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The individual contribution of DSM 5 symptom clusters of PTSD, life events, and childhood adversity to frontal oscillatory brain asymmetry in a large sample of active combatants

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ABSTRACT

Post-Traumatic Stress Disorder (PTSD) has been linked to deviations in lateralized frontal functional oscillatory activity. This is possibly because left and right DLPFC have differential roles in regulating both memory and stress response, which are both dysfunctional in PTSD. However, previous results are heterogeneous, and could be attributable to individual symptom clusters, traumatic or aggressive life events, early life stress, or the interaction of these factors. In a large sample of active combatants (N = 401), we regressed these factors on frontal electroencephalography (EEG) asymmetry across 5 frequency bands (delta: 2–4 Hz; theta: 4–8 Hz; alpha: 8–12 Hz; beta: 12–24 Hz; gamma: 24–48 Hz). Negative cognition and mood was associated with stronger relative left delta and theta band power. Traumatic life events showed stronger right alpha and beta band power. Traumatic life events in interaction with hyperarousal predicted stronger relative right left-right imbalance (theta, alpha, and beta bands), whereas childhood adversity, in interaction with negative cognition and mood, predicted stronger relative left left-right imbalance (delta, theta, alpha and beta bands). The contribution of lateralized DLPFC dysfunction to PTSD is thus dependent on the individual complexities of subsymptom clusters and life history, and future studies need to take these factors into account.

1. Introduction

Posttraumatic Stress Disorder (PTSD) describes a chronic pathological response to traumatic events, characterized by intrusive memories (nightmares, flashbacks), anxiety, negative cognition and mood, and sometimes dissociation (American Psychiatric Association, 2013). In its early conception it was thought to be unique amongst mental disorders in having an unambiguous triggering cause, i.e. a trauma. The more researchers discover about it, the more complex this becomes. The likelihood of PTSD developing is far more dependent upon the number of traumatic events across the lifespan than an individual trauma (Neuner, Schauer, & Karunakara, 2004). Moreover, examinations of early childhood stress show that this affects the developing brain and is a major general factor for vulnerability to future mental illness (Andersen & Teicher, 2008). This study attempts to examine these factors simultaneously, applying electroencephalography (EEG) measures of frontal resting state oscillations to a large population to create an

epidemiological picture considering symptom clusters, and adverse life-events.

The crucial brain structures associated with PTSD include the amygdala, the hippocampus, and regions of the prefrontal cortex (PFC) (see Brewin, Gregory, Lipton, and Burgess (2010) and Shin, Rauch, and Pitman (2006) for review). They are crucial for different aspects of responses to life-threatening situations. For example, the PFC and amygdala encode potentially threatening stimuli, with the former judging the level of threat, and amygdala regulating the activation of automatic threat responses (Blair, 2004). All structures play a role in both the encoding and retrieval of memories, and the regulation of the hypothalamic-pituitary-adrenal axis (de Quervain, Schwabe, & Roozendall, 2017; Steudte-Schmiedgen, Kirschbaum, Alexander, & Stalder, 2016; Yehuda, 2009). One curious aspect of these studies is the frequently observed asymmetry of dysfunction. Yehuda et al. (2009) in fact made the observation that "To date, almost every study examining the hippocampus, amygdala, or ACC [anterior cingulate gyrus] has found effects to be

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restricted to one hemisphere, or directionally different in the two hemispheres." Though this claim is very strong, the presence of hemispheric differences is strong enough to merit further scrutiny. This is found for structural studies, such as the small left amygdala volume in PTSD groups (Karl et al., 2006) or smaller left cingulate after chronic stress (Cerqueira, Almeida, & Sousa, 2008). Volumetric changes have also been found in the premotor cortex, with people with PTSD exposed to urban violence having thinner cortical structures in right premotor areas (Rocha-Rego et al., 2012). Functional findings also show stronger activity in one or the other hemisphere, e.g. increased right amygdala activity in PTSD patients (Shin et al., 2005), and in general a more pronounced emotional memory recall (Bisby, Horner, Horlyck, & Burgess, 2015).

