronization may play a mechanistic role in the relationship between PTSD symptomatology and reduced sustained attention ability.

From a mechanistic perspective, the relationship between PTSD symptomatology and DAN synchronization dovetails with the DAN's functional role in supporting proactive attentional control (Rajan et al., 2021). Core nodes of the DAN such as the frontal eye fields (FEF) are retinotopically organized to facilitate top-down control over visual

information processing (Vossel, Geng, & Fink, 2014). More specifically, the DAN instantiates top-down attentional control by causally biasing the visual system to preferentially process certain stimulus features (e.g., size, orientation, color, etc.) that are most relevant for behavioral response selection (Morishima et al., 2009). In the gradCPT, behavioral response selection (initiate vs. inhibit) is guided by visual features that effectively differentiate between city scenes (e.g., straight edges) and mountain scenes (e.g., curved edges), which are dynamically blended between trials. Given these dynamic visual inputs, it is necessary to proactively engage attentional control processes both prior to and in response to endogenous fluctuations in attention that may interfere with visual feature discrimination. Thus, PTSD-related reductions in DAN synchronization may disrupt sustained attention ability by delaying proactive engagement of attentional control resources that stabilize visual feature discrimination across endogenous attention states.

When interpreting these findings, it is important to consider that impaired sustained attention is not specific to PTSD, but instead characterizes a diverse range of distinct psychiatric disorders (Fortenbaugh et al., 2017b). Based on neuropsychological measures more broadly, attention is disrupted in disorders ranging from anxiety and mood disorders to psychotic spectrum disorders (for a review, see Abramovitch, Short, & Schweiger, 2021). Based on task-based fMRI more specifically, previous work suggests that individuals with attention-deficit hyperactivity disorder (ADHD) or Major Depressive Disorder (MDD) also exhibit impaired sustained attention ability and task-related DAN dysfunction (Keller, Leikauf, Holt-Gosselin, Staveland, & Williams, 2019; Yamashita et al., 2021a). Moreover, PTSD is frequently comorbid with MDD and ADHD, which are each similarly characterized by attention impairments (Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995; Harrington et al., 2012; Hankin, Spiro, Miller, & Kazis, 1999; Campbell et al., 2007; Nichter, Norman, Haller, & Pietrzak, 2019; Richardson et al., 2017). Consistent with this pattern of comorbidity, over 50% of TRACTS Veterans exhibit three or more comorbid psychiatric conditions (McGlinchey et al., 2017). Therefore, we cannot definitively conclude that reduced DAN synchronization with endogenous attentional fluctuations reflects a PTSD-specific neural correlate of impaired sustained attention. Instead, it is possible that reduced DAN synchronization impairs sustained attention transdiagnostically. Future research will be needed to determine if PTSD and other psychiatric disorders similarly or distinctly modulate brain-behavior synchronization during sustained attention demands.

Beyond these considerations, it is important to note several limitations of the current study. First, the current study did not include a healthy control group that was not trauma-exposed. Given the lack of a healthy control group, we cannot rule out the possibility that behavioral and neural patterns observed at lower levels of PTSD symptoms reflect a resilience to trauma exposure, rather than normative functioning. Therefore, it will be necessary for future work to directly compare individuals with PTSD, trauma-exposed individuals without PTSD, and individuals without any history of trauma exposure. Second, veteran samples are not demographically representative of the larger population of trauma-exposed adults in the United States (Lippa et al., 2015). Although we replicated our results in a more racially diverse sample of Veterans, it will nevertheless be important for future studies to attempt to replicate these findings in more nationally representative samples of adults with PTSD. Third, we did not collect measures of physiological reactivity during fMRI scanning such as heart rate or respiration in Study 2, which exert an influence on BOLD signal variability and functional connectivity during resting-state (Murphy, Birn, & Bandettini, 2013). Although we observed similar results after using bandpass filtering to exclude variability in higher frequency bands commonly associated with cardiac and respiratory periodicity, we cannot rule out the possibility that individual differences in physiological reactivity may contribute to PTSD-related differences in functional brain activitity. Finally, we did not employ a strict multiple comparison correction for our neural analyses given our *a priori* hypotheses regarding the role of brain-behavior synchronization in sustained attention ability. Thus, our neural results should be interpreted more cautiously prior to replication in an independent sample.

