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Characterizing Prevalence of Psychiatric Conditions and the Fear-Potentiated Startle Response in Trauma-Exposed People with Epilepsy

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Abstract

Characterizing Prevalence of Psychiatric Conditions and the Fear-Potentiated Startle Response in Trauma-Exposed People with Epilepsy

By Helena Zeleke

Epilepsy is a neurological condition characterized by recurrent, uncontrolled neuronal activity and affects ~50 million people globally. Prior literature suggests that depression, PTSD, and suicidality are more prevalent among people with epilepsy than in people without epilepsy; however, most prior studies are limited in their generalizability as their sampling excludes racially marginalized and highly trauma-exposed individuals and/or fails to include seizure-free comparison groups. Existing knowledge of the overlapping neurocircuitry between certain types of epilepsy (e.g., medial temporal lobe epilepsy) and PTSD also suggests that people with epilepsy may exhibit PTSD-like alterations in their psychophysiological responses, namely altered fear-potentiated startle response (FPS). However, this hypothesis has yet to be systematically tested. This study examined prevalence of PTSD symptoms, depression symptoms, suicidality, and history of suicide attempt among 3,012 racially marginalized and low resourced civilians. Additionally, we measured and compared FPS in 8 people with epilepsy to the FPS of 8 rigorously matched seizure-free controls. The modified PTSD symptom (mPSS) scale was used to measure PTSD symptoms and Beck's Depression Inventory was used to measure depression and suicidality symptoms. Self-report survey questions were used to assess past suicide attempt and seizures/epilepsy status. FPS was measured using EMG data collected during a fear conditioning acoustic startle task. Participants with seizures/epilepsy showed significantly higher prevalence of depression symptoms, suicidality, history of suicide attempt, PTSD symptoms, and probable PTSD diagnosis than participants without seizures/epilepsy, even after controlling for trauma load. FPS did not differ significantly between the epilepsy and no epilepsy groups; however, a near-significant interaction between task phase and epilepsy status was detected. Our study shows that, within a majority racially-marginalized sample with high levels of trauma exposure, people with epilepsy are still more likely to have a variety of psychiatric comorbidities than people without epilepsy. This finding underscores the vulnerability of individuals with a history of seizures/epilepsy as well as the importance of accessible psychotherapy for this at-risk group. Furthermore, our FPS data serves as a first step in characterizing the fear response of people with epilepsy, our understanding of which can be bolstered with future studies using larger sample sizes.

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****[Characterizing Prevalence of Psychiatric Conditions and the Fear-Potentiated Startle Response in Trauma-Exposed People with Epilepsy] by Helena Zeleke is a derivative of "Characterizing the Prevalence of Psychiatric Conditions and Fear-Potentiated Startle Response in Civilians with a History of Trauma and Seizures" by Trinidi Prochaska, Helena Zeleke, et al., which is licensed CC BY-NC 4.0.****

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Introduction

Characteristics and Prevalence of Epilepsy

Epilepsy is a neurological condition characterized by recurrent, uncontrolled neuronal activity and affects ~50 million people globally [1]. The synchronous neuronal activity characteristic of epilepsy can be localized to neurons of a specific brain area or localized to a network of brain regions, and this activity results in the physical signs of seizure [2]. The International League Against Epilepsy recognizes three different seizure types (focal, generalized, and unknown), which manifest in four epilepsy types (focal, generalized, combined generalized and focal, and unknown), which when taken together with EEG and imaging characteristics, can then be classified into a myriad of epilepsy syndromes [3]. Temporal lobe epilepsy (TLE) is the most common type of focal epilepsy and is characterized by epileptiform activity originating in the hippocampus, extrahippocampal cortex, and adjacent brain regions [4].

Epilepsy, Trauma, and Post-traumatic Stress Disorder

Post-traumatic stress disorder (PTSD) is a condition that some people develop after experiencing or witnessing a traumatic event, which is defined by the National Institute of Mental Health as "a shocking, scary, or dangerous experience that can affect someone emotionally and physically"[5]. Symptoms of PTSD include re-experiencing the trauma, avoiding reminders of the trauma, as well as changes in mood and fear learning behaviors [6]. PTSD affects approximately 3.6% of U.S. adults [7]; however, prevalence of lifetime trauma and PTSD have been estimated to be 87.8% and 18.8%, respectively, among low-resourced adults living in inner-city neighborhoods, which suggests that socioeconomically disenfranchised individuals are at a considerably higher risk of experiencing trauma as well as developing post-traumatic stress disorder than the general population [8].

A 2021 systematic literature review found that PTSD is the most common anxiety disorder amongst people with epilepsy [9]. A cross-sectional study of 54 patients with EEG-confirmed epilepsy and 61 controls found that participants with epilepsy were more likely to have experienced a traumatic event and exhibit PTSD symptoms above the diagnostic criteria than participants without epilepsy [10]. Heightened trauma exposure for people with epilepsy may be attributable to the safety hazards that seizures pose [11], as well as seizures themselves being traumatic and life-threatening experiences for many people with epilepsy [10]. Some people with epilepsy who have endured a traumatic experienced seizure (TES) may develop post epileptic seizure PTSD (PS-PTSD), which entails hyperarousal, avoidance, and reexperiencing symptoms related to a traumatic seizure [10,12]. Furthermore, studies have shown that trauma exposure, and relatedly, PTSD, may predispose individuals to developing epilepsy later in life. A longitudinal study in Taiwan using a national database with a large sample size (n(PTSD) = 6425; n(total) = 24,980) to measure epilepsy risk in people with PTSD detected a significantly higher risk of developing epilepsy in people with PTSD, as well as an earlier age of onset, as compared to age and sex-matched controls [13]. Chronic stress has also been linked to disease progression in epilepsy by upregulating neuroinflammatory pathways [14].

Since people who live in under-resourced, urban communities experience higher rates of trauma exposure and PTSD than the general public [15], and the existing literature suggests that PTSD and epilepsy are interrelated, it is important to understand how these conditions interact in a demographic with high civilian trauma exposure.

However, most prior studies conducted to approximate the prevalence of PTSD in people with epilepsy have been limited in their generalizability due to a number of factors, including low levels of civilian trauma exposure, small sample size, limited representation of racially marginalized individuals, and an overrepresentation of individuals with severe forms of epilepsy. Thus, fewer studies have examined

PTSD prevalence in people with epilepsy using a large U.S. sample of mostly racially marginalized women with high levels of civilian trauma exposure and unskewed epilepsy symptomatology.

Other Psychiatric Comorbidities in Epilepsy

Systematic literature reviews have demonstrated a heightened prevalence of multiple psychiatric comorbidities in people with epilepsy [9,16]. However, many studies of these psychiatric comorbidities, namely depression and suicidality, are also limited in their generalizability due to the aforementioned reasons (small sample size, limited demographic representation, and an overrepresentation of individuals with severe forms of epilepsy).

