ORIGINAL ARTICLE

Use of Electroencephalography for Treatment Validation and Symptom Classification in Patients with Combat-Related Post-Traumatic Stress Disorder

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Colton Flippen[1,2]
Celia Higginbotham[1,2]
Carloe Leung[1]
Danielle Royer[1]
Faisal R. Jahangiri [1,3]

[1]School of Behavioral & Brain Sciences, The University of Texas at Dallas, Richardson, Texas, USA.
[2]The University of Texas at Dallas Neurolab Callier Center, Dallas, TX, USA.
[3]Global Innervation LLC, Dallas, Texas, USA.

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ABSTRACT

Post-traumatic stress disorder (PTSD) is a debilitating mental health condition that can develop in individuals who experience a traumatic event. In the United States, it can be estimated that up to 30% of veterans may develop a form of combat-related PTSD. Treatment options today have various challenges and limitations for managing PTSD. In this review, we analyzed the use of electroencephalography (EEG) to identify symptoms and monitor different approaches to treatment for combat-related PTSD.

A total of 1,264 combat-exposed veterans were evaluated in this review across ten published studies using EEG to either identify PTSD symptoms or validate different applications of treatment and patient outcomes. The main findings include the use of EEG to identify biomarkers that predict PTSD symptom presentations and subtypes, such as spectrum differences and weak connectivity across different brain regions. Improvements in patients with PTSD over time or in real-time using novel and traditional treatments can also be validated using EEG. The integration of EEG with an individualized multimodal psychotherapy approach for treating combat-related PTSD was found to be an effective treatment option for improving patient outcomes. Future studies could improve on these findings and find possible applications for treating non-combat-related PTSD.

INTRODUCTION

Over the last 25 years, our understanding of Post-Traumatic Stress Disorder (PTSD) has deepened as advances in neuroscience and psychology have blended to elucidate the biology of behavior and thought. We are beginning to move away from masking symptoms with medications, an approach that has led to problems with polypharmacy and drug misuse, especially in the veteran community. Evidence-based

treatments, however, like Cognitive Processing Therapy (CPT), Cognitive Behavioral Therapy (CBT), Eye Movement Desensitization and Reprocessing (EMDR), and Prolonged Exposure therapy (PE) are plagued by non-response, dropout rates as high as 50%, relapse, and failure to generalize outside the therapeutic condition [1]. When we consider that "About 5 out of every 100 adults (or 5%) in the U.S. has PTSD in any given year," [2]. This equates to more than 16 million Americans battling a disorder and needing help that focuses on the neurobiology of PTSD and not merely symptom reduction. Two different general approaches dominate the neurobiological approach to PTSD. The first insists on the primacy of genetic predisposition and/or pediatric exposure to abuse in the development of PTSD. It focuses research on predicting who is likely to develop the disorder. The second focuses on treatment outcomes based on targeting affected brain regions. Our focus for this meta-analysis aligns with this second approach, particularly the use of EEG in comparing pre-treatment and post-treatment outcomes for combat-related PTSD and the use of EEG for symptom prediction and PTSD-type classification.

PTSD is described by the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) as a cluster of symptoms that is not the physiological result of another medical condition, medication, drugs, or alcohol and causes clinically significant distress or impairment in an individual's social interactions, capacity to work or other important areas of functioning [3]. This cluster of symptoms is generally categorized as re-experiencing, avoidance, negative cognitions and mood, and arousal (also called hypervigilance). The cause of impairment is exposure to actual or threatened death, serious injury, or sexual violation. As might be imagined, given these parameters, the causes of PTSD are varied. A trained physician or mental health provider determines the diagnosis of PTSD. While different assessments and physical exams may be used for baseline diagnosis, the single most used diagnostic test for PTSD is the Clinician-Administered PTSD Scale - 5 (CAPS-5), which is matched to the DSM-V criteria [4]. Criterion A, the traumatic event(s), allows a provider to determine the main trigger for PTSD symptomology: childhood trauma and/or sexual abuse, adult physical or sexual assault, or natural disaster-related or combat-related PTSD.

Each of these causes of PTSD affects different areas of the brain, so PTSD cannot be considered a monolithic neurobiological malady [5-8]. The diversity of affected regions represented by PTSD subtypes necessitates a focus on a single subtype to compare data. We chose to focus on combat-related PTSD because this subtype has a single region of dominant impact and because incidence rates are higher in the veteran (i.e., combat-exposed) population than in the civilian (i.e., non-combat-exposed) population. As previously mentioned, about 5% of the total US population has PTSD. By comparison, estimates of PTSD in the veteran population range from slightly more than the civilian population to as high as 30%, depending on what source is reporting. The United States Veterans Association indicates that incidence rates vary with service era, as reported in Table 1 [9].

Service Era	PTSD in the Past Year	PTSD at Some Point in Life
Operations Iraqi Freedom (OIF) and Enduring Freedom (OEF)	15 out of 100 (15%)	29 out of 100 (29%)
Persian Gulf War (Desert Storm)	14 out of 100 (14%)	21 out of 100 (21%)
Vietnam War	5 out of 100 (5%)	10 out of 100 (10%)
World War II (WWII) and Korean War	2 out of 100 (2%)	3 out of 100 (3%)
NOTE: The data in this table is from Veterans alive at the time of the study. As such, it does not include Veterans in any service area who have died and may have had PTSD.		

Table 1: Veterans with PTSD Varies by Service Era.