It is possible that hemispheric differences can be related back to differential activation of dorsolateral prefrontal cortex (DLPFC). The phenomenon of asymmetry in functional oscillatory activity in the DLPFC has been intensively investigated in emotional neuropsychology (Coan & Allen, 2004; Harmon-Jones, Gable, & Peterson, 2010). In particular, the ratio of right vs. left frontal activity in the prominent alpha band (8–12 Hz) has been consistently linked to a variety of state, trait, and psychopathological characteristics. For example, this has associated with both stable personality traits (Harmon-Jones et al., 2010; Spielberg et al., 2012), as well as psychopathological phenomena, such as depression and anxiety (Harmon-Jones et al., 2008; Thibodeau, Jorgensen, & Kim, 2006), and can be manipulated experimentally via neurofeedback, or repetitive Transcranial Magnetic Stimulation (rTMS) (Harmon-Jones & Gable, 2017).

If alpha oscillations are interpreted as an inhibitory gating mechanism, then a reduction in alpha power, or desynchronization would indicate greater neural activity (Oakes et al., 2004).[1] Studies frequently link a left frontal desynchronization with greater approach-related motivation (e.g. responses to food, erotic stimuli), and conversely greater right frontal desynchronization with greater withdrawal-related motivation (Harmon-Jones & Gable, 2017). As applied to psychopathology, a meta-analysis of collective findings from Thibodeau et al. (2006) suggest that the withdrawal related relative right desynchronization (i.e. reduced relative right alpha power) is related to both depression and anxiety symptoms.

There could be a link between the structural and functional asymmetries found in PTSD noted above, and the oscillatory alpha asymmetry associated with psychopathology. In their review of PTSD and frontal alpha asymmetry, Meyer et al. (2015) build a theoretical model linking frontal alpha asymmetry with stress- and memory-related brain function. They postulate that left and right DLPFC play opposing roles in both regulation of the hypothalamic-pituitary-adrenal axis (HPA axis), and memory consolidation and recall. For HPA axis regulation, stimulating activity via repetitive transcranial magnetic stimulation (rTMS) in the left DLPFC is related to increased processing of positive stimuli, and decreased processing of negative stimuli (Baeken, Van Schuerbeek et al., 2011), as well as a suppressed cortisol response (Baeken, Vanderhasselt, Remue, & Rossi, 2014), whereas stimulating activity in the right DLPFC with rTMS increases cortisol output in anxious patients (Baeken, Vanderhasselt, & De Raedt, 2011). For memory, the separate functions of encoding and retrieval also appear to be lateralized. Left DLPFC is associated with encoding (Paller & Wagner, 2002), particularly in the alpha/beta bands (Hanslmayr, Matuschek, & Fellner, 2014), whereas right DLPFC activity is associated with recall (Sandrini, Censor, Mishoe, & Cohen, 2013; Turriziani et al., 2012), particularly in the theta band (Waldhauser, Johansson, & Hanslmayr, 2012).

On this theoretical basis, there is ample reason to expect systematic differences in frontal asymmetry in people with varying levels of PTSD, seeing as it manifests both dysfunctional memory (Brewin, 2014; Elbert, Rockstroh, Kolassa, Schauer, & Neuner, 2006), and deviations in HPA axis function (Daskalakis, Mcgill, Lehrner, & Yehuda, 2016). However, results for PTSD are complex (see Eidelman-Rothman, Levy & Feldman, (2016) and Meyer et al. (2015), for review). Some studies have not found differences between PTSD and control participants in alpha asymmetry (e.g. Gordon, Palmer, & Cooper, 2010; Wahbeh & Oken, 2013). Other studies have shown a decreased relative right alpha power in PTSD patients, interpreted as greater approach activity in response to provocation (McCaffrey, Lorig, Pendrey, McCutcheon, & Garrett, 1993; Rabe, Beauducel, Zöllner, Maercker, & Karl, 2006). Alpha band activity has traditionally received the most attention in emotion and motivation related EEG research. However, other oscillatory bands, either slow wave delta and theta bands, or faster beta and gamma bands could similarly provide biomarkers of PTSD related phenomena. Two separate studies from (Begić, Hotujac, & Jokić-Begić, 2001) and (Jokić-Begić & Begić, 2003) found bilaterally increased beta power, particularly in frontal regions, in combat veterans with PTSD, which they attributed to increased hyperarousal. There was also increased central theta power, which could be linked to either changed amygdala function or structural changes in hippocampal volume.