Epilepsy and Depression

Depression is described as a debilitating, long-lasting feeling of sadness and dejection which interferes with a person's daily activities [17]. Studies have estimated that 23.1% of people with epilepsy have active depression [18]. A cross-sectional study of 150 patients with epilepsy found that 22% had depression, and that depression symptoms were associated with antiepileptic drug load and the timing of diagnosis [19]. Surprisingly, this study found that patients with a longer history of epilepsy reported less depression symptoms than people with newer onset epilepsy [19]. Depression and epilepsy may also have a reciprocal relationship, with depression symptoms like sleep disruption, predisposing people with epilepsy to seizures [20].

Epilepsy and Suicidality

Suicidality, or suicidal ideation, refers to a person's wish or desire to end their own life. Although psychiatric comorbidities significantly contribute to the risk of attempting suicide for people with epilepsy, suicide risk is still higher for people with epilepsy than controls even after controlling for psychiatric comorbidities in nation-wide epidemiologic analyses [21]. There is mixed and largely inconclusive evidence for differences in level of suicide risk based on type of epilepsy as well as type and

number of antiepileptic drugs [22,23]. However, a longitudinal study of 2,450 patients with epilepsy in New England demonstrated that suicidal ideation was associated with aspects of disease progression like seizure frequency, severity, and recency [24]. A study of 410 people with epilepsy recruited from an epilepsy center in Addis Ababa, Ethiopia also found that 14.1% of respondents had a lifetime prevalence of suicide attempt [25]. Estimates of suicide attempt prevalence for people with epilepsy is strikingly higher than the prevalence of suicide attempt amongst the U.S. general population, for which the 2020 past year prevalence was estimated at 0.5% [26]. Interestingly, some studies have proposed a bidirectional relationship between suicide attempts and epilepsy, with a history of suicide attempt predisposing people to developing epilepsy later in life [27,28].

Startle Response and Fear Neurocircuitry in Epilepsy

The startle response occurs across species and refers to the action of the orbicularis oculi muscle in response to extreme stimuli of all different modalities. The acoustic startle response (ASR) refers to the behavioral response that all mammals have to sudden, loud acoustic stimuli [29]. Baseline ASR varies between individuals and can be modulated by various experimental mechanisms [29]. The presentation of a less intense noise prior to the acoustic startle tone ("prepulse inhibition") reduces ASR in humans [30], and repetitive presentations of the startle tone ("habituation") has been demonstrated to reduce the ASR in humans [29]. Presenting a noxious stimulus, like an air-blast to the larynx prior to presentation of the startle tone ("sensitization"), heightens ASR in rodents [31]. In humans, ASR has also been evidenced to be heightened in the dark [32].

Studies have demonstrated a difference between adults with epilepsy and adults without epilepsy in habituation to acoustic stimuli [33], lower probability of startle response to acoustic stimuli for people with epilepsy as opposed to controls [34,35] as well as no statistically significant difference between ASR in adults with epilepsy and controls [36]. However, the stimuli that were used in these studies were not

paired with a fear conditioning paradigm. There have also been other small case reports/series examining acoustic startle response in adults with seizures/epilepsy; however most of these studies fail to compare the level of startle response to matched controls [37].

ASR can also be investigated in combination with fear learning paradigms, wherein a neutral stimulus is paired with a noxious stimulus (like a foot shock in rodent experiments) and then the conditioned stimulus is presented again with the acoustic startle pulse. ASR is typically elevated for individuals when the acoustic pulse is presented after presentation of a conditioned stimulus, as the individual is now also anticipating the noxious stimulus. The heightened startle response exhibited after an individual is presented with a conditioned stimulus is referred to as the fear-potentiated startle response (FPS). Hyperarousal to neutral stimuli is a symptom of PTSD that can manifest in heightened fear-potentiated startle responses [38]. Veterans with PTSD have exhibited heightened baseline fear-potentiated startle responses than veterans without PTSD [39] and, in a study with 75 women exposed to the same mass trauma, higher levels of PTSD symptoms were associated with higher fear-potentiated startle responses to both conditioned and unconditioned stimuli during early extinction [40].

The neurobiological processes underlying PTSD symptomatology are complicatedly interrelated; however, studies have consistently shown that the function and structure of medial temporal lobe structures, primarily the amygdala and hippocampus, are altered in PTSD [41]. Activation of the amygdala, a brain structure critical for fear processing, in response to fearful stimuli habituates (decreases over repeated presentations) more markedly in people with PTSD [42], and amygdala reactivity to fearful stimuli predicts PTSD symptom development after trauma exposure [43]. Volume of the hippocampus, a brain structure critical for memory consolidation, is smaller in people with PTSD [44] and people with PTSD also exhibit diminished hippocampal activity in situations which require the use of contextual memory[45].

Some studies have highlighted that seizure activity in temporal lobe regions (e.g., hippocampus and amygdala) may affect fear neurocircuitry and thus may be the cause for heightened PTSD in people with medial temporal lobe epilepsy. This is supported by evidence that psychiatric comorbidity is implicated most strongly in temporal lobe epilepsy as opposed to other epilepsy types [9]. A case report of a patient whose temporal lobe seizures began to involve reexperiencing symptoms post-trauma exposure hypothesized that the patient's limbic seizures were now "exploiting" her fear circuitry because of the overlap in neural networks responsible for producing temporal lobe seizures and PTSD symptomatology [46]. Other studies have documented differences in amygdala activation in response to fearful stimuli between people with medial temporal lobe epilepsy and controls [47,48]. Rodent studies have also suggested that seizure activity in the amygdala impairs fear learning [49], and that rodents who have been subjected to chemically-induced seizures develop heightened acoustic startle response than control rodents [50].

Based on these findings, it is plausible that seizure activity, whether localized to medial temporal structures or more generalized, may alter connections to and from the amygdala as well as other brain structures responsible for vigilance and arousal, thus resulting in a fear-potentiated startle (FPS) response that is similar to that which is observed in people with PTSD. However, fewer studies have been conducted to examine the ways that the fear-potentiated startle response (FPS) differs in epilepsy. A better characterization of FPS in people with epilepsy, as well as a better understanding of how characteristics of the FPS in epilepsy compares to those of FPS in PTSD, may give insight on which underlying neurobiological processes may be shared by the two conditions.

Study Aims

The first aim of our study is to determine if there is an increased level of psychiatric comorbidities in people with self-reported seizures as compared to people without seizures and/or epilepsy using self-

reported psychological symptom and epilepsy status data from a large, highly trauma-exposed civilian population. Since prior literature suggests that temporal lobe epilepsy recruits similar neural networks as those involved in PTSD, our second aim is to determine whether people with epilepsy, when matched with people without epilepsy of similar symptom levels and demographic backgrounds, will exhibit alterations in their fear-potentiated startle response (FPS) that mirror alterations present in PTSD. We hypothesize that people with epilepsy will exhibit a significantly higher prevalence of psychiatric comorbidities like PTSD. Moreover, we anticipate that the FPS of people with epilepsy will indicate lessened fear discrimination than people without epilepsy who are matched on most other factors.