If left untreated, combat-related PTSD can lead to detachment from loved ones, mistrust of others, disinterest in previously enjoyed activities, heightened vigilance, poor sleep, reduced overall physical health, substance abuse, job loss, violence, and suicide. It is vital to our veteran population that treatment outcomes are improved and that the data showing improvement is concrete and not purely anecdotal. Electroencephalography (EEG) can be a key tool for gathering objective data. We hypothesize that EEG will show positive change in treatment studies and positive predictive value in subtype studies. This meta-analysis was performed to examine (a) The use of EEG in connection with baseline vs. post-treatment data in resting state, attention, and reactivity to perceived threat for participants with combat-related PTSD and (b) The use of EEG for predicting subtypes of combat PTSD.

METHODS

Protocols and Registration

This meta-analysis was reported following the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) statement [10]. Figure 1 shows the PRISMA flow diagram.

Selection Criteria

Only English empirical peer-reviewed papers related to (a) PTSD treatment outcomes of combat veterans via the use of EEG or (b) the prediction of PTSD symptoms and type classification using EEG data were included in this meta-analysis. Studies that included combat-exposed veterans who had PTSD were

included, whereas patients who developed PTSD due to other reasons (e.g., sexual abuse, car accidents) were not included. Moreover, we included studies published in the recent ten years (i.e., from 2013 to 2023).

Search Strategies

Systematic searches were conducted from September to October 2023 using UTD library search. The year of search for the papers was from January 1st, 2013, to December 31st, 2023. Four keywords were used: PTSD, EEG, treatment, and combat.

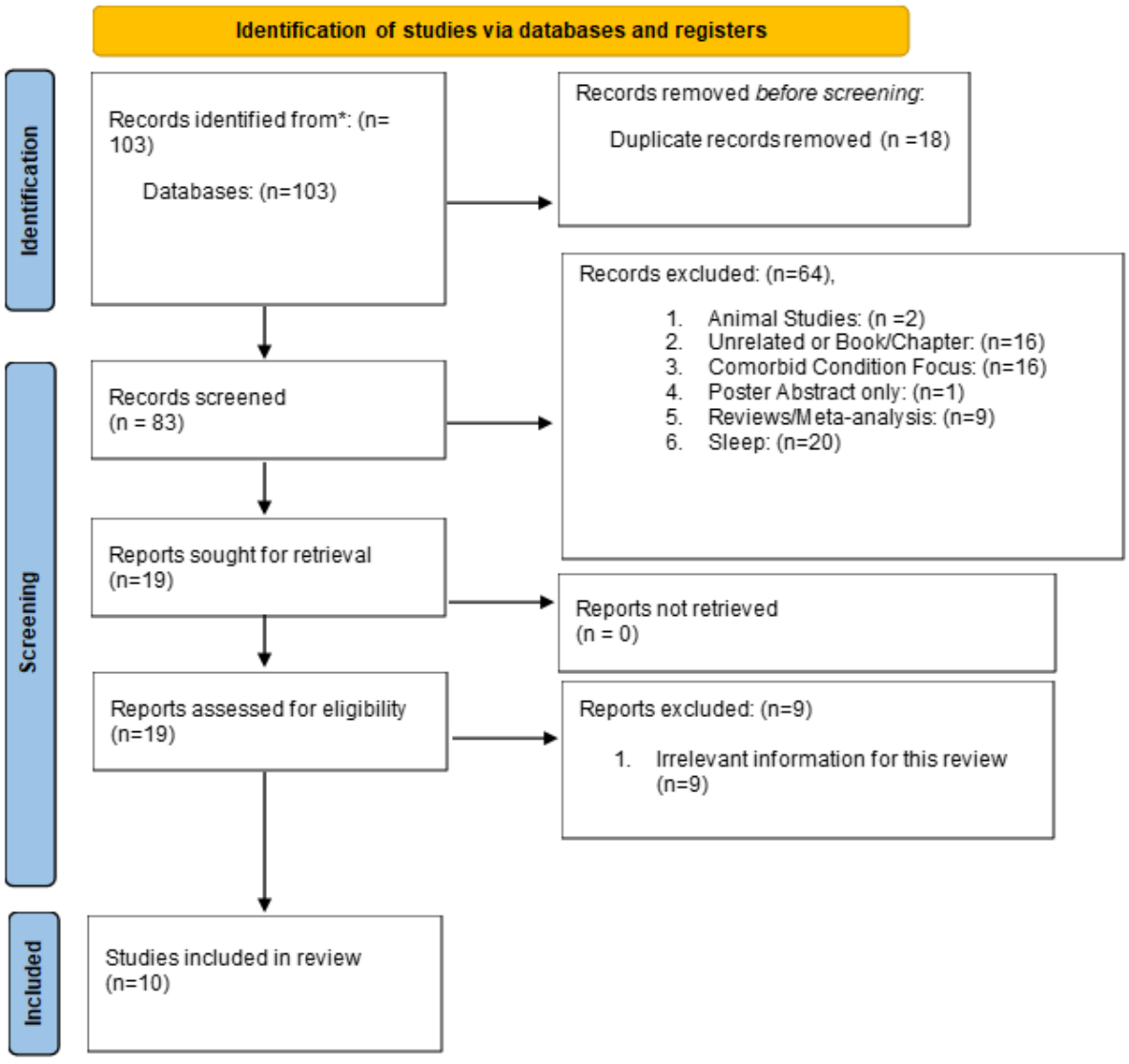

Figure 1: PRISMA flow diagram—study elimination process. The PRISMA flow diagram depicts the flow of information through the different phases of systematic reviews and meta-analyses. It maps out the number of records identified, included, and excluded and the reasons for exclusions.

Screening and Data Extraction

The search results with attachments were imported to Zotero for title and abstract screening, full-text screening, and data extraction. All authors worked independently to determine the paper's eligibility. Data on participants' demographics, EEG recording methods, treatment, patient outcomes, and application were extracted. Table 2 presents the included studies related to the use of EEG for PTSD treatment validation use. Table 3 presents the included studies related to the use of EEG for PTSD symptom prediction or classification use.