Although differences between case and controls are consistently found, they are heterogeneous, complicating the interpretation of the meaning of these studies. The problem stems in part from the fact that PTSD is a very heterogeneous disorder, with symptoms of depression, anxiety, dissociation, and intrusions (American Psychiatric Association, 2013). EEG studies that recruit from a particular group of PTSD sufferers, such as war veterans or survivors of sexual violence, may be measuring a preponderance of one subsymptom over another, e.g. combatants may be chronically hyperaroused, ready for defensive aggressive responses, whereas victims of sexual violence may more easily switch to a dissociative response (Schauer & Elbert, 2010).

Many different factors apart from present subsymptoms could influence EEG measures of PTSD patients, accounting for the heterogeneity of results. It is well established that the number of traumatic experiences is predictive of the likelihood of developing PTSD symptoms. This phenomenon is termed 'the building block effect' (Neuner et al., 2004). These life experiences are correlated with structural brain change independently of PTSD symptomatology. This is supported by the finding that the brains of traumatized participants who nevertheless had no PTSD, showed smaller hippocampal volumes than healthy controls (Karl et al., 2006). Thus, structural changes in stress-related brain structures could be a reflection of an adaptation to a violent environment, rather than PTSD.

To further complicate this picture, it is likely that traumatic events have different effects upon the individual in childhood, when the brain undergoes radical developmental changes and the brain is especially plastic. For example, Burghy et al. (2012) showed that prefrontal/amygdala connectivity abnormalities were not related to adult psychopathology, but could be linked most strongly to early childhood stress, mediated by early childhood cortisol. Many other studies suggest effects of early childhood stress on functional brain activity, including frontal lateralized disorder (Ito, Teicher, Glod, & Ackerman, 1998; Miskovic, Schmidt, Georgiades, Boyle, & MacMillan, 2009). Several studies also show an effect of early childhood stress on left frontal development (Schalinski, Moran, Elbert, Reindl, & Wienbruch, 2017; Van Harmelen et al., 2010).

In addition to the individual symptoms and life events, it is also important to analyze the interaction between symptoms and life events. This is important as there is a wide variety of variation in susceptibility to trauma, which is only beginning to be mapped genetically and epigenetically. Genetic variation preconditions some people to be more vulnerable to PTSD (de Quervain et al., 2007). Similar variability can be

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[1] To minimize confusion, in this paper follows the dominant interpretation of alpha band power increases as reflecting reduced 'activity', though this is theoretical (Klimesch, Sauseng, & Hanslmayr, 2007). However, because in this paper, we also look at other frequency bands, for which there are varying interpretations of their function, we otherwise refer to increased or decreased 'power' i.e. directly observed phenomena of squared amplitudes of measured oscillations.

postulated in the relation between childhood adversity and subsequent vulnerability to stress-related disorders, with early adversity bringing about epigenetic changes HPA axis function (Hecker, Radtke, Hermenau, Papassotiropoulos, & Elbert, 2016). Thus the brain of an individual preconditioned to certain environmental circumstances via genes or early experience, may show a fundamentally different way of responding to trauma, reflected in functional brain activity. Conversely, changes wrought by early experiences may only present themselves at certain levels of current symptomatology. In both cases, there is an imperative to test for interactions of symptom and life experience in the participants.