Despite these limitations, we believe the current studies offer potential mechanistic insights into PTSD-related impairments in sustained attention. At the behavioral level, we demonstrated that PTSD symptomatology is selectively associated with sustained attention ability, but not more impulsive response strategies. At the neural systems level, PTSD symptomology was associated with reduced and delayed synchronization between DAN activation and attentional fluctuations, which may disrupt proactive recruitment of attentional control. Collectively, these results provide a more mechanistic characterization of the relationship between PTSD symptomatology and sustained attention, which may be useful towards the development of neuroscience-informed treatments that remediate attention dysfunction in PTSD.

Funding

This research was supported by the U.S. Department of Veterans Affairs through the Translational Research Center for TBI and Stress Disorders, a VA Rehabilitation Research and Development Traumatic Brain Injury National Research Center (B9254-CAQ18 and B3001-C) to R.M., a Merit Review Award from the VA Clinical Sciences Research and Development Service (I01CX001653) to M.E, T32 post-doctoral training award from the National Institute of Health (2T32MH01983621) to A.J. R., and an Office of Academic Affairs fellowship to T.E.

CRediT authorship contribution statement

Travis C. Evans: Conceptualization, Methodology, Formal analysis, Writing – original draft, Visualization. **Marina Rodriguez Alonso:** Methodology, Visualization, Writing – original draft, Writing – review & editing. **Audreyana Jagger-Rickels:** Methodology, Writing – original draft, Writing – review & editing. **David Rothlein:** Investigation, Methodology, Writing – review & editing. **Agnieszka Zuberer:** Methodology, Writing – review & editing. **John Bernstein:** Project administration, Writing – review & editing. **Catherine B. Fortier:** Investigation, Project administration, Data curation, Writing – review & editing. **Jennifer R. Fonda:** Project administration, Data curation, Writing – review & editing. **Audri Villalon:** Project administration, Data curation, Writing – review & editing. **Ricardo Jorge:** Investigation, Project administration, Data curation, Writing – review & editing. **William Milberg:** Investigation, Project administration, Resources, Writing – review & editing. **Regina McGlinchey:** Investigation, Project administration, Resources, Writing – review & editing. **Joseph DeGutis:** Conceptualization, Visualization, Writing – review & editing. **Michael Esterman:** Conceptualization, Methodology, Formal analysis, Investigation, Resources, Data curation, Visualization, Supervision, Project administration, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2022.103146.

References

Abramovitch, A., Short, T., Schweiger, A., 2021. The c factor: cognitive dysfunction as a transdiagnostic dimension in psychopathology. Clin. Psychol. Rev. 86, 102007 https://doi.org/10.1016/j.cpr.2021.102007.

Akiki, T.J., Averill, C.L., Abdallah, C.G., 2017. A network-based neurobiological model of ptsd: Evidence from structural and functional neuroimaging studies. Current psychiatry reports, 19(11), 81-81. doi: 10.1007/s11920-017-0840-4.

Alon, Y., Naim, R., Pine, D.S., Bliese, P.D., Bar-Haim, Y., 2019. Validity of attention bias variability indices for posttraumatic stress disorder research: Evidence from patient data. J. Trauma. Stress 32 (5), 791–798. https://doi.org/10.1002/jts.22443.

Amick, M.M., Clark, A., Fortier, C.B., Esterman, M., Rasmusson, A.M., Kenna, A., Milberg, W.P., McGlinchey, R., 2013. Ptsd modifies performance on a task of affective executive control among deployed oef/oif veterans with mild traumatic brain injury. J. Int. Neuropsychol. Soc.: JINS 19 (7), 792–801. https://doi.org/10.1017/S1355617713000544.

Association, A.P., 2013. Diagnostic and statistical manual of mental disorders: Dsm-v (5th edition. ed.). Washington, DC; American Psychiatric Publishing, a division of American Psychiatric Association.

Aupperle, R.L., Melrose, A.J., Stein, M.B., Paulus, M.P., 2012. Executive function and ptsd: Disengaging from trauma. Neuropharmacology 62 (2), 686–694. https://doi.org/10.1016/j.neuropharm.2011.02.008.

Blake, D.D., Weathers, F.W., Nagy, L.M., Kaloupek, D.G., Gusman, F.D., Charney, D.S., Keane, T.M., 1995. The development of a clinician-administered ptsd scale. J. Trauma. Stress 8 (1), 75–90.