1. Treatment Validation Use of EEG

STUDY DETAILS									OUTCOMES	
AUTHOR	DATE	n =	PT DEMOGRAPHICS	DURATION	EEG recording	EEG MONTAGE	BRAIN REGION/WAVES	DESCRIPTION	PATIENT IMPROVEMENT	APPLICATION
Makale et al.	2023	185 combat veterans	Age range = 34 - 75 years, with a mean of almost 53 years. Approximately a 1:1 ratio of males to females.	4-6 weeks	Resting-state (awake, eye-closed, and seated)	19 electrodes. High impedance dry electrode EEG headset.	alpha	prTMS + psychotherapy; EEG guidance for stimulation loci (cortical treatment sites) and frequency. EEG was used before prTMS and at the start of every week for approximately 6 weeks.	significant clincal improvement, increased cortical alpha center frequency and alpha oscillatory synchronization.	DMN targeting for individualized novel preventitive, diagnostic, and therapeutic strategies; possible application to non-combat PTSD
Fitzgerald et al.	2016	50 combat veterans: 25 with PTSD, 25 without	Without PTSD: mean age 32.84, SD 7.77, 88% males, 52% Caucasian; With PTSD: mean age 30.16, SD 7.80, 96% males, 76% Caucasian	Single session of training followed by 3 blocks of 25 images. Each image lasted 7sec, followed by 1sec of fixation cross, self-timed rest between blocks.	EEG recording was conducted during the task (Emotion Regulation Task, in which negative and neutral pictures were presented)	34 electrodes: 32-channel cap + FCZ, IZ	Negative and neutral picture-elicited LPP (Late Positive Potential) amplitude in the centro-parietal region (dLPFC)	Emotion regulation task using images from IAPS; cognitive reappraisal	No between group difference during reappraisal; LPP reduced in both groups over time	1. PTSD pts did not display measurable deficits in reappraisal-related reductions in the LLP. 2. Reappraisal effectively modulates the LLP. 3. PTSD pts did not show increased LLPs during sustained processing of negative stimuli which supports evidence of "emotional blunting".
Tillman et al.	2023	55 veterans with combat-PTSD (served in combat areas between 2001 and 2016)	Sham rTMS + CPT group: Age range = 21-42, mean 31.36, SD = 4.87; Active rTMS + CPT group: age range = 26-52, mean 34.23, SD = 7.73.	12 weeks	EEG recording was conducted during the task.	64-channel cap, reference at midline between CZ and CPZground at APZ	P3a amplitude and latency from five frontal (F3, F1, Fz, F2, F4) and five frontocentral (FC3, FC1, FCz, FC2, FC4).	EEG pre and post treatment; treatment active/sham rTMS +CPT (cognitive processing therapy)	P3a amplitude and response time to trauma related stimuli decrease correlated to decrease in PTSD symptoms; greater decrease for active rTMS+CPT	The presence of an objective, physiological marker of treatment response can enhance a study and possibly account for underlying mechanistic changes associated with a successful treatment response. P3a is an objective marker of change in PTSD severity.
Wahbeh and Oken	2013	n=86	59 with PTSD 27 without; all male	1 session that included 30 min pre-trial lab acclimation followed by a 5-minute baseline	Resting-state	32 active electrode channels: 20 (10-20 system) & 12 (10-10 system) electrodes	delta, theta, alpha, beta amplitude; frontal alpha symmetry, and peak alpha frequency	assessing respiration, EEG, and heart rate variability as potential biofeedback markers	No current improvement stats. This was to develop prarameters for biofeedback treatment.	Peak high-frequency HRV and peak alpha frequency are sensitive to PTSD status and may be potential biofeedback parameters
Zotev et al.	2018	Final sample: 15 combat veterans in the experimental group (mean age 31, SD = 5); 8 combat veterans in the control group (mean age 37, SD = 8)	all male	8 sessions, 1x/week; only sessions 4-6 were treatment	Each session included seven runs. The initial and final rest runs were resting-state (participants were asked to relax and rest while looking at a fixation cross). The other five were conducted during the task.	EEG recordings were performed simultaneously with fMRI using a 32-channel MR-compatible EEG system.	Alpha; LA (left amygdala) and the left DLPFC.	rtfMRI-nf paired with EEG for 40 sec blocks of H,C, R to "teach" brain regulation	80% reduction in CAPS scores significantly correlated with enhancement in functional connectivity.	Findings suggest that real time mri/eeg neurofeedback can correct amygdala-pfc deficiencies seen in PTSD patients.

Table 2: Study Selection for Treatment Validation Use of EEG

Use of EEG

EEG with 64 channels was commonly used for data collection among the included studies [11-14]. Interestingly, as TMS was used simultaneously with EEG in Etkin et al. (2019), the 64 channels EEG cap had rotatable electrodes compatible with TMS use. 32-channel EEG was another commonly used montage [15-17]. However, it is important to note that in Fitzgerald et al. (2016), besides the standard 32 channels, FCz and Iz were added. Also, in Zotev et al. (2018), magnetic resonance (MR)-compatible 32-channel EEG and EEG recordings were performed simultaneously with functional magnetic resonance imaging (fMRI). Two of the included studies used 19-channel EEG [18,19]. Only one study used 22-channel EEG [20].