Methods

Demographic and Clinical Variables

The Grady Trauma Project (GTP) is an ongoing study of the effects of civilian trauma on (mental) health in people accessing care at the largest safety-net hospital in Atlanta, GA (Grady Memorial Hospital). GTP has self-report data for >12,000 participants, the large majority of whom are people with lower incomes and are African American/Black women, collected by way of interviews [51]. Self-report data from the GTP dataset were used for the analyses in the present study. In participant interviews, history of seizures/epilepsy was assessed using the yes/no question: “Have you ever had seizures, or have you ever been diagnosed with epilepsy?”. A demographics questionnaire was used to determine participants’ age, sex, ethnicity, race, employment status, and pregnancy/breastfeeding status. The Beck’s Depression Inventory (BDI, available for N = 2959), a 21-item measure that queries participants’ experience of 21 different depression symptoms over the 2-week period prior to their interview (score range = 0 - 63), is utilized in the present study as a measure of depression symptoms [52]. BDI total scores of less than 10 are considered minimal symptoms, scores of 10-18 correspond to mild - moderate depression symptoms, scores of 19-29 are considered moderate - severe depression symptoms, and

scores of 30-63 correspond to severe depression [53]. The ninth item on the BDI asks participants to select the statement that best describes their relation to suicidality from the following choices: “I don't have any thoughts of killing myself”, “I have thoughts of killing myself, but I would not carry them out”, “I would like to kill myself”, and “I would kill myself if I had the chance”. Responses to this question (available for N = 2967) was used to measure level of suicidal ideation (i.e., suicidal wishes), whereas responses to the survey question “Have you ever attempted suicide?” (for N = 3008) was used to determine actual history of suicide attempt. The Modified PTSD Symptom Scale (mPSS, available for N = 2670) is an 18-item scale that was administered to participants to assess PTSD symptoms based on DSM-IV criteria [54,55]. mPSS items query three PTSD symptom clusters (intrusive thoughts, avoidance/numbing behaviors, hyperarousal symptoms). The mPSS scale asks participants to rate how frequently they’ve been experiencing items related to each cluster on a scale from 0 (“not at all/only once”) to 3 (“5 or more times a week/almost always”) over the past two weeks and then asks them to specify for how long they’ve been experiencing all symptoms on a scale from 0 (<1 month) to 3 (>1 year). The mPSS total score for each participant was calculated by summing their 0-3 response for each question (score range: 0 - 54). Participants (N = 2675) were considered to have a probable, current PTSD diagnosis if they reported experiencing at least one item in the intrusive thoughts symptom cluster, at least three items in the avoidance/numbing behaviors symptom cluster, and at least two items in the hyperarousal symptom cluster for at least one month on the mPSS. Use of the mPSS to assess probable, current PTSD diagnosis based on the aforementioned criteria has been validated in previous literature showing that this criteria correlates with diagnosis per the more extensive clinician-administered PTSD scale (CAPS) interview [56]. The Traumatic Events Inventory (TEI, for N = 2994), which is a 19-item questionnaire developed by our team to query a comprehensive range of traumatic experiences [57,58], was administered to measure lifetime trauma (score range = 0 - 19). The Childhood Trauma Questionnaire (CTQ, for N = 2984) is a 28-item measure that was administered to participants to

approximate the level of exposure to traumatic events in childhood (score range: 25 - 125), specifically between the ages of 0-18 [59,60].

Statistical analyses

Chi-square analyses were conducted to compare our categorical variables of interest (history of suicide attempt, PTSD diagnosis, suicidal ideation, race, sex, and employment status) between participants with and without self-reported seizures/epilepsy. Independent samples T-tests were conducted to compare our continuous variables of interest (Modified PTSD Symptom Scale total score, Beck's Depression Inventory total score, Childhood Trauma Questionnaire total score, Traumatic Events Inventory total score, and age) between participants with and without self-reported seizures/epilepsy.

Sensitivity analyses were conducted to evaluate the impact of trauma exposure. For each of the clinical outcome measures (except for suicidal ideation), logistic or linear regression analyses were performed with seizure/epilepsy status as the predictor and childhood and lifetime trauma as covariates.

Fear-Potentiated Startle Response Data Collection and Analysis

Participants

Ten of the participants who reported experiencing seizures and/or having epilepsy in the GTP dataset had also completed an acoustic fear-potentiated startle task. These ten participants were matched with ten participants from the GTP sample who reported not experiencing seizures and/or having epilepsy and also had completed the acoustic fear-potentiated startle task.

Eight of the 10 participants with seizures/epilepsy were matched to participants without seizures/epilepsy using successive runs of the case-control function in SPSS (Version 28.0.1.0). For each matching attempt, the match tolerance was kept at zero for the variables of race, sex, history of suicide attempt, PTSD diagnosis, and pregnancy status. The match tolerance for the variables of BDI total score,

TEI total score, CTQ total score, and age; however, was zero for the first matching attempt and then was increased by 1 for each successive matching attempt until each of the 8 participants had a match (final match tolerances ranging from 2-18). The match that was selected for each participant was the one that appeared in the run using the lowest match tolerance(s).

The remaining two participants were also matched using successive runs of the case-control function in SPSS. However, because we could not find matches for these participants using the aforementioned protocol, we removed pregnancy status as a matching variable, included ethnicity as a matching variable with 0 tolerance, and increased age in a stepwise manner (starting with match tolerance of 5 and then increasing the match tolerance by 2 every 2 matching runs that followed, final match tolerances of 7 and 15) when matching these two participants (final match tolerances ranging from 6-14 for BDI total score, TEI total score, and CTQ total score).

Startle procedure

Startle procedures used in the present study follow prior work [61–64] (Figure 1). Participants were presented with various stimuli throughout the startle procedure: an aversive air puff to the larynx (unconditioned stimulus "UCS"), a colored shape that was paired with presentation of the UCS (danger cue "CS+") as well as a startling tone, and a different colored shape that was only paired with the startling tone and no UCS (safety cue "CS-").

Before the start of the startle procedure, two Ag/AgCl electrodes were plastered over participants' right orbicularis oculi muscle along with a ground electrode which was positioned at the back of their ear. Participants were then instructed to sit in a booth facing a computer screen and wear both a set of headphones and a vest with an air puff dispenser apparatus strapped to their chest.

Participants first underwent a brief habituation period, wherein 2 different shapes (the CS+ and CS-) were presented with the startle noise (106-dB [A] SPL, lasting 40 ms) but without any UCS. Following

habituation, participants were presented with a 3-block series of CS+/-, startle tone, and UCS presentation. Each of the three blocks consisted of 4 startle noise alone (NA) trials, 4 CS+ trials, and 4 CS- trials. During CS+ trials, participants were presented with the CS+ shape, then the startle tone, and then finally the UCS air puff (140 p.s.i) to their larynx lasting 250 ms. During CS- trials, participants were presented with the CS- shape and then the startle tone (no aversive air puff). During NA trials, participants were presented with only the startle noise (no shape or UCS). The shape remained on the screen for the entire duration of the trial (6s). Participants thus went through 36 startle trials, with each trial being separated by a randomized time interval (9-22 seconds).