Understanding the complexity of the frontal oscillatory activity in PTSD requires a study that can encompass the complexity of symptom manifestations and life events and their interactions. To achieve this, we gathered data from a large group of active combatants in the Burundian army who grew up and participated in the civil war that took place between 1993 and 2006. They had a high risk of early childhood adversities, a generally high trauma load, and thus a high risk of PTSD. EEG measures of frontal oscillatory asymmetry were taken using a small mobile EEG device, for over 400 soldiers. Clinical interviews assessed individual DSM 5 symptom clusters of PTSD (intrusions, avoidance, hyperarousal, negative cognition and mood), the number of traumatic events and aggressive events across the lifespan, as well as childhood adversity. We also analyzed interactions for Aggression Life Events (i.e. self-perpetrated violence) and Traumatic Life Events separately. Soldiers experience significant trauma in their working lives. However, they are also required to carry out violence in the line of duty, and there has been debate about whether and under what conditions, self-perpetrated acts of violence are traumatic (Elbert, Schauer & Moran, 2017; Grossman, 1996; MacNair, 2002). Many studies have indeed shown that a higher trait propensity to enjoy aggression ('Appetitive Aggression') blunts the consequences of repeated experiences of trauma (see Elbert, Moran, & Schauer, 2016 for review). As such, it is necessary to analyze Aggressive Life Events and their interaction with PTSD symptom clusters separately from other forms of Traumatic Life Events.

Although this study of the five frequency bands is exploratory, some predictions can be made based on the established alpha asymmetry findings. Depression and anxiety symptoms are more strongly associated with stronger relative right activity (i.e. decreased right alpha oscillatory power). The depression and anxiety related subsymptoms of PTSD (negative mood and cognition, and hyperarousal, respectively) map onto depression and are similarly associated with right lateralized alpha activity. In contrast, intrusions are related to deficits in memory encoding, which have been shown to be related to left-sided activity (Hanslmayr et al., 2014), then it is possible that intrusions will be more strongly left-lateralized in alpha and beta bands.

2. Materials and methods

2.1. Participants

A sample of 542 Participants were drawn from the Burundian army soldiers taking part in the African Union mission to Somalia (AMISOM). The experiment was part of a major longitudinal study of soldiers, taking into account psychological, genetic, and epigenetic effects of combat, trauma and childhood adversity (Nandi et al., 2017; Nandi, Crombach, Bambonye, Elbert, & Weierstall, 2015). The study examined soldiers before and after a mission to the Somalia, to evaluate the effects of combat upon trauma, aggression, and the way in which they interact with other psychological and genetic factors. The present study examined male participants who were newly returned from combat.

Participation was voluntary, and soldiers were not given financial compensation for their time. Research was carried out with the approval of the Ethics Committees of the University of Konstanz and the Lumière University, Bujumbura, Burundi and was conducted in accordance with the declaration of Helsinki. Anonymity of participation

was ensured through encrypted electronic coding and storage of the data.

2.2. Apparatus and physiological data collection

The EEG data was collected using an 8 Sensor portable (AvatarEEG™, Electrical Geodesics, Inc., EGI). We used Ag/AgCl sintered ring electrodes, using ethyl propyl to clean the skin and Abralyt HiCl (1000 g), a high-chloride, abrasive electrolyte gel. Impedances were higher than commonly expected in an EEG experiment, with impedances ranging from 2 to 75 kOmega ($M = 29.66$, $SD = 12.54$). This was possibly attributable to greater quantities of oil or dirt in the scalp of participants, or as all soldiers had shaved heads, tougher skin from constant sun exposure. Although lower impedances < 10 kOmega are traditionally recommended, improvements in high input-impedance amplifiers and digital filters mean that much higher tolerances are permissible (Ferree, Luu, Russell, & Tucker, 2001).

The neuroelectric signals were digitized with a sampling rate of 500 Hz. The electrode layout used the 10–20 system, with electrodes placed symmetrically in frontal positions: with Fp1, F3, F7 representing left activity, and Fp2, F4, F8 representing right activity. Referencing was provided by physically linked mastoid electrodes, and a ground electrode was attached to the forearm.