Most EEG recordings in our review were conducted as participants completed tasks or during resting-state conditions. Three of the included studies recorded brain signals using EEG when participants were performing a task [11,13,15]. These studies used a visual task including stimuli of threatening or negative images and non-threatening or neutral images. Other studies conducted resting-state EEG recordings [14,16,18-20]. For example, in Toll et al. (2020), participants were told to remain awake and let their minds wander while sitting comfortably on a reclining chair. They underwent an eye-closed paradigm for 3 minutes and an eye-open paradigm for 3 minutes. In Li et al. (2022) and Wahbeh and Oken (2013), brain data were recorded during an attentive resting state. During the eye-closed paradigm, participants were asked to open their eyes when they heard a tone [20] or to click the left trigger button after hearing a low tone and the right trigger button after hearing a high tone [16]. In Zotev et al. (2018), EEG recordings were conducted during a happy emotion induction task and resting-state conditions. Specifically, they used fMRI and EEG simultaneously. There were seven runs of brain scanning, in which the first and last runs were resting (i.e., participants were asked to relax and rest while looking at a fixation cross). The other runs were conducted during the task. Likewise, Etkin et al. (2019) conducted EEG recording simultaneously with single-pulse TMS (transcranial magnetic stimulation).

Most included studies analyzed the recorded EEG signals in multiple frequency bands. Toll et al. (2020) filtered the resting-state EEG data into theta, alpha, beta, and gamma frequency ranges. Sheerine et al. (2018) analyzed the absolute power in four frequency ranges, which include delta, theta, alpha, and beta, and they specifically looked at the data at 10 electrode sites (right frontal - FP2, F8; left frontal - FP1, F7; right occipital-temporal - T4, T6, O2; left occipital-temporal - T3, T5, O1). Likewise, Wahbeh and Oken (2013) analyzed the amplitude of the signals in the delta, theta, alpha, and beta bands. Additionally, they included the measure of the frontal alpha asymmetry and peak alpha frequency. Brain data were extracted from EEG channels F3, F4, C3, C4, P3, P4, PO3, PO4, Fz, Cz, Pz, Oz. In the study by Etkin et al. (2019), data was filtered into four frequency ranges: theta, alpha, beta, and low gamma. Li et al. (2022) analyzed brain data in five frequency ranges: delta, theta, alpha, beta, and gamma. A few studies selected a specific frequency band for data analysis. In Delarosa et al. (2020) study, they looked at the frontal theta power at FPz, while Makale et al. (2023) and Zotev et al. (2018) looked at the alpha band.

Apart from brain oscillations, two studies focused on event-related brain signals. In Fitzgerald et al. (2016),

the negative and neutral picture-elicited LPP (Late Positive Potential) amplitudes in the centro-parietal region (dlPFC; dorsolateral prefrontal cortex) were analyzed. It was used to indicate the sustained attention and processing of the pictures. Tillman et al. (2023) analyzed the P3a amplitude and latency from five frontal (F3, F1, Fz, F2, F4) and five frontocentral (FC3, FC1, FCz, FC2, FC4) sites.

2. Symptom Prediction/Classification Use of EEG

STUDY DETAILS									OUTCOMES	
AUTHOR	DATE	n =	PT DEMOGRAPHICS	DURATION	EEG recording	EEG MONTAGE	BRAIN REGION/WAVES	DESCRIPTION	PATIENT IMPROVEMENT	APPLICATION
Etkin et al.	2019	control = 117, PTSD = 128	Study 1: all female, non-combat PTSD; Study 2: all male, combat-related PTSD	Study 1: PE therapy (typical duration of 3months; Study 2: no therapy	EEG measurements concurrent with single-pulse TMS stimulation	64-channel cap with rotatable electrode compatible with TMS use	Full: theta, alpha, beta, low gamma	fMRI prior to EEG + spTMS	PTSD causes impairments in the delayed recall of verbal memory and resting-state fMRI connectivity in the VAN.	identified a neurobehavioral phenotype within the broader clinical syndrome of PTSD that is not a result of TBI.
Li et al.	2022	202 combat exposed Danish veterans	53% probable PTSD, 47% controls	10 minutes of EEG data	Resting-state	22 channels	Delta, theta, alpha, beta, gamma	implemented a novel comprehensive framework for applying machine learning to investigate the ability of common resting-state EEG features to classify combat-related PTSD	62% accuracy for predicting PTSD patients	use of EEG to identify biomarkers that predict PTSD subtypes
Sheerin et al.	2018	n=147 [polytrauma population with variable PTSD and mild TBI (mTBI) diagnoses]	Male= 96% Caucasian (72.8%) Avg age= 27.8 (SD=7.9)	EEG was assessed for 10 minutes, with eyes closed	Resting-state	10-20 system: 19 electrode sites using Mitsar 201 amplifier system with sampling rate of 500Hz	delta, theta, alpha, and beta (right and left frontal, right and left occiptial temporal)	Regional averages of absolute power in alpha, beta, delta, and theta frequency bands were computed to estimate a single EEG common factor per band.	mTBI have a higher overall EEG power compared to those without. Removing the mTBI, the residual EEG factor can be used to predict the four symptom factors	evidence for possible neurobiological basis for the four PTSD symptom factors: avoidance, numbing, re-experiencing, & hyperarousal.
Toll et al.	2020	healthy control n = 36, n =201 combat exposed veterans	201 combat exposed veterans; 95 control, 106 PTSD	EEG was assessed for 6 minutes, 3 min EO and 3min EC	Resting-state	64-channel resting EEG (eyes open and closed), 5kHz sampling rate	theta, alpha, beta, gamma	74 brain region connections were significantly reduced in PTSD. Under-connectivity of the orbital and anterior middle frontal gyri were most prominent.	connectivity abnormality was related to an objective cognitive impairment but not subjective clinical symptoms	Discovered biomarker provided good classification performance, demonstrating its generalization capability for identifying PTSD patients.
DeLarosa et al.	2020	42 combat exposed vets	vets PTSD= 29, vets PTSD= 13 ; 37 Male, 5 Female	EEG task time of 20 min	EEG recording was conducted during the task	64-electrode cap, 1kHz sample	theta	using EEG to study brain dynamics in PTSD; to understand neurophysiological characteristics of PTSD such as threat-processing	Longer reaction time to threatening images for the PTSD group was for all threatening images regardless of category membership.	cortico-limbic dysfunction in PTSD; low theta power

Table 3: Study Selection for Symptom Prediction/Classification Use of EEG.