Campbell, D.G., Felker, B.L., Liu, C.-F., Yano, E.M., Kirchner, J.E., Chan, D., Rubenstein, L.V., Chaney, E.F., 2007. Prevalence of depression–ptsd comorbidity: Implications for clinical practice guidelines and primary care-based interventions. J. Gen. Intern. Med. 22 (6), 711–718. https://doi.org/10.1007/s11606-006-0101-4.

Campbell, T.A., Nelson, L.A., Lumpkin, R., Yoash-Gantz, R.E., Pickett, T.C., McCormick, C.L., 2009. Neuropsychological measures of processing speed and executive functioning in combat veterans with ptsd, tbi, and comorbid tbi/ptsd. Psychiatric Annals 39 (8).

Catarino, A., Küpper, C.S., Werner-Seidler, A., Dalgleish, T., Anderson, M.C., 2015. Failing to forget: Inhibitory-control deficits compromise memory suppression in posttraumatic stress disorder. Psychol. Sci. 26 (5), 604–616. https://doi.org/10.1177/0956797615569889.

Clemans, Z.A., El-Baz, A.S., Hollifield, M., Sokhadze, E.M., 2012. Single trial time–frequency domain analysis of error processing in post-traumatic stress disorder. Neurosci. Lett. 525 (2), 105–110. https://doi.org/10.1016/j.neulet.2012.07.051.

Danielmeier, C., Ullsperger, M., 2011. Post-error adjustments. Front. Psychol. 2, 233.

DeGutis, J., Esterman, M., McCulloch, B., Rosenblatt, A., Milberg, W., McGlinchey, R., 2015. Posttraumatic psychological symptoms are associated with reduced inhibitory control, not general executive dysfunction. J. Int. Neuropsychol. Soc. 21 (5), 342–352. https://doi.org/10.1017/s1355617715000235.

Dutilh, G., van Ravenzwaaij, D., Nieuwenhuis, S., van der Maas, H.L.J., Forstmann, B.U., Wagenmakers, E.-J., 2012. How to measure post-error slowing: a confound and a simple solution. J. Math. Psychol. 56 (3), 208–216. https://doi.org/10.1016/j.jmp.2012.04.001.

Dutra, S.J., Marx, B.P., McGlinchey, R., DeGutis, J., Esterman, M., 2018. Reward ameliorates posttraumatic stress disorder-related impairment in sustained attention. Chronic Stress (Thousand Oaks), 2. doi: 10.1177/2470547018812400.

Esterman, M., Rothlein, D., 2019. Models of sustained attention. Curr. Opin. Psychol. 29, 174–180. https://doi.org/10.1016/j.copsyc.2019.03.005.

Esterman, M., Noonan, S.K., Rosenberg, M., DeGutis, J., 2013. In the zone or zoning out? Tracking behavioral and neural fluctuations during sustained attention. Cereb. Cortex 23 (11), 2712–2723. https://doi.org/10.1093/cercor/bhs261.

Esterman, M., Reagan, A., Liu, G., Turner, C., DeGutis, J.M., 2014a. Reward reveals dissociable aspects of sustained attention. J. Exp. Psychol. Gen. 143 (6), 2287–2295.

Esterman, M., Rosenberg, M.D., Noonan, S.K., 2014b. Intrinsic fluctuations in sustained attention and distractor processing. J. Neurosci. 34 (5), 1724–1730. https://doi.org/10.1523/jneurosci.2658-13.2014.

Esterman, M., Fortenbaugh, F.C., Pierce, M.E., Fonda, J.R., DeGutis, J., Milberg, W., McGlinchey, R., 2019. Trauma-related psychiatric and behavioral conditions are uniquely associated with sustained attention dysfunction. Neuropsychology 33 (5), 711–724. https://doi.org/10.1037/neu0000525.

Esterman, M., Stumps, A., Jagger-Rickels, A., Rothlein, D., DeGutis, J., Fortenbaugh, F., Romer, A., Milberg, W., Marx, B.P., McGlinchey, R., 2020. Evaluating the evidence for a neuroimaging subtype of posttraumatic stress disorder. Sci. Transl. Med. 12 (568) https://doi.org/10.1126/scitranslmed.aaz9343.