2.3. Procedure

The participants in the entire project (N = 542) underwent psychological assessment before testing This clinical interview lasted on average 2 h. All clinical interviews were administered either by psychologists with local translators, or local psychology students under supervision, as all questions were verbally administered, there was no distortion of the responses through illiteracy. State-of-the-art procedures to maximize validity and reliability of questionnaire administration were employed (e.g. blind back-translation into the Kirundi dialect, randomization of translators to avoid interviewer effects). All details can be found in Nandi et al. (2017). After this, they were offered the possibility of taking part in the EEG experiment. The EEG was often carried out on the same day, but not necessarily. Appointments were booked at the convenience of the soldiers. There was no selection of participants based upon the interview data, some participants could not be fitted into the schedule for logistical reasons (e.g. not available for appointment (N = 24), some declined to take part (N = 20)). Of the 499 EEGs carried out, 32 were excluded prior to analysis for technical reasons (see section Preprocessing and Artifact Correction below), leaving N = 467 EEGs, as there were missing values in the behavioral data, the regression removed 66 datasets, leaving a final sample size of N = 401 for the analyses. The EEG team consisted of two people, one University researcher or technician, and one Burundian translator, who briefed the participant and assisted with setting up each EEG. Care had to be taken to ensure properly informed consent from the participants, who for the most part were unfamiliar with the EEG technology. EEGs were measured in rooms at the army barracks. Disturbances, such as electricity or ambient noise were noted in the protocol. The measure consisted of two basic conditions: Five minutes of passive measurement with eyes open, participants fixated on a point in front of them, followed by five minutes of passive measurement with eyes closed. Due to the noisy measuring conditions, an exact timing of measurement was not made, but was lengthened where the experimenters felt that it was noisy. The entire measure, including explanation of proceedings, EEG preparation, and measurements, took approximately 45 min. Measurements were taken throughout the day from 8 am to 6 pm. Although there are methodological arguments holding that time of measurement of resting state activity is a potential confound variable (Duncan & Northoff, 2013), the quantity of measurements undertaken and its coordination with clinical interviews, which took place in the same time period, meant that measuring all participants at the same

time was not possible. Pearson correlations between lateralization coefficients in the five measured bands, and time of measurement, showed no significant effects (all r < |0.1|, p > 0.3).

2.4. Behavioral data

The study has a large behavioral database (see Nandi et al. (2017) for further details). Age, recent medical problems, and neurological illness and injury were taken as possibly relevant variables influencing the neural signals.

2.4.1. Neurological illness and injury

Lifetime head injury with or without loss of consciousness, concussion, meningitis, and neurological disorders, such as epilepsy were recorded, and summed to make a potential score from 0 to 4.

2.4.2. Handedness

Handedness was also measured, as the sum score of the following 5 questions: Which hand do you use when writing (note if they do not write); eat with a spoon; sweep with a broom; open a bottle; pull trigger of a gun/rifle? As only 9 of the sample could be counted as left-handers, (statistically less than the norm, suggesting a cultural bias or the obfuscating influence of illiteracy (Lansky, Feinstein, & Peterson, 1988)), this variable was excluded as unlikely to be interpretable or valid. These participants remained in the analysis, but this was replicated with them removed.

2.4.3. Illness, medication & drug abuse

The larger study included an illness and medication checklist of nine common physical complaints in Burundi (cough, flu, headache, fever, skin rash, diarrhea, malaria, stomach pain, other complaints), as well as medication, common medication included paracetamol, quinine, antibiotics. There were no soldiers on psychopharmaceutical drugs. A sum score was made of illnesses and number of medications (range: 0–9) to take into account possible indirect influences of recent or chronic physical depredation. Similarly, alcohol abuse in the previous two weeks (A score of 0–14, signifying number of days where more than 1.0 l of beer/0.5 l of wine/0.1 l of vodka/brandy was consumed) was also added as a separate variable.

There was no reported use of other drugs such as Khat and Marijuana in the interviews, which are known to be widely consumed in the Great Lakes region (Odenwald, 2007) and could have an effect on brain activity.

2.4.4. PTSD symptom scale – interview (PSS-I-5) for DSM 5

An interview based on the items of the DSM-V was used (Foa & Capaldi, 2013). Each symptom experienced in the last two weeks, is rated on a four-point likert scale, from 0 (Not at all), to 3 (5 or more times per week/almost always). Applying the DSM V concept to this particular sample resulted in satisfying psychometric properties for the questionnaire (see Nandi et al., 2017 for details). Possible score range was 0–60. Four subscales corresponding to DSM 5 criteria were separated: Intrusions (0–15), Avoidance (0–6), Negative Cognitions and Mood (0–21), and Hyperarousal (0–18).

2.4.5. Childhood familial adversity

A 30-item checklist of adverse experiences up until the age of 18, based on the work of Catani, Schauer, Elbert and Missmahl (2009) was included. It covers physical violence, sexual abuse, emotional abuse, neglect, and witnessed violence. It is scored dichotomously yes (1) or no (0), and summed.