Startle data processing

Biopac MP150 for Windows (Biopac Systems, Inc.) was utilized to collect participants' electromyography (EMG) data. EMG data was sampled at 1000 Hz and amplified using the EMG module of the Biopac system. MindWare (MindWare Technologies, Ltd.) was used to filter and rectify EMG data (28- 500 HZ), as well as to smooth EMG data and prepare it for SPSS analysis. Peak EMG signal 20-200 ms following the startling tone was considered the "startle response". EMG data for each participant was used to calculate fear-potentiated startle response (FPS) for each cue of each block of the startle task, calculated by taking the difference between participants' startle response to cue trials and participant's startle response to no-cue trials in a given block, dividing that difference once again by their startle response to no-cue trials in that block, and then multiplying the resulting value by 100%: Fear-Potentiated Startle (FPS) Response = (EMG startle response during CS (+ or -) trials – NA startle)/(NA startle) x 100.

Statistical analyses

Participants whose FPS was more than 2 standard errors away from the mean were excluded from subsequent analyses (N = 1). One other participant was excluded from analyses since they did not have FPS data for all 3 of the blocks of the task. Repeated measures analysis for CS x Block x Seizure/Epilepsy

Status was conducted to determine if there were differences in FPS based on participants' seizure/epilepsy status, task block, and/or type of startle cue (CS+ or CS-). Follow-up analyses were performed if statistically significant interactions were observed. Demographic analyses were also conducted on the group of 16 participants whose startle data were kept in FPS analyses.

Results

Participant Demographics

Participants with self-report seizures/epilepsy and control participants did not differ significantly on the demographic variables of race, age, and sex (see Table 1). However, in the seizures/epilepsy group, a significantly higher proportion of individuals were unemployed than in the control group. Participants with self-report seizures/epilepsy also had a significantly higher CTQ mean score than controls, as well as a significantly higher TEI mean score than controls (Table 1).

Psychological Symptoms in People with and without Seizures/Epilepsy

History of suicide attempt, suicidal ideation, mPSS total scores, BDI total scores, and probable, current PTSD diagnosis were significantly more prevalent in people with self-report seizures/epilepsy than controls (Table 2, Figure 2).

Relationship Between Trauma Exposure, Seizure/Epilepsy Status, and Psychological Symptoms

Given greater levels of childhood and adulthood trauma levels in the seizures/epilepsy group (Table 1), sensitivity analyses were performed for the majority of our outcome variables, with seizures/epilepsy as a predictor and trauma measures (CTQ total and TEI total) as covariates. Seizures/epilepsy status still predicted PTSD symptoms, PTSD diagnosis, and history of suicide attempt after correcting for childhood trauma and lifetime trauma (Tables 4, 6, & 7). Seizure/epilepsy status only significantly predicted BDI

total when correcting for either childhood trauma ($F(2, 2950) = 370.34$, $B = .035$, $p = .036$) or lifetime trauma ($F(2, 2950) = 328.76$, $B = .039$, $p = .021$), but not when both trauma exposures were included in one model (Table 5).

Relationship Between Fear-Potentiated Startle Response and Epilepsy

Participants with self-report seizures/epilepsy did not differ significantly from matched control participants on any demographic or psychological symptom variables, confirming successful matching (see Table 3). Repeated measures ANOVA analyses did not show a significant interaction between CS type (CS+, CS-), block (1, 2, or 3), and seizure/epilepsy status. However, there was a significant interaction between CS and block ($F = 4.23$, $df = 2$, $p = .039$). Paired sample t-tests were conducted to determine for which block this interaction produced a significant difference in FPS. Results of these analyses demonstrated that the difference between participants' CS+ vs. CS- response in block 2 was statistically significant ($t = 2.50$, $df = 15$, $p = .024$), showing that participants successfully learned the difference between the cues throughout the course of the three blocks of the startle task (Figure 3B). The interaction between block and seizure/epilepsy status was almost significant ($F = 3.446$, $df = 2$, $p = .063$). This near-significant interaction was driven by the seizure/epilepsy group having a sharp increase in aggregate fear-potentiated startle response (response averaged across cue types) from block 1 to block 2, while the no seizure/epilepsy group maintained a relatively constant aggregate fear-potentiated startle response throughout all three blocks (Figure 3C). Additionally, paired samples t-tests (using CS+ and CS- response within each block as pairs) were conducted for the seizures/epilepsy and no seizures/epilepsy group separately and showed that there were no statistically significant differences between each paired CS+ and CS- response (Figure 3A).

Discussion

PTSD, depression symptoms, suicidality, and suicide attempt, were all more prevalent among people with epilepsy as opposed to people without epilepsy in a majority racially-marginalized and highly trauma-exposed sample. Furthermore, our analyses demonstrate that both lifetime and childhood trauma exposure are more severe for people with epilepsy as opposed to people without epilepsy. Unlike many of the existing studies examining psychiatric comorbidities in epilepsy, ours is unique in that it is unbiased towards medically refractory epilepsy, as we did not recruit from an epilepsy clinic, it utilizes a large sample of participants (n = 3,012, n(epilepsy) = 221) with high levels of civilian trauma exposure, and that our participants are from demographics that are typically underrepresented in research focused on psychiatric comorbidities in epilepsy (racially and economically marginalized individuals). Participants with epilepsy did not exhibit significantly lessened fear discrimination or higher baseline fear-potentiated startle responses than matched participants without epilepsy. Our study is unique from existing papers examining FPS in people with epilepsy due to our relatively large sample size, our robustly matched control comparison group, and our inclusion of participants with epilepsy who have not necessarily received resective surgery to treat their epilepsy.

Although prior studies have documented a heightened PTSD prevalence among people with epilepsy [10], fewer studies have measured this heightened risk in racially marginalized and highly trauma-exposed people with epilepsy. Studies which have used trauma-exposed samples to measure PTSD comorbidity in people with epilepsy have failed to include a seizure-free comparison group and have relied on data from veterans, which skews participants' traumas towards those related to military combat [65]. Nonetheless, the present study confirms that PTSD symptoms are more prevalent among people with epilepsy in a U.S. sample of trauma-exposed, racially marginalized civilians. PTSD may be more prevalent in epilepsy due to effects of seizure activity on medial temporal lobe structures, which are implicated in

PTSD. Our finding that trauma exposure is more severe for people with epilepsy than people without epilepsy is also in line with prior reports, most of which did not share the same sample characteristics as the sample included in our present study (i.e. low levels of civilian trauma & mostly white participants) [10]. The existing literature suggests that this heightened exposure to trauma experienced by people with epilepsy may be attributable to the unsafe physical condition that sometimes is caused by seizures themselves [11]; however, future studies should investigate whether this reasoning applies to racially marginalized and highly trauma-exposed individuals.

Prior studies have also found that depression symptoms [18] and suicide [21] are more prevalent among people with epilepsy. However, relatively few studies of depression and suicidality in epilepsy have utilized a sample of majority racially marginalized individuals, and those that have have either lacked a seizure-free comparison group [66–76] or had a relatively small sample size of non-white people with epilepsy [77]. Thus, our finding expands on the existing literature by demonstrating that the prevalence of depression and suicidality among people with epilepsy is significantly higher than that which is observed in people without epilepsy who are of a similarly racially marginalized demographic. Future studies should be conducted to clarify which aspects of epilepsy (neurobiological, social, economic, etc.) for racially marginalized people contribute to this heightened risk for developing depression and suicidality.