Etkin, A., Maron-Katz, A., Wu, W., Fonzo, G.A., Huemer, J., Vértes, P.E., Patenaude, B., Richiardi, J., Goodkind, M.S., Keller, C.J., Ramos-Cejudo, J., Zaiko, Y.V., Peng, K.K., Shpigel, E., Longwell, P., Toll, R.T., Thompson, A., Zack, S., Gonzalez, B., Edelstein, R., Chen, J., Akingbade, I., Weiss, E., Hart, R., Mann, S., Durkin, K., Baete, S.H., Boada, F.E., Genfi, A., Autea, J., Newman, J., Oathes, D.J., Lindley, S.E., Abu-Amara, D., Arnow, B.A., Crossley, N., Hallmayer, J., Fossati, S., Rothbaum, B.O., Marmar, C.R., Bullmore, E.T., O'Hara, R., 2019. Using fmri connectivity to define a treatment-resistant form of post-traumatic stress disorder. Sci. Transl. Med. 11 (486) https://doi.org/10.1126/scitranslmed.aal3236.

Evans, T.C., DeGutis, J., Rothlein, D., Jagger-Rickels, A., Yamashita, A., Fortier, C.B., Fonda, J.R., Milberg, W., McGlinchey, R., Esterman, M., 2021. Punishment and reward normalize error-related cognitive control in ptsd by modulating salience network activation and connectivity. Cortex 145, 295–314.

Fortenbaugh, F.C., DeGutis, J., Germine, L., Wilmer, J.B., Grosso, M., Russo, K., Esterman, M., 2015. Sustained attention across the life span in a sample of 10,000: Dissociating ability and strategy. Psychol. Sci. 26 (9), 1497–1510. https://doi.org/10.1177/0956797615594896.

Fortenbaugh, F.C., Corbo, V., Poole, V., McGlinchey, R., Milberg, W., Salat, D., DeGutis, J., Esterman, M., 2017a. Interpersonal early-life trauma alters amygdala connectivity and sustained attention performance. Brain Behav. 7 (5), e00684.

Fortenbaugh, F.C., DeGutis, J., Esterman, M., 2017b. Recent theoretical, neural, and clinical advances in sustained attention research. Ann. N. Y. Acad. Sci. 1396 (1), 70–91. https://doi.org/10.1111/nyas.13318.

Fortenbaugh, F.C., Rothlein, D., McGlinchey, R., DeGutis, J., Esterman, M., 2018. Tracking behavioral and neural fluctuations during sustained attention: A robust replication and extension. NeuroImage 171, 148–164. https://doi.org/10.1016/j.neuroimage.2018.01.002.

Fortier, C.B., Amick, M.M., Grande, L., McGlynn, S., Kenna, A., Morra, L., Clark, A., Milberg, W.P., McGlinchey, R.E., 2014. The boston assessment of traumatic brain injury-lifetime (bat-l) semistructured interview: evidence of research utility and validity. J. Head Trauma Rehabil. 29 (1), 89–98. https://doi.org/10.1097/HTR.0b013e3182865859.

Ham, T., Leff, A., de Boissezon, X., Joffe, A., Sharp, D.J., 2013. Cognitive control and the salience network: An investigation of error processing and effective connectivity. J. Neurosci. 33 (16), 7091–7098. https://doi.org/10.1523/jneurosci.4692-12.2013.

Hankin, C.S., Spiro 3rd, A., Miller, D.R., Kazis, L., 1999. Mental disorders and mental health treatment among u.S. Department of veterans affairs outpatients: the veterans health study. Am. J. Psychiatry 156 (12), 1924–1930. https://doi.org/10.1176/ajp.156.12.1924.

Harrington, K.M., Miller, M.W., Wolf, E.J., Reardon, A.F., Ryabchenko, K.A., Ofrat, S., 2012. Attention-deficit/hyperactivity disorder comorbidity in a sample of veterans with posttraumatic stress disorder. Compr. Psychiatry 53 (6), 679–690. https://doi.org/10.1016/j.comppsych.2011.12.001.

Jagger-Rickels, A., Stumps, A., Rothlein, D., Park, H., Fortenbaugh, F., Zuberer, A., Fonda, J.R., Fortier, C.B., DeGutis, J., Milberg, W., McGlinchey, R., Esterman, M., 2021. Impaired executive function exacerbates neural markers of posttraumatic stress disorder. Psychol. Med. 1–14 https://doi.org/10.1017/s0033291721000842.