RESULTS

EEG and Therapeutic Validation

Many studies in the past decade have produced evidence that EEG is a valuable metric for validating the efficacy of PTSD treatment. As previously mentioned, PTSD is often treated with a variety of therapeutic measures, such as cognitive processing therapy or cognitive behavioral therapy. One subset of cognitive behavioral therapy is emotional regulation tasks, and EEG has been used to measure the effectiveness of these tasks as PTSD treatment. One study utilized EEG while PTSD patients performed an emotional regulation task [15]. The study aimed to strengthen the cognitive reappraisal skills of the patients by measuring sustained attention toward and processing of neutral and negative pictures and scoring their

emotional response based on instructions to either maintain or down-regulate their response. The late positive potential (LPP) was used to measure the patient's initial response, and the results demonstrated that both PTSD and non-PTSD groups had similar initial LPP amplitudes that decreased because of cognitive reappraisal. However, time-dependent increases in LPP amplitude were only observed in the non-PTSD group, which indicates that PTSD damages the patient's emotional processing. The study also endorses using EEG as a metric for measuring therapeutic progress.

Other biological factors have also been used alongside EEG to create biofeedback parameters as a treatment option. Based on the notion that biofeedback could be a viable PTSD treatment option, respiration, and heart rate variability (HRV) were assessed alongside EEG for their capability as biofeedback parameters in a potential clinical trial [16]. The patient population consisted of veterans with and without PTSD, and data was recorded in an attentive resting state. These metrics were analyzed to identify sensitivity to PTSD status as well as their relationship to PTSD symptoms as defined by scores on CAPS, Post-traumatic Stress Disorder Checklist Scale (PCL), and the Beck Depression Inventory (BDI). Both groups had similar alpha, beta, delta, and theta frequency amplitudes and frontal alpha symmetry. Still, the peak alpha frequency was also found to be higher in the PTSD group than the non-PTSD group in the anterior, posterior, right, and left regions. Post-hoc analysis revealed that peak alpha frequency was greater on the right than on the left in the PTSD group, in contrast to the non-PTSD group, which expressed even peak alpha frequency. Furthermore, this difference in peak frequency was correlated with total PTSD symptoms, as measured by CAPS, PCL, and PCL sub-scores of re-experiencing, hyper-arousal, and numbing-avoiding. Additionally, Peak high-frequency HRV was the only biometric found to be higher in the PTSD group but lower when the respiration is adjusted for. EEG has also been used in fMRI studies to confirm the findings of the study.

One study used real-time (rtfMRI) to provide neurofeedback to the subject while the subject performed a happy emotion induction task, which they called rtfMRI-nf [17]. The goal of rtfMRI-nf in this study is to monitor BOLD changes in the left amygdala during the task, and EEG was recorded simultaneously with fMRI. PTSD severity was measured with the CAPS scale before and after training; patients who received rtfMRI-nf demonstrated a reduction in CAPS scores (80% of patients) compared to those who received sham training (38% of patients). During the initial rtfMRI-nf run, functional connectivity in the left amygdala, orbitofrontal cortex, dorsolateral prefrontal cortex, and left-lateralized upper alpha EEG coherence were enhanced; both findings positively correlated with the initial CAPS scores. Furthermore, enhancement between the left amygdala and dorsolateral prefrontal cortex was significantly correlated with the reduction in CAPS scores between the first and last rtfMRI-nf session. EEG data supported these findings; the EEG coherence slope for the upper EEG band across the four trial runs in the first rtfMRI-nf session correlated with initial CAPS ratings, further supporting the connection between alpha signal and PTSD symptomology. CAPS scores continued to correlate with the EEG coherence slope, particularly for channel pairs located in the prefrontal and temporal cortex in the left hemisphere. EEG coherence slope was also correlated with the fMRI connectivity slope; the average fMRI connectivity slope between the left amygdala and three 10 mm diameter ROIs (approximately located under EEG channels F3, F7, and T7) was

significantly correlated with each respective EEG connectivity slope. The findings of this study validate the use of EEG in supporting the observations of rtfMRI-nf experiments to address PTSD-specific connectivity deficiencies. Overall, much evidence supports using EEG as a treatment validation tool, independently and in tandem with other modalities.

Repetitive Transcranial Magnetic Stimulation (rTMS) with EEG monitoring

Another treatment method validated in several studies is repetitive transcranial magnetic stimulation (rTMS). This common therapy method elicits action potentials by rapidly and repeatedly passing an electromagnetic current through a coil placed on the subject's head [21]. The rTMS is also used with other forms of therapy, like cognitive processing therapy (CPT). In these rTMS studies, EEG is used to monitor therapy progress. When EEG was used pre- and post-rTMS and CPT treatment, EEG recordings demonstrated that P3a amplitude was correlated with decreased response to trauma-related stimuli and, therefore, decreased PTSD symptoms [13]. Notably, these results were observed in both rTMS+CPT and sham rTMS+CPT groups, which supports CPT's use in PTSD treatment and also validates the efficacy of rTMS as a treatment option for PTSD. Furthermore, increased P3a amplitude in response to trauma-related stimuli has previously been associated with PTSD, so this observed reduction supports the efficacy of rTMS+CPT as a PTSD treatment method. Another study employed rTMS in a manner that was individually optimized for the patient by stimulating multiple motor sensory and frontal cortical sites at reduced power and adjusting the loci of cortical treatment and stimulus frequency as treatment progressed [18]. This form of rTMS, termed personalized-rTMS (prTMS), was used alongside psychotherapy, and EEG was used to monitor the progress of this joint therapy.