Despite evidence that psychiatric comorbidities are more prevalent among people with epilepsy, recent studies have shown that psychiatric conditions, namely depression, are undertreated in this at-risk group [78]. Furthermore, a growing number of studies have been published documenting the efficacy of a variety of psychotherapeutic models for people with epilepsy and comorbid psychiatric conditions [79–81], some of which have been adapted such that they are more accessible for racially marginalized people with epilepsy [82]. Novel detection practices, including automated screening assessments disseminated via patients' electronic medical record portals, have also shown promise for the time and cost-effective

identification of psychiatric comorbidities in people with epilepsy [83]. Thus, a greater effort needs to be made to implement these detection and treatment approaches in epilepsy clinics as well as other healthcare modalities through which people with epilepsy receive care.

We hypothesized that people with epilepsy would exhibit characteristics of FPS that are more commonly observed in people with PTSD (e.g., impairment in fear discrimination) based on the understanding that seizure activity could exploit and impact the neurocircuitry involved in PTSD. However, we observed instead that the characteristics of FPS demonstrated by participants with epilepsy do not necessarily coincide with characteristics of FPS that are observed in PTSD. Participants with epilepsy were able to discriminate between danger and safety signals just as well as participants without epilepsy (i.e., no impairment in fear discrimination). However, participants with epilepsy did show a near-significant difference from participants without epilepsy in their unique increase in FPS to later presentations of startle cues (irrespective of whether cues were danger or safety). This finding does not necessarily negate the possibility that epileptic seizures, especially those observed in temporal lobe epilepsy, affect PTSD-involved neurocircuitry. Instead, it suggests that seizure activity in these brain regions produce a psychophysiological signature that is unique from other conditions (including PTSD) and may be representative of the unique neurobiological environment produced by seizure activity. Future studies should be conducted to further elucidate the neurobiological underpinnings of this unique psychophysiological signature and to more concretely identify the overlapping and disparate neurobiological mechanisms of epilepsy and PTSD. A better understanding of the neurobiological processes that underlie the epilepsy FPS response may provide insight as to what brain areas are implicated in producing the heightened risk that people with epilepsy have for developing psychiatric conditions like PTSD.

Limitations and Future Directions

The number of participants included in our FPS analyses was relatively small and we may have thus been too underpowered to detect potential differences between the startle responses of the seizure/epilepsy and no seizure/epilepsy groups. Future studies should include more participants (both epilepsy and controls) in order to clarify whether there are additional differences between the FPS of both groups. Self-report data was used to measure psychological symptoms and demographics, which may have introduced self-report bias or variability. Additionally, the data that was used to determine participants' seizure/epilepsy status did not include detailed information about seizure semiology, video-EEG confirmation, and/or other specifications about their experience of seizures/epilepsy. Future studies may also use more detailed information on participants' seizures/epilepsy in order to clarify whether associations exist between certain types of psychopathology or psychophysiological responses and certain epilepsy types or characteristics.

Conclusion

Our study demonstrates that, in a trauma-exposed, racially marginalized sample, psychiatric comorbidities (namely depression symptoms, PTSD, and suicidality) are still disproportionately prevalent among people with epilepsy. Our FPS data also serves as a first step in characterizing the psychophysiological fear response of people with epilepsy, our understanding of which can be bolstered with future studies using larger sample sizes. Our findings underscore the importance of providing accessible psychotherapy to racially marginalized people with epilepsy and urges medical professionals and researchers to implement policies that allow for the improved detection and treatment of comorbid psychiatric conditions in this group.

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Figures and Tables

Demographic Variable	Seizures/Epilepsy N = 221	No Seizures/Epilepsy N = 2791	Significance
Sex (% Female)	85.0%	89.0%	$\chi2 = 3.24$, $p = .077$
Age (Years)	41.2 ± .84	40.7 ± .26	$F(264.26) = 6.67$, $p = .563$
Race (% Black / African American)	91.0%	94.0%	$\chi2 = 10.43$, $p = .064$
Employment Status (% Unemployed)	73.2%	61.9%	$\chi2 = 11.09$, **$p < .001$**
Childhood Trauma Questionnaire Total Score	46.3 ± 1.44	40.8 ± .34	$F(239.54) = 12.95$, **$p < .001$**
Traumatic Events Inventory Total Score	5.5 ± .25	4.6 ± .06	$F(246.14) = 8.94$, **$p < .001$**

Table 1. Participant Demographics. Mean ± SEM for continuous demographic variables (age, CTQ, and TEI Scores) as well as proportions of categorical demographic variables (sex, race, employment status) for participants included in psychological symptom data analyses, broken down by seizure/epilepsy status. F values (df) are reported for all continuous variables, and $\chi2$ values are reported for all categorical variables. Some participants did not respond to all demographic questions. Number of respondents for each demographic variable are as follows: sex (n = 3009), age (n = 3010), race (n = 3008), employment status (n = 3008), CTQ (n = 2984), and TEI (n = 2994). Significant differences ($p < 0.05$, **bolded**) between groups were detected for CTQ total score, TEI total score, and employment status.

Symptom Variable	Seizures/Epilepsy N = 221	No Seizures/Epilepsy N = 2791	Significance
Depression Symptoms (BDI Total)	17.9 ± .91	14.7 ± .23	F(245.84) = 4.54, **p =.033**
PTSD Symptoms (mPSS Total)	16.5 ± .94	12.8 ± .24	F(220.15) = 11.45, **p <.001**
Suicidal Ideation (% Reporting each statement)			
I don't have any thoughts of killing myself.	84.3%	90.1%	$\chi2$ = 11.70, **p = .008**
I have thoughts of killing myself, but I would not carry them out.	14.3%	9.6%	
I would like to kill myself.	0.5%	0.1%	
I would kill myself if I had the chance	0.9%	0.2%	
History of Suicide Attempt (% Attempted)	25.8%	13.9%	$\chi2$ = 22.89, **p < .001**
Probable, Current PTSD Diagnosis (% with PTSD)	44.9%	32.0%	$\chi2$ = 13.61, **p < .001**

Table 2. Psychological Symptom Scores for Participants with and without Seizures/Epilepsy. Mean ± SEM for continuous symptom variables (BDI total and mPSS total) as well as proportions for all categorical symptom variables (suicidal ideation, history of suicide attempt, PTSD diagnosis) for participants included in psychological symptom data analyses, broken down by seizure/epilepsy status. F values (df) are reported for all continuous variables, and $\chi2$ values are reported for all categorical variables. Some participants did not respond to all symptom measures. Number of respondents for each symptom variable are as follows: BDI total (n = 2959), mPSS total (n = 2670), suicidal ideation (n = 2967), history of suicide attempt (n = 3008), and PTSD diagnosis (n = 2675). Significant differences ($p < .05$, **bolded**) between groups were detected for all symptom variables.