Jagger-Rickels, A., Rothlein, D., Stumps, A., Evans, T.C., Bernstein, J., Milberg, W., McGlinchey, R., DeGutis, J., Esterman, M., 2022. An executive function subtype of ptsd with unique neural markers and clinical trajectories. Transl. Psychiatry 12 (1), 262. https://doi.org/10.1038/s41398-022-02011-y.

Jun, J., Lee, V.G., 2021. Perceptual and response factors in the gradual onset continuous performance tasks. Atten. Percept. Psychophys. 83 (7), 3008–3023.

Jun, J., Remington, R.W., Koutstaal, W., Jiang, Y.V., 2019. Characteristics of sustaining attention in a gradual-onset continuous performance task. J. Exp. Psychol. Hum. Percept. Perform. 45 (3), 386–401. https://doi.org/10.1037/xhp0000604.

Keller, A.S., Leikauf, J.E., Holt-Gosselin, B., Staveland, B.R., Williams, L.M., 2019. Paying attention to attention in depression. Transl. Psychiatry 9 (1), 279. https://doi.org/10.1038/s41398-019-0616-1.

Kessler, R.C., Sonnega, A., Bromet, E., Hughes, M., Nelson, C.B., 1995. Posttraumatic stress disorder in the national comorbidity survey. Arch. Gen. Psychiatry 52 (12), 1048–1060. https://doi.org/10.1001/archpsyc.1995.03950240066012.

Koch, S.B.J., van Zuiden, M., Nawijn, L., Frijling, J.L., Veltman, D.J., Olff, M., 2016. Aberrant resting-state brain activity in posttraumatic stress disorder: a meta-analysis and systematic review. Depression and Anxiety 33 (7), 592–605. https://doi.org/10.1002/da.22478.

Kucyi, A., Hove, M.J., Esterman, M., Hutchison, R.M., Valera, E.M., 2016. Dynamic brain network correlates of spontaneous fluctuations in attention. Cereb. Cortex 27 (3), 1831–1840. https://doi.org/10.1093/cercor/bhw029.

Langner, R., Eickhoff, S.B., 2013. Sustaining attention to simple tasks: a meta-analytic review of the neural mechanisms of vigilant attention. Psychol Bull 139 (4), 870–900. https://doi.org/10.1037/a0030694.

Lippa, S.M., Fonda, J.R., Fortier, C.B., Amick, M.A., Kenna, A., Milberg, W.P., McGlinchey, R.E., 2015. Deployment-related psychiatric and behavioral conditions and their association with functional disability in oef/oif/ond veterans. J. Trauma Stress 28 (1), 25–33. https://doi.org/10.1002/jts.21979.

Lovibond, P.F., Lovibond, S.H., 1995. The structure of negative emotional states: Comparison of the depression anxiety stress scales (dass) with the beck depression and anxiety inventories [Press release].

Marcum, J., 1960. A statistical theory of target detection by pulsed radar. IRE Trans. Inf. Theory 6 (2), 59–267.

McGlinchey, R.E., Milberg, W.P., Fonda, J.R., Fortier, C.B., 2017. A methodology for assessing deployment trauma and its consequences in oef/oif/ond veterans: the tracts longitudinal prospective cohort study. Int. J. Methods Psychiatric Res. 26 (3), e1556.

Morishima, Y., Akaishi, R., Yamada, Y., Okuda, J., Toma, K., Sakai, K., 2009. Task-specific signal transmission from prefrontal cortex in visual selective attention. Nat. Neurosci. 12 (1), 85–91. https://doi.org/10.1038/nn.2237.

Murphy, K., Birn, R.M., Bandettini, P.A., 2013. Resting-state fmri confounds and cleanup. NeuroImage 80, 349–359. https://doi.org/10.1016/j.neuroimage.2013.04.001.

Neria, Y., 2021. Functional neuroimaging in ptsd: From discovery of underlying mechanisms to addressing diagnostic heterogeneity. Am. J. Psychiatry 178 (2), 128–135.

Nichter, B., Norman, S., Haller, M., Pietrzak, R.H., 2019. Psychological burden of ptsd, depression, and their comorbidity in the u.S. Veteran population: Suicidality, functioning, and service utilization. J. Affect. Disord. 256, 633–640. https://doi.org/10.1016/j.jad.2019.06.072.

Quinones, M.M., Gallegos, A.M., Lin, F.V., Heffner, K., 2020. Dysregulation of inflammation, neurobiology, and cognitive function in ptsd: an integrative review. Cogn. Affective Behav. Neurosci. 20 (3), 455–480. https://doi.org/10.3758/s13415-020-00782-9.