EEG recordings identified that therapy led to significant improvement, characterized by a decrease in overall alpha-band oscillatory peak center frequency in those who responded to prTMS. This decrease is attributed to greater synchrony in the frontal cortex, which was not observed in those who did not respond to prTMS. Furthermore, analysis of the EEG power spectrum 1/f aperiodic component to understand the synchronicity of neuronal spikes demonstrated that the aperiodic regression slope was steeper after prTMS, which demonstrated greater synchrony and, therefore, greater signaling efficiency in those who responded to prTMS (the first demonstration of its kind). These two studies present strong evidence of the benefit of using EEG to confirm therapeutic success.

PTSD Subtype Classification and EEG

EEG has also been proven to be an effective tool in predicting the subtype classification of those already diagnosed with PTSD. Like its use in treatment validation, it can be used alongside other modalities such as fMRI. It has specifically been used alongside fMRI with concurrent spTMS (single pulses of transcranial magnetic stimulation) to understand the influence of the region of interest on downstream processes,

thereby providing clarity on the connectivity observed in the fMRI [12]. This was accomplished by establishing a spTMS/EEG circuit in the ventral attention network (VAN), the study's region of interest, and having patients perform a delayed recall test. fMRI connectivity was correlated with the results from the spTMS and EEG. Initially, a correlation between decreased within-VAN fMRI connectivity and increased desynchronization in the alpha frequency range in the VAN was observed, but in a second iteration of the study, patients with increased fMRI connectivity demonstrated only modest or no desynchronization; this desynchronization is thought to be a product of prolonged circuit interference to TMS pulses. The EEG findings provide substantial clinical evidence for variations in PTSD and implicate the use of EEG in identifying differing quantifiable and objective features of PTSD that may vary across patients. EEG has also been used to provide greater clarity on the viability of EEG biomarkers to characterize PTSD and subsequent subtypes [20]. Five minutes of eyes-open and eyes-closed EEG was recorded in 202 combat-exposed veterans undiagnosed with PTSD to establish a machine-learning framework that could be used to classify patients. The framework generated a classifier system that obtained up to 62.9% accuracy for predicting if a patient has PTSD. Furthermore, two subtypes were also identified, one based on combat-exposed controls and the other on greater global functional connectivity; these subtypes were predicted with an even greater accuracy than the initial diagnosis prediction at 79.4%. One feature that was deemed critical for correct prediction was alpha connectivity observed in the dorsal and ventral attention network, as it was positively correlated with arousal scores, a prominent indicator of PTSD.

In another study that sought to differentiate between symptom factors of PTSD, combat-exposed veterans with variable PTSD and traumatic brain injuries recorded resting state EEG for 10 minutes with their eyes closed and completed the PTSD checklist [19]. A single EEG common factor for each band (alpha, beta, delta, and theta) was identified based on regional power averages and an analysis model was created to fit the items in the PTSD checklist; analysis revealed that residual EEG parameter path estimates were negatively correlated with the EEG factors predicting symptom factors (avoidance, hyperarousal, re-experiencing, numbing) except for a single positive path for beta predicting numbing (though this only occurred when factor prediction effects were not differentiated). The most significant was the inverse relationship between delta and theta frequency bands and avoidance and numbing symptom factors. These findings provide support for the use of EEG in identifying patterns in PTSD symptom subtypes.

Another avenue that has been used to predict PTSD classification is identifying behavioral correlates by analyzing the differences in resting-state EEG connectivity between combat veterans with and without PTSD [14]. 64-channel resting EEG was recorded while the patients had open and closed eyes. The data revealed that a total of seventy-four correlations between power envelopes (amplitude of oscillatory signals across regions) between brain regions were significantly reduced in PTSD patients, predominantly in the connection between the orbital and anterior middle frontal gyri. These findings were exclusively when patients had open eyes and primarily in the theta frequency range. Power envelopes were correlated with the patient's performance on a digit span task, and performance differences were mapped onto the

connectivity in twenty-five of the seventy-four pairs, which included areas related to dorsal attention, ventral attention, and frontoparietal control. This information was then used to assess the capability of the power envelope connectivity as a biomarker to distinguish between PTSD and non-PTSD patients. A machine learning classifier was generated from the orthogonalized connectivity values to distinguish between PTSD patients and trauma-exposed controls. The resulting ROC curve performed very well as a classifier, generating an area under the curve of 0.898, a sensitivity of 80.2%, and a specificity of 84.9%. Further cross-validation analysis affirmed the classification capability of the biomarker by generating an area under the curve of 0.813, a sensitivity of 76.3%, and a specificity of 74.9%. These findings provide strong evidence for the use of connectivity data from EEG as a biomarker for identifying PTSD.

EEG has also been used to identify neurophysiological origins for prominent symptoms of PTSD [11]. This study focused exclusively on Operation Enduring Freedom and Iraqi Freedom veterans, the most specific patient population of all studies mentioned. Patients completed an implicit visual threat semantic memory recognition task with stimuli that varied across categories (animals, items, nature, and people) and feature (threatening and nonthreatening) membership, including trauma-related stimuli. Analysis revealed that combat veterans with PTSD had increased reaction times (meaning that they were slower) for the threatening stimuli relative to the combat-exposed group. Trauma-specific effects were also observed in frontal regions, as demonstrated by theta band EEG power reductions in the FPZ region for the threatening combat scenes in the PTSD patients but not in the combat-exposed group. Furthermore, the relationship between trauma-specific frontal theta power and hyperarousal symptoms (defined by CAPS Scores) was determined to be moderately negatively correlated, meaning that lower frontal theta power is associated with higher hyperarousal scores for threatening trauma-specific images. Ultimately, EEG studies have presented ample evidence that supports the use of EEG as a classification tool for PTSD in general, as well as clinical subtypes based on behavior, biometrics, and clinical scores.