Variable	Seizures/Epilepsy N = 8	No Seizures/Epilepsy N = 8	Significance
Depression Symptoms (BDI Total)	15.3 ± 3.59	18.0 ± 5.11	F(14) = 2.17, p = .667
PTSD Symptoms (mPSS Total)	13.5 ± 9.91	20.6 ± 5.70	F(11.64) = 7.04, p = .305
Suicidal Ideation (% Reporting each statement)			
I don't have any thoughts of killing myself.	87.5%	87.5%	$\chi2 = 0.00$, p = 1.000
I have thoughts of killing myself, but I would not carry them out.	12.5%	12.5%	
I would like to kill myself.	0.0%	0.0%	
I would kill myself if I had the chance	0.0%	0.0%	
History of Suicide Attempt (% Attempted)	25.0%	25.0%	$\chi2 = 0.00$, p = 1.000
Probable, Current PTSD Diagnosis (% with PTSD)	37.5%	50.0%	$\chi2 = 0.25$, p = .614
Sex (% Female)	87.5%	87.5%	$\chi2 = 0.00$, p = 1.000
Pregnancy Status (% Pregnant/Breastfeeding)	25.0%	12.5%	$\chi2 = 0.41$, p = .522
Age (Years)	37.0 ± 3.54	36.8 ± 3.64	F(14) = 0.12, p = .961
Race (% Black/ African American)	100.0%	100.0%	$\chi2$ = NS, p = NS
Ethnicity (% Hispanic/Latinx)	0.0%	0.0%	$\chi2$ = NS, p = NS
Employment Status (% Unemployed)	75.0%	50.0%	$\chi2 = 1.07$, p = .302
Childhood Trauma Questionnaire Total Score	50.3 ± 9.81	57.8 ± 10.43	F(14) = 0.127, p = .609
Traumatic Events Inventory Total Score	5.25 ± 1.44	7.4 ± 1.43	F(14) = 0.03, p = 0.312

Table 3. Demographics and Psychological Symptom Scores for Participants Included in Fear-Potentiated Startle Response Analyses. Mean ± SEM for continuous demographic/symptom variables (BDI total, mPSS total, age, CTQ total, TEI total), as well as categorical demographic/symptom variables (suicidal ideation, history of suicide attempt, PTSD diagnosis, sex, pregnancy status, race, ethnicity, employment status) for participants included in fear-potentiated startle response analyses, broken down by seizure/epilepsy status. F values (df) are reported for all continuous variables, and $\chi2$ values are reported for all categorical variables. NS = Not Significant. There were no significant differences ($p < .05$) between demographics and/or psychological symptom scores between groups.

PTSD Symptoms		F	B	p-value
Model		F (3, 2662) = 318.39		
	Seizures/Epilepsy		.04	**.024**
	CTQ		.25	**<.001**
	TEI		.33	**<.001**

Table 4. Results of Linear Regression Analysis for PTSD Symptoms (PSS Total Score), with Seizures/Epilepsy Status as Predictor and CTQ and TEI as Covariates. F statistic (regression df, total df) is reported for the whole model. Standardized coefficients Beta and p-values are also reported for seizures/epilepsy status as well as both trauma measures (CTQ & TEI). Significant values ($p < .05$) are in bold. Both CTQ ($B = .25$, $p < .001$) and TEI ($B = .33$, $p < .001$) scores explain a significant amount of the variance observed in PTSD symptom scores; however, seizures/epilepsy still significantly predicts PTSD symptom scores even with both of these trauma measures being included in the linear regression model ($B = .04$, $p = .024$).

Depression Symptoms		F	B	p-value
Model		F (3, 2950) = 316.87		
	Seizures/Epilepsy		.03	.087
	CTQ		.30	**<.001**
	TEI		.25	**<.001**

Table 5. Results of Linear Regression Analysis for Depression Symptoms (BDI Total Score), with Seizures/Epilepsy Status as Predictor and CTQ and TEI as Covariates. F statistic (regression df, total df) is reported for the whole model. Standardized coefficients Beta and p-values are also reported for seizures/epilepsy status as well as both trauma measures (CTQ & TEI). Significant values ($p < .05$) are in bold. Both CTQ ($B = .30$, $p < .001$) and TEI ($B = .25$ $p < .001$) scores explain a significant amount of the variance observed in depression symptom scores. Seizures/epilepsy did not significantly predict depression symptom scores when both trauma measures were included in the same model.

PTSD Diagnosis		χ2	Nagelkerke R^2	B	SE	Wald	Exp (B)	p-value
Model		$\chi2$ (3) = 498.46	.24					
	Seizures/Epilepsy			.35	.17	4.23	1.42	**.040**
	CTQ			.02	.00	69.38	1.03	**<.001**
	TEI			.22	.02	156.91	1.25	**<.001**

Table 6. Results of Logistic Regression Analysis for PTSD Diagnosis, with Seizures/Epilepsy Status as Predictor and CTQ and TEI as Covariates. $\chi2$ (df) and Nagelkerke R^2 values are reported for the whole model. Beta values, standard errors, Wald statistics, odds ratios, and p-values are also reported for seizures/epilepsy status as well as both trauma measures (CTQ & TEI). Significant values ($p < .05$) are in bold. Both CTQ (B = .02, $p < .001$) and TEI (B = .22, $p < .001$) scores are significant predictors of PTSD diagnosis; however, seizures/epilepsy still significantly predicts PTSD diagnosis even with both trauma measures being included in the logistic regression model (B = .35, p = .040).

Suicide Attempt History		χ2	Nagelkerke R^2	B	SE	Wald	Exp (B)	p-value
Model		$\chi2$ (3) = 377.79	.21					
	Seizures/Epilepsy			.52	.18	8.12	1.69	**.004**
	CTQ			.03	.00	110.28	1.03	**<.001**
	TEI			.14	.02	54.94	1.15	**<.001**

Table 7. Results of Logistic Regression Analysis for Suicide Attempt History, with Seizures/Epilepsy Status as Predictor and CTQ and TEI as Covariates. $\chi2$ (df) and Nagelkerke R^2 values are reported for the whole model. Beta values, standard errors, Wald statistics, odds ratios, and p-values are also reported for seizures/epilepsy status as well as both trauma measures (CTQ & TEI). Significant values ($p < .05$) are in bold. Both CTQ (B = .03, $p < .001$) and TEI (B = .14, $p < .001$) scores are significant predictors of suicide attempt history; however, seizures/epilepsy still significantly predicts suicide attempt history even with both trauma measures being included in the logistic regression model (B = .52, p = .004).