Rajan, A., Meyyappan, S., Liu, Y., Samuel, I.B.H., Nandi, B., Mangun, G.R., Ding, M., 2021. The microstructure of attentional control in the dorsal attention network. J. Cognit. Neurosci. 33 (6), 965–983. https://doi.org/10.1162/jocn_a_01710.

Regev, S., Meiran, N., 2014. Post-error slowing is influenced by cognitive control demand. Acta Psychol. (Amst.) 152, 10–18. https://doi.org/10.1016/j.actpsy.2014.07.006.

Richardson, J.D., Ketcheson, F., King, L., Shnaider, P., Marlborough, M., Thompson, A., Elhai, J.D., 2017. Psychiatric comorbidity pattern in treatment-seeking veterans. Psychiatry Res. 258, 488–493. https://doi.org/10.1016/j.psychres.2017.08.091.

Riley, E., Esterman, M., Fortenbaugh, F.C., DeGutis, J., 2017. Time-of-day variation in sustained attentional control. Chronobiol. Int. 34 (7), 993–1001. https://doi.org/10.1080/07420528.2017.1308951.

Ross, M. C., & Cisler, J. M. (2020). Altered large-scale functional brain organization in posttraumatic stress disorder: a comprehensive review of univariate and network-level neurocircuitry models of ptsd. NeuroImage. Clin., 27, 102319-102319. doi: 10.1016/j.nicl.2020.102319.

Rothlein, D., DeGutis, J., Germine, L., Wilmer, J., McGlinchey, R., Esterman, M., 2018. Sensitivity to stimulus similarity is associated with greater sustained attention ability. Atten. Percept. Psychophys. 80 (6), 1390–1408. https://doi.org/10.3758/s13414-018-1504-0.

Samuelson, K.W., Newman, J., Abu Amara, D., Qian, M., Li, M., Schultebraucks, K., Purchia, E., Genfi, A., Laska, E., Siegel, C., Hammamieh, R., Gautam, A., Jett, M., Marmar, C.R., 2020. Predeployment neurocognitive functioning predicts postdeployment posttraumatic stress in army personnel. Neuropsychology 34 (3), 276–287. https://doi.org/10.1037/neu0000603.

Sarter, M., Givens, B., Bruno, J.P., 2001. The cognitive neuroscience of sustained attention: where top-down meets bottom-up. Brain Res. Brain Res. Rev. 35 (2), 146–160. https://doi.org/10.1016/s0165-0173(01)00044-3.

Schaefer, A., Kong, R., Gordon, E.M., Laumann, T.O., Zuo, X.N., Holmes, A.J., Eickhoff, S. B., Yeo, B.T.T., 2018. Local-global parcellation of the human cerebral cortex from intrinsic functional connectivity mri. Cereb. Cortex 28 (9), 3095–3114. https://doi.org/10.1093/cercor/bhx179.

Scott, J.C., Matt, G.E., Wrocklage, K.M., Crnich, C., Jordan, J., Southwick, S.M., Krystal, J.H., Schweinsburg, B.C., 2015. A quantitative meta-analysis of neurocognitive functioning in posttraumatic stress disorder. Psychol. Bull. 141 (1), 105–140. https://doi.org/10.1037/a0038039.

Shenhav, A., Musslick, S., Lieder, F., Kool, W., Griffiths, T.L., Cohen, J.D., Botvinick, M. M., 2017. Toward a rational and mechanistic account of mental effort. Annu. Rev. Neurosci. 40, 99–124. https://doi.org/10.1146/annurev-neuro-072116-031526.

Sheynin, J., Duval, E.R., Lokshina, Y., Scott, J.C., Angstadt, M., Kessler, D., Zhang, L., Gur, R.E., Gur, R.C., Liberzon, I., 2020. Altered resting-state functional connectivity in adolescents is associated with ptsd symptoms and trauma exposure. NeuroImage: Clin. 26, 102215 https://doi.org/10.1016/j.nicl.2020.102215.

Smith, M.W., Schnurr, P.P., Rosenheck, R.A., 2005. Employment outcomes and ptsd symptom severity. Mental Health Services Res. 7 (2), 89–101. https://doi.org/10.1007/s11020-005-3780-2.