DISCUSSION

PTSD is an illness that has the potential to result in many subtypes. This dichotomy necessitates a focus on a single subtype to compare data. We chose to focus on combat-related PTSD because this subtype has a single region of dominant impact and because incidence rates are higher in the veteran (i.e., combat-exposed) population than in the civilian (i.e., non-combat-exposed) population. PTSD patients with childhood trauma and/or sexual abuse causal events show elevated activation of the cingulate cortex, hippocampus, amygdala, and medial frontal cortex [6]. PTSD patients with adult physical or sexual assault causal events show changes in the perigenual anterior cingulate cortex (pACC), bilateral middle frontal gyri, and the left temporoparietal junction [5]. PTSD patients with causal events stemming from natural disasters show weaker connections between the mPFC and the limbic system and weaker connections between the inferior orbitofrontal cortex and the hippocampus [7]. PTSD patients with combat-related causal events

show less recruitment of the dLPFC, which impacts volition, self-regulation, and increased negative affective states [8].

EEG and Treatment Validation

The studies discussed in this paper present strong support for the use of EEG as a supplementary metric for validating PTSD treatment results and demonstrated progress. The first study reviewed utilized EEG to supplement changes observed on LPP after cognitive reappraisal. It was based on prior work that demonstrated that the effects of cognitive reappraisal on the LPP are typically observed towards the end of an episode of portions of picture viewing, where the LPP is likely to be at its maximum at frontal electrode sites [15]. Although they did not observe a group difference in the LPP generated by negative stimuli before therapy, they observed a post-therapy group difference in LPP generated by negative pictures presented in the maintained condition, meaning that veterans with PTSD showed no change in LPP during negative reactivity maintenance, where controls showed an increase in the LPP over time in the same condition. Their results were supported by prior work that suggests that sustained attention toward negative imagery increases the LPP in healthy patients. This lack of increase in LPP in PTSD patients is potentially a result of emotional blunting. Overall, the success of EEG as an identifier of PTSD symptomology in this study validates its use as a supplemental treatment tool.

The rTMS has also been validated as an effective treatment method for PTSD by EEG monitoring. When EEG was recorded before and after rTMS + CPT throughout the therapy program, P3a amplitude from 10 electrode sites (F3, F1, Fz, F2, F4, FC3, FC1, FCz, FC2, and FC4) decreased from baseline regardless of whether the patient was receiving proper rTMS, albeit more pronounced in the rTMS group [13]. Furthermore, specific EEG sites were correlated with various changes in CAPS scores—FC3 signal changes predicted hyperarousal score change, and F3 signal changes predicted avoidance and numbing score change. In addition to rTMS being validated by EEG findings, CPT was also shown to reduce emotional reaction to combat images. Before CPT, the P3a amplitude after being shown combat images was similar to the resulting amplitude when shown the target stimuli. Still, post-treatment P3a amplitude in response to combat images was comparable to the response to non-target images. This implicates a reduction in emotional arousal from combat images, therefore reducing one of the hallmark afflictions of PTSD. Identifying specific symptom changes based on EEG signal change and reduction in undesirable emotional response further promotes using EEG as a useful tool for tracking treatment progress.

Consistent Neurophysiological Findings with EEG Use in Treatment Validation

In terms of EEG-specific qualities, several studies have provided evidence for the connection between PTSD symptoms and increased peak alpha frequency. One study observed that peak alpha frequency differed across hemispheres within the PTSD group; this finding is supported by many studies that conclude that frontal alpha asymmetry is present and well-documented in mood disorders [16]. The previous studies

utilized various EEG methods, but the present study selected a local average reference so that surface data would best represent underlying brain sources. They identified that peak alpha frequency was higher in the PTSD group than the non-PTSD and greater on the left side in the PTSD group (no lateralization in the non-PTSD group); they also correlated the increase in peak alpha frequency with total PTSD. They offer several explanations for this result. One is that slower peak alpha frequencies are associated with relaxation, which suggests that higher peak alpha frequency in the PTSD group is reflective of greater anxiety within that group. They also mention that higher peak alpha may be a result of greater cognitive preparedness, which is supported by presentations of increased situational vigilance in those who suffer from PTSD. Observations of alpha frequency changes in PTSD patients have also been supported by multimodal studies. The use of EEG in conjunction with real-time fMRI (rtfMRI) resulted in functional connectivity in the left dorsolateral prefrontal cortex, orbitofrontal cortex, and amygdala, and upper alpha frequency coherence in the left hemisphere was both enhanced and positively correlated with patients' CAPS scores [17]. This finding was consistent through therapeutic improvement, as enhancement between the left dorsolateral prefrontal cortex and left amygdala was correlated with the difference in CAPS scores from the first and last rtfMRI session, which also supports the use of EEG as a metric for therapeutic progress. When EEG was recorded alongside a joint prTMS + psychotherapy program, the recordings identified a significant decrease in alpha band oscillatory peak center frequency, only observed in those who responded to prTMS [18]. Not only does this study provide further evidence for changes in alpha being a critical observation for identifying PTSD morphology in patients, but it also provides a standard for determining the success of rTMS treatments. Made evident by the results of single-mode and multimodal studies, EEG has a well-supported basis for identifying key neurophysiological abnormalities, as demonstrated by the replicated correlation between peak alpha frequency changes and PTSD symptomology, as a confirmatory basis for therapeutic progress and success.