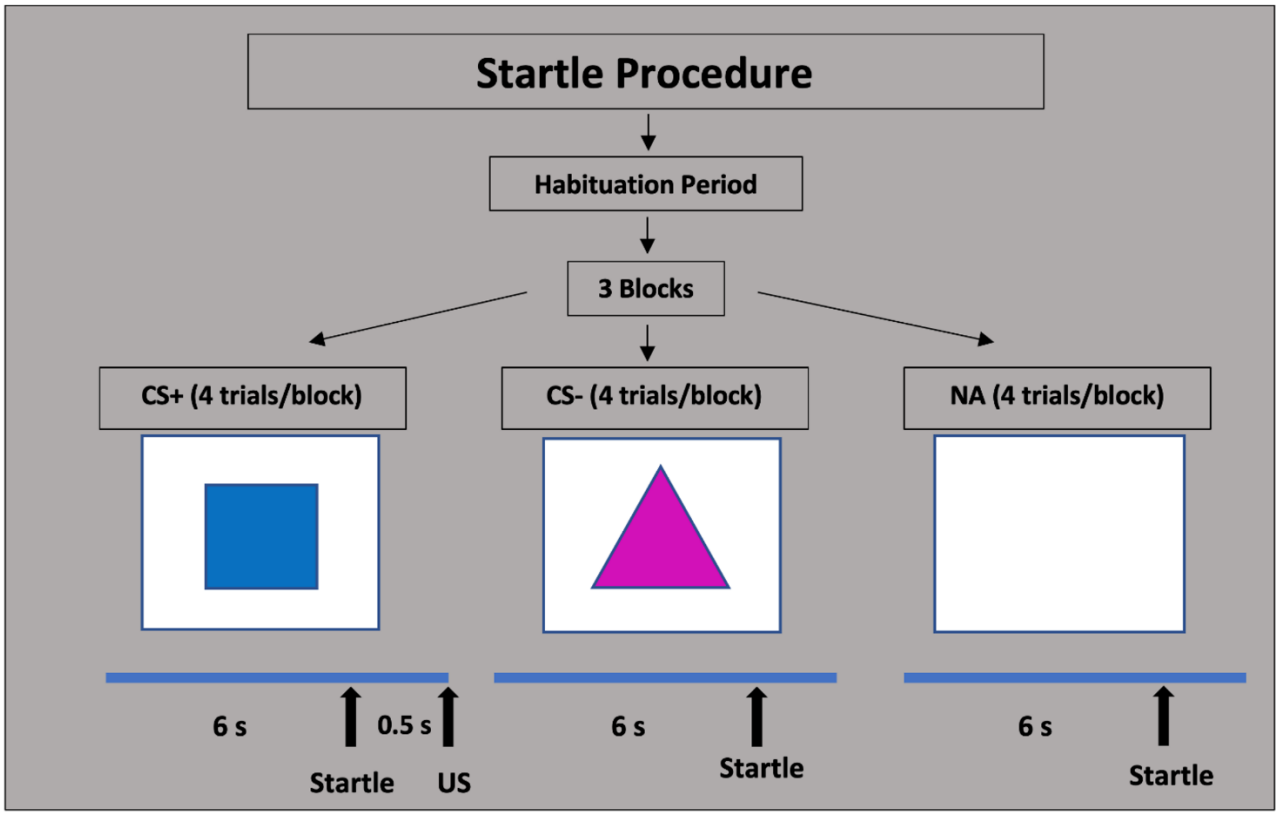

Figure 1. Schematic of startle task procedure. Participants first underwent a brief habituation period, wherein 2 different shapes (the CS+ and CS-) were presented with the startle noise (106-dB [A] SPL, lasting 40 ms) but without any UCS. Following habituation, participants were presented with a 3-block series of CS+ (blue square) / CS- (purple triangle), startle tone, and UCS presentation. Each of the three blocks consisted of 4 startle noise alone (NA) trials, 4 CS+ trials, and 4 CS- trials. During CS+ trials, participants were presented with the CS+ shape, then the startle tone, and then finally the UCS air puff (140 p.s.i) to their larynx lasting 250 ms. During CS- trials, participants were presented with the CS- shape and then the startle tone (no aversive air puff). During NA trials, participants were presented with only the startle noise (no shape or UCS). The shape remained on the screen for the entire duration of the trial (6s). Participants thus went through 36 startle trials, with each trial being separated by a randomized time interval (9-22 seconds).