Swick, D., Ashley, V., 2017. Enhanced attentional bias variability in post-traumatic stress disorder and its relationship to more general impairments in cognitive control. Scientific Rep., 7(1), 14559-14559. doi: 10.1038/s41598-017-15226-7.

Swick, D., Ashley, V., 2020. The specificity of inhibitory control deficits in post-traumatic stress disorder: a dissociation between the speed and reliability of stopping. J. Anxiety Disord. 75, 102278 https://doi.org/10.1016/j.janxdis.2020.102278.

Swick, D., Honzel, N., Larsen, J., Ashley, V., Justus, T., 2012. Impaired response inhibition in veterans with post-traumatic stress disorder and mild traumatic brain injury. J. Int. Neuropsychol. Soc. 18 (5), 917–926. https://doi.org/10.1017/s1355617712000458.

Swick, D., Honzel, N., Larsen, J., Ashley, V., 2013. Increased response variability as a marker of executive dysfunction in veterans with post-traumatic stress disorder. Neuropsychologia 51 (14), 3033–3040. https://doi.org/10.1016/j.neuropsychologia.2013.10.008.

Swick, D., Honzel, N., Turken, U., 2015. Intact error monitoring in combat veterans with post-traumatic stress disorder. Psychiatry Res. 234 (2), 227–238. https://doi.org/10.1016/j.pscychresns.2015.09.016.

Tanielian, T. L., Tanielian, T., Jaycox, L., 2008. Invisible wounds of war: Psychological and cognitive injuries, their consequences, and services to assist recovery (Vol. 1): Rand Corporation.

Tursich, M., Ros, T., Frewen, P.A., Kluetsch, R.C., Calhoun, V.D., Lanius, R.A., 2015. Distinct intrinsic network connectivity patterns of post-traumatic stress disorder symptom clusters. Acta Psychiatr. Scand. 132 (1), 29–38. https://doi.org/10.1111/acps.12387.

Vasterling, J.J., Brailey, K., Constans, J.I., Sutker, P.B., 1998. Attention and memory dysfunction in posttraumatic stress disorder. Neuropsychology 12 (1), 125–133. https://doi.org/10.1037/0894-4105.12.1.125.

Vasterling, J.J., Duke, L.M., Brailey, K., Constans, J.I., Allain Jr., A.N., Sutker, P.B., 2002. Attention, learning, and memory performances and intellectual resources in vietnam veterans: Ptsd and no disorder comparisons. Neuropsychology 16 (1), 5–14. https://doi.org/10.1037//0894-4105.16.1.5.

Vossel, S., Geng, J.J., Fink, G.R., 2014. Dorsal and ventral attention systems: Distinct neural circuits but collaborative roles. Neuroscientist 20 (2), 150–159. https://doi.org/10.1177/1073858413494269.

Wu, J., Ge, Y., Shi, Z., Duan, X., Wang, L., Sun, X., Zhang, K., 2010. Response inhibition in adolescent earthquake survivors with and without posttraumatic stress disorder: A combined behavioral and erp study. Neurosci. Lett. 486 (3), 117–121. https://doi.org/10.1016/j.neulet.2010.07.040.

Yamashita, A., Rothlein, D., Kucyi, A., Valera, E.M., Esterman, M., 2021a. Brain state-based detection of attentional fluctuations and their modulation. NeuroImage 236, 118072. https://doi.org/10.1016/j.neuroimage.2021.118072.

Yamashita, A., Rothlein, D., Kucyi, A., Valera, E.M., Germine, L., Wilmer, J., DeGutis, J., Esterman, M., 2021b. Variable rather than extreme slow reaction times distinguish brain states during sustained attention. Sci. Rep. 11 (1), 14883. https://doi.org/10.1038/s41598-021-94161-0.

Yamashita, A., Rothlein, D., Kucyi, A., Valera, E.M., Germine, L., Wilmer, J., DeGutis, J., Esterman, M., 2021c. Variable rather than extreme slow reaction times distinguish brain states during sustained attention. Sci. Rep. 11 (1), 1–13.

Yeo, B.T., Krienen, F.M., Sepulcre, J., Sabuncu, M.R., Lashkari, D., Hollinshead, M., Roffman, J.L., Smoller, J.W., Zöllei, L., Polimeni, J.R., 2011. The organization of the human cerebral cortex estimated by intrinsic functional connectivity. J. Neurophysiol.