2.4.6. Trauma event list

Lifetime trauma event types were measured with a dichotomously coded (yes = 1, no = 0), 19-item list, relating to war and civilian life, based on a previous measure from (Neuner et al., 2004). Exact

frequencies of trauma events were not measured, as these are deemed to be less reliably recalled than trauma types (Kolassa et al., 2010). See Nandi et al. (2017) for psychometric properties.

2.4.7. Aggression event types

A dichotomously-coded (yes = 1, no = 0), checklist of 14 different violent acts perpetrated (rather than experienced) by the participants (e.g. rape, murder, mutilation), drawn from Weierstall and Elbert (2011) was used that has proven its validity in different studies with war-affected populations, covering several thousand individuals.

2.5. EEG analysis

2.5.1. Preprocessing and artifact correction

Each dataset was visually inspected for eye artifacts, muscle, channel jumps and miscellaneous non-neural artifacts. Filtering was offline, with a 48 Hz low-pass filter. We then used a 2 Hz high-pass digital filter with a Butterworth characteristic. Filtering had an infinite impulse response, order 2, zero-phase (thus an effective order 4). The cut-off frequency represents the −3 dB point of the filter's transfer function. Though this high pass filter is higher than the current standard for laboratory research, the noisy recording conditions of a bush setting, with greater vulnerability to slow artifacts, necessitated it. Although there is a compromise in the filtered delta band amplitude, this is across the whole dataset, and we are not testing any hypotheses related to the absolute delta power. The filters were applied to the continuous data, rather than the subsequently cut trials, thus excluding the possibility of ringing artifacts. Affected segments were cut for all sensors even if only one sensor was affected. Where there were so many artifacts that less than 2 min of the total 5 min of activity remained, then the entire dataset was cut from the sample (N: 499–27 = 472). The EO condition was not further analyzed, as it was seen in the visual inspection that very many datasets were contaminated by excessive eye movement. The mean number of trials left in the EC dataset was 151 (SD = 12.98, Range: 101–210).

Remaining EC conditions were cut into 2-second excerpts. At a sampling frequency of 500 Hz, this meant 1000 sampling points for each epoch. The fast Fourier transform was applied to the epochs, and required 1024 sampling points, thus there is an overlap of 24 points for each epoch. A spectral analysis was run on these for the following frequency bands using in house software (uV/sqrt(Hz)): Delta (2–4 Hz), Theta (4–8 Hz), Alpha (8–12 Hz), Beta (12–24 Hz), and Gamma (24–48 Hz). After the power analysis, there were nevertheless some participants that showed improbably high power, which could not have a neural source. We defined this as > 10 uV/sqrt(Hz). We created an average of right sensors (Fp2, F4, F8) and left sensors (Fp1, F3, F7) for each frequency band. If more than 1 sensor on either side was affected, then it was cut from the sample (N: 472–5 = 467). All frequency bands for the affected sensors were uniformly affected by electrode distortion. We then took the natural logarithm of Left averaged sensors was then subtracted from the natural logarithm of the Right averaged sensors, to provide an index of lateralization. Thus, a positive number indicates a higher right lateralized power, relative to left. Since this metric is an intrasubject comparison, there was no need for further normalization to account for variable skin impedance, and skull thickness (Knyazev et al., 2003).

2.6. Data analysis

Statistical analysis was carried out in R and SPSS 23. Robust regression equations were created entering the following variables:

1. Control variables: Brain Injury; Age; Alcohol Abuse, Number of Illnesses & Medication.
2. DSM 5 PTSD Symptom Clusters: Intrusions; Avoidance; Negative Cognition & Mood; Hyperarousal

Table 1
Descriptive statistics for all variables included in the initial regression prior to AIC model reduction.–