Alpha Frequency Changes as an Indicator of Subtype Classification

Once patients are diagnosed with PTSD, there are still subtypes of the disorder that the patient can fall under, potentially requiring specific changes or modifications to the patient's treatment plan to ensure success. Several studies have identified neurophysiological changes that may indicate that a patient falls into a more treatment-resistant subtype of PTSD. Similar to the studies that focused on using EEG to support findings related to treatment progress and efficacy, studies focused on determining signs of treatment-resistant forms of PTSD have also identified alpha waves as signals of interest in PTSD morphology. EEG was used concurrently with spTMS and fMRI to investigate the ventral attention network (VAN) [12]. A spTMS/EEG circuit was established in the VAN, and fMRI was recorded concurrently to be correlated with the results from spTMS/EEG. There was initially a correlation between within-VAN fMRI connectivity and alpha desynchronization in the VAN, but further study failed to reproduce these findings. They further elucidated that this desynchronization was responsible for the reduced within-VAN activity,

made evident by increased circuit disturbance from single TMS pulses in the right anterior prefrontal region of the VAN. This localization of within-VAN disturbance establishes evidence for clinically relevant variation in PTSD manifestation, which was made possible by the recognition of changes in EEG signals. EEG was also utilized to characterize PTSD subtypes through EEG biomarkers. This was accomplished by generating a framework designed to predict whether a patient has PTSD. This framework resulted in a 62.9% prediction accuracy rate. Two PTSD subtypes were further identified, one characterized by greater global functional activity and the other characterized by combat-exposed controls. The prediction framework generated for subtype prediction resulted in an even greater accuracy rate of 79.4%. In the case of both predictive models, changes in alpha connectivity in the ventral and dorsal attention network continued to be a crucial component for classification due to its strong positive correlation with arousal scores. The relationship between behavioral manifestation and alpha signal increases.

Theta Frequency Changes as an Indicator of Subtype Classification

In addition to observed changes in the alpha frequency band, other frequency bands have proven interesting in investigating identifiable features of PTSD subtypes. One study focused on regional power averages that were based on a single EEG common factor for each frequency band to identify contrasts between PTSD symptoms [19]. Although most residual EEG parameter path estimates were negatively correlated with avoidance, numbing, re-experiencing, and hyperarousal, theta and delta frequency bands presented a significant, negative correlation with avoidance and numbing symptom factors. These results present a foundation for the relationship between PTSD symptom subtypes and specific EEG frequency bands. Behavioral correlates have also been used to classify PTSD subtypes through a comparison of resting-state EEG connectivity between combat veterans with and without PTSD [14]. Power envelopes were used to identify differences, and it was observed that several brain regions were reduced in patients diagnosed with PTSD, particularly in the orbital and anterior middle frontal gyri, as indicated by a decrease in the theta frequency range. These changes in theta frequency correlate with areas related to dorsal attention, ventral attention, and frontoparietal control. This relationship establishes the importance of the power envelope connectivity of the prefrontal theta band for PTSD. It connects its changes to a cognitive deficit in PTSD, further implicating EEG's use as an identifier of relevant biomarkers. Based on this information, a machine learning classifier was created to predict whether a patient was a PTSD patient or a trauma-exposed control. The framework resulted in a successful classifier, with a sensitivity of 76.3% and a specificity of 74.9%, providing empirical evidence for using EEG in PTSD biomarker identification. The inverse relationship between theta frequency and PTSD symptoms is supported by the observation that trauma-specific reactions to threatening stimuli were characterized by decreased theta band EEG power in the FPZ regions, resulting in higher hyperarousal scores for trauma-respondent images [11]. It is evident that theta reductions also have prominent effects on behavioral correlates of PTSD subtypes, as demonstrated by the relationship between reduced theta and increased PTSD symptomology across studies.

EEG is a powerful and consistent tool for demonstrating frequency changes in specific brain regions. These changes, when replicated and validated by multimodal studies and behavioral results, have the potential to be critical indicators of nuances and specific variations in how PTSD presents itself across patients, which can then be used to optimize treatment options for PTSD patients regardless of individual variability.

Limitations

Several limitations of this meta-analysis prevent us from drawing broader conclusions. The first is that there was negligible consistency between samples. Samples varied by size, gender, age, and control population (civilian, combat non-PTSD). This impedes us from drawing overarching conclusions across studies. Another key limitation is the variation in study design. While most studies were based on some therapeutic training, others were based on resting-state EEG recording. Perhaps the most influential limitation was the lack of consistency in EEG region/feature of interest. All studies had various goals; some were rooted in specific electrode locations, while others were focused on observing bands across locations. Within the investigation of frequency bands, specific features of the bands also differed. Due to this, it is difficult to conclude the study results truly.

CONCLUSION

The studies in this review show promising applications of EEG for treating and evaluating symptom biomarkers in patients with combat-related PTSD. Also, using EEG to monitor treatment by combining novel therapeutic strategies, such as rTMS with traditional cognitive-based therapies, was found to have clinical relevance in bettering patient outcomes. However, more research is needed to find more efficient ways to treat combat-related PTSD. Studies with more diverse patient populations with non-combat-related PTSD are needed to confirm the effectiveness of EEG in treating PTSD. Future studies may also seek to include novel multimodal approaches by combining different forms of approved therapeutic interventions that could improve the long-term effectiveness of such treatment in patients.

ORCID

Colton Flippen https://orcid.org/0009-0001-4614-3475

Celia Higginbotham https://orcid.org/0009-0009-6757-6104

Carole Leung https://orcid.org/0000-0002-0577-5804

Danielle Royer https://orcid.org/0009-0004-2230-4109

Faisal R. Jahangiri https://orcid.org/0000-0002-1342-1977

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