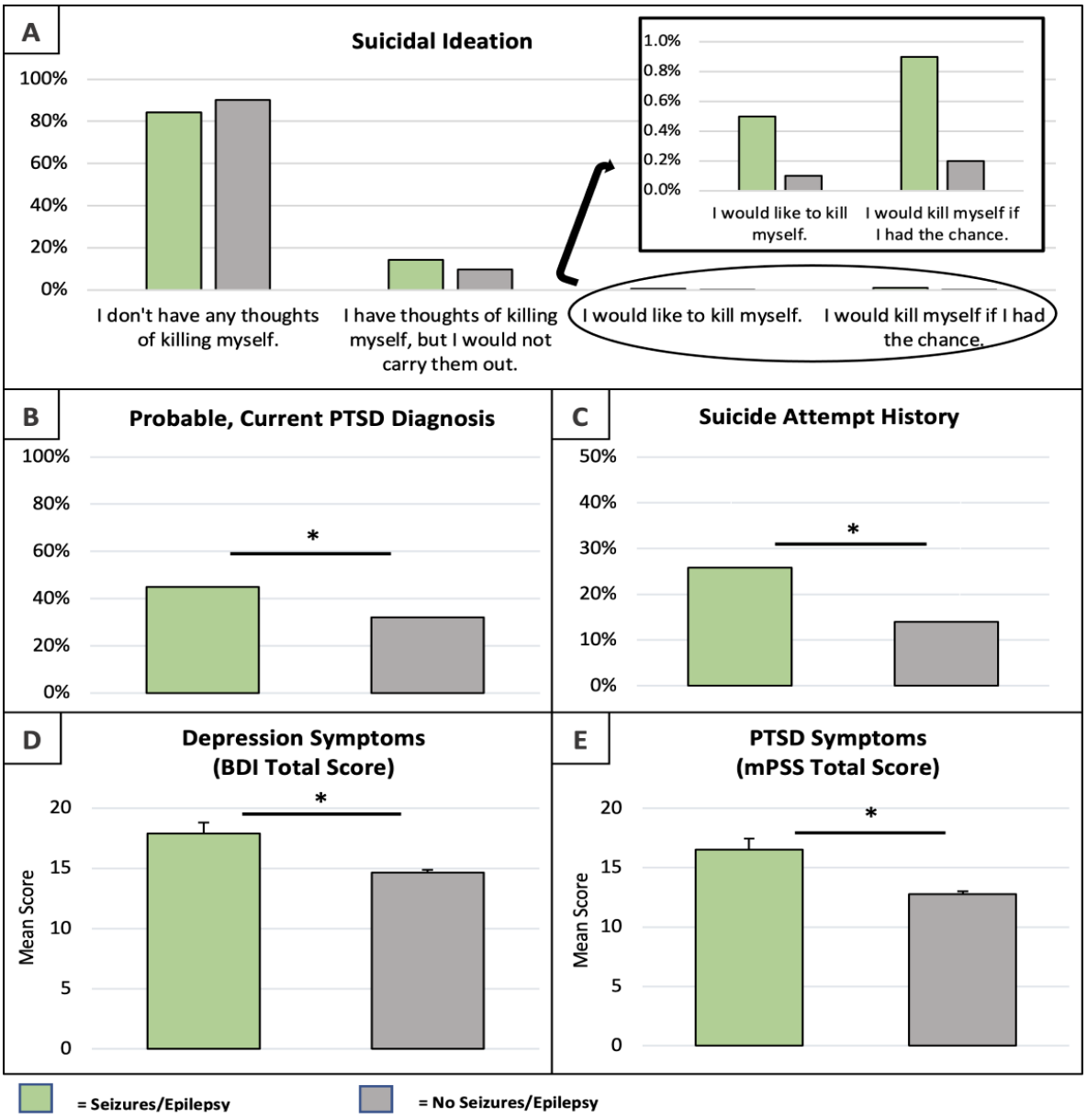

Figure 2. Psychological Symptom Scores for Participants with and without Seizures/Epilepsy. Asterisks denote significant differences ($p < .05$), columns in green represent seizure/epilepsy group and columns in gray represent controls, and SEM denoted by error bars. **A. Suicidal Ideation Response Proportions Separated by Response Type and Seizure/Epilepsy status.** The graph in the top right corner of the figure represents an expanded graph of the proportions for the two most symptomatic response types. Suicidal ideation was more prevalent among participants with seizures/epilepsy as opposed to control participants. **B. Proportion of Participants with a Probable, Current PTSD Diagnosis Separated by Seizure/Epilepsy Status.** Probable, current PTSD diagnosis was significantly more prevalent among participants with seizures/epilepsy as opposed to control participants (44.9% vs. 32.0%). **C. Proportion of Participants with a History of Suicide Attempt Separated by Seizure/Epilepsy Status.** Prior suicide attempt was significantly more prevalent among participants with seizures/epilepsy as opposed to control participants. **D. Depression Symptoms (BDI Total Scores) Separated by Seizure/Epilepsy Status.** Mean BDI total score was significantly higher for seizure/epilepsy group than control group (17.9 ± .91 vs. 14.7 ± .23). **E. PTSD Symptoms (mPSS Total Scores) Separated by Seizure/Epilepsy Status.** SEM denoted by error bars. Mean mPSS score was significantly higher for seizure/epilepsy group than control group (16.5 ± .94 vs. 12.8 ± .24).

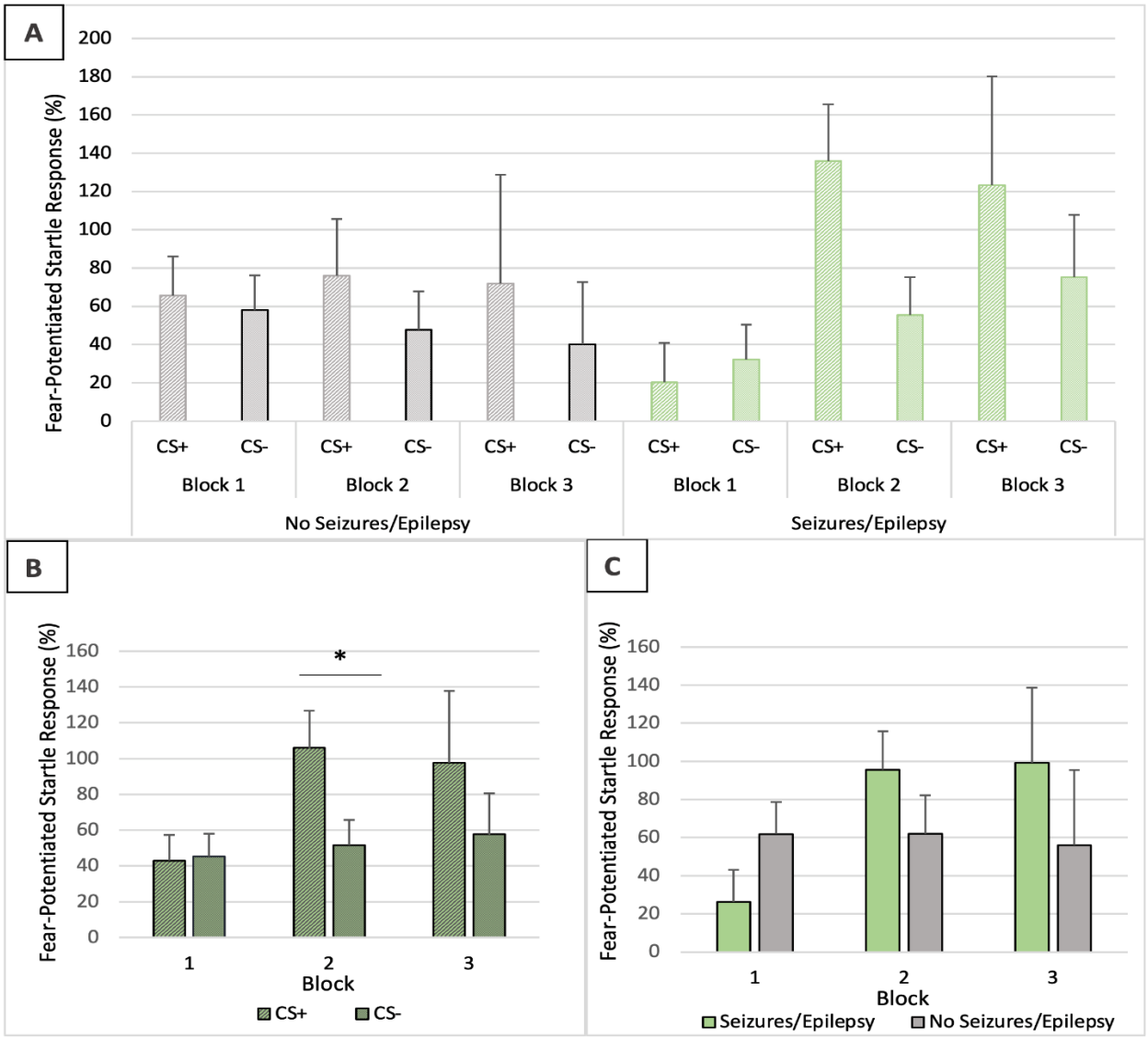

Figure 3. Fear-Potentiated Startle Response for Participants with and without Seizures/Epilepsy. A. Fear-potentiated startle response (mean FPS) for participants in each group (seizures/epilepsy, no seizures/epilepsy) separated by Block (1, 2, and 3) as well as CS type (CS+, CS-). No statistically significant difference ($p < .05$) was detected between each paired CS+ and CS- response within each block for neither seizures/epilepsy nor control group. **B. Fear-potentiated startle response across groups separated by block and CS type.** An interaction was detected between CS type and block ($F = 4.23$, $df = 2$, $p = .039$). Specifically, a significant difference (denoted by asterisk) was observed between participants' CS+ and CS- response in block 2 ($t = 2.50$, $df = 15$, $p = .024$). **C. Fear-potentiated startle response across CS types separated by group and block.** An interaction that neared, but did not reach significance, was observed between group and block ($F = 3.45$, $df = 2$, $p = .063$).