Descriptive statistics (N = 401)	M *(SD)* [Range]
Age	33.15 *(4.56)* [22–50]
Total Brain Injuries	0.27 *(0.55)* [0–4]
Number of Illnesses & Medication	2.87 *(2.23)* [0–9]
Alcohol Abuse (days in two weeks)	4.64 *(5.31)* [0–14]
PSS-I DSM 5	3.88 *(5.65)* [0–36]
B Intrusions	1.14 *(1.95)* [0–9]
C Avoidance	0.57 *(1.05)* [0–6]
D Negative Cognition & Mood	0.94 *(1.81)* [0–15]
E Hyperarousal	1.22 *(2.00)* [0–13]
Lifetime Trauma Events	8.69 *(2.95)* [0–15]
Lifetime Aggression Events	4.17 *(3.37)* [0–14]
Childhood Adversity	9.18 *(4.57)* [0–24]

  3. Life Events: Trauma Events; Aggression Events; Childhood Adversity
  4. Two-way interactions of Life Events and DSM 5 PTSD Symptom Clusters

Model reduction was carried out using Akaike's information criterion (AIC) (Akaike, 1987). The final sample size incorporating case-wise elimination of missing values over all measured behavioral and neurooscillatory variables was N = 401 (see (Table 1) for descriptive statistics). For a linear multiple regression, variance and linearity assumptions were fulfilled. There were deviations from normality for residuals according to Kolmogorov-Smirnov tests. However, visual inspection of histograms suggested that these variations were only slight considering the large sample size (West, Finch, & Curran, 1995). A linear regression with bootstrapping (1000 permutations) was deemed the most robust analysis strategy appropriate to the data. All variables were mean-centered to reduce potential multicollinearity (Kleinbaum, Kupper, Nizam, & Rosenberg, 2013).

3. Results

3.1. Behavioral variables

3.1.1. Robust regressions of EEG outcomes

Table 2 shows outcomes of regression models for each individual frequency band. Delta, theta, alpha and beta models showed stable models, only a small amount of variance in gamma could be accounted for by the models. This is possibly attributable to the greater difficulty of measuring gamma band activity outside of controlled laboratory conditions, and is not further discussed. For the EEG-related control variables, Illness & Medication as well as Brain Injury were consistently a part of the delta, theta and alpha bands, with the beta band including only an effect of brain injury. Age and alcohol abuse were not influential predictors of frontal oscillatory asymmetry, and were automatically eliminated from final models. For the PTSD symptom clusters, Negative Cognition & Mood as well as Hyperarousal were consistently included in the models. In the beta band model, Intrusions were also found to be influential. Relatively stronger right frontal power was related to the interaction of hyperarousal with trauma events across theta, alpha and beta bands, and with hyperarousal and Aggressive Life Events in the delta band. In contrast, the interaction of Negative Cognition & Mood and Childhood Adversity was consistently related to relative left frontal power across delta, theta, alpha and beta bands. There were isolated individual interactions, including stronger relative left beta power being predicted by the interaction of intrusions and trauma events, and the interaction of avoidance and trauma predicting relative left alpha power.

4. Discussion

This study used a large sample to simultaneously evaluate the different factors related to PTSD that could account for previously observed variations in functional neural asymmetry. Delta, theta, alpha and beta frequency bands yielded stable models incorporating DSM 5 symptom clusters of PTSD and life-events. Although many previous studies have shown differences between PTSD and controls, the larger sample size enabled us to parse out the relative impact of the different DSM 5-defined clusters of PTSD symptoms. The predicted right alpha desynchronization relating to Depression and Anxiety-related symptoms was not found. A stronger right left-right imbalance was found for Negative Cognition and Mood in the delta and theta bands. Lifetime Trauma Events across the lifespan also showed a stronger relative right left-right imbalance for delta, theta, alpha, and beta bands. Lifetime Aggression Events showed a main right lateralized effect in the theta band. The pattern of interactions showed interesting dissociations. In general, the subsymptoms of PTSD showed their strongest associations with frontal asymmetry when in interaction with adverse life events (Lifetime Trauma Events, Lifetime Aggression Events, and Childhood Adversity), rather than by themselves. Soldiers with a high level of childhood adversity, and a currently higher level of Negative Cognition and Mood, showed a stronger relative left frontal asymmetry across delta, theta, alpha, and beta bands. In contrast, soldiers with a higher number of Lifetime Trauma Events across the lifespan, and a currently higher level of hyperarousal showed a greater amount of right left-right imbalance in theta, alpha, and beta bands. Similarly, when soldiers reported a high level of Lifetime Trauma Events together with current intrusion symptoms, they were also more likely to show relatively strong left left-right imbalance beta power.

There are different ways of interpreting the interactions of life events and current symptoms. One is in diathesis-stress terms. Lifetime Trauma or Aggression experiences, or early Childhood Adversity have an influence on brain development and functional organization, but the effects of this reorganization may be most apparent when the individual is manifesting symptoms. Another possibility is that people with high amounts of early life events have a qualitatively different type of depression, or anxiety symptoms than those without.

The relation between Childhood Adversity and left left-right imbalance is congruent with research showing that Childhood Adversity impacts more strongly on left frontal brain development. Neuroscientific research has shown that the left hemisphere of the brain goes through a critical period of intense growth from ages 2 to 4 (Thatcher, Walker, & Giudice, 1987), coinciding with intensive phase of language acquisition (Corballis, 1991), which could thereby be more strongly affected by Childhood Adversity. Other studies also show this association between early life stress and left frontal developmental abnormalities (Ito et al., 1998; Miskovic et al., 2009; Schalinski et al., 2017; Thatcher, North, & Biver, 2008; Van Harmelen et al., 2010).

Childhood stress during sensitive periods of development has been linked to the later development of depression. The prefrontal cortex regulates emotion and cognitive appraisal, gauging both the achievement and frustration of reward. Long-term frustration of goals or lack of positive affectivity, particularly in adolescence, is a factor in developing depressive episodes (Davey, Yücel, & Allen, 2008). Frontal brain regions develop slowly across childhood and adolescence, making them particularly vulnerable to alteration via stress (Andersen et al., 2008; Andersen & Teicher, 2008). In this study, similar stronger relative left left-right imbalance was found across delta, theta, beta and alpha bands for the interaction of Negative Cognition and Mood and Childhood Adversity. However, the main effect of Negative Cognition and Mood showed the opposite stronger right left-right imbalance for delta and theta bands. This contrary pattern of responses is difficult to interpret. People with higher levels of childhood adversity are more vulnerable to development of mental health problems, including depression and anxiety disorders (Bandoli et al., 2017), the functional differences in

Table 2

Regression models for sample (N = 401) with the five frequency bands as outcome variables. Predictor variables were: control variables, PTSD Symptom clusters, as measured by the PSS-I-5, life events, and two-way interactions. The variables presented were those remaining after data-driven model reduction by the AIC.

		Delta Band Ratio β [bootstrapped CIs]	Theta Band Ratio β [bootstrapped CIs]	Alpha Band Ratio β [bootstrapped CIs]	Beta Band Ratio β [bootstrapped CIs]	Gamma Band Ratio β [bootstrapped CIs]
Control Variables	Illness & Medication	−0.096* [−0.194, −0.006]	−0.107* [−0.196, −0.013]	−0.109* [−0.196, −0.019]	–	–
	Brain Injury	0.146** [0.062, 0.250]	0.152** [0.066, 0.244]	0.126** [0.036, 0.216]	0.126* [0.027, 0.230]	0.076 [−0.032, 0.200]
PSS-I DSM 5	B Intrusions	–	–	–	−0.032 [−0.149, 0.080]	−0.008 [−0.116, 0.117]
	C Avoidance	–	–	0.054 [−0.086, 0.162]	0.091 [−0.032, 0.198]	–
	D Negative Cognition & Mood	0.162** [0.053, 0.286]	0.158** [0.044, 0.272]	0.125 [0.005, 0.275]	–	0.083 [−0.027, 0.188]
	E Hyperarousal	0.025 [−0.083, 0.121]	0.021 [−0.080, 0.123]	−0.005 [−0.120, 0.108]	–	–
Life Events	Trauma Life Events	0.141* [0.023, 0.256]	−0.090 [−0.213, 0.041]	0.119* [0.023, 0.219]	0.135* [0.013, 0.261]	0.009 [−0.147, 0.137]
	Aggression Life Events	−0.047 [−0.161, 0.080]	0.177** [0.055, 0.290]	–	−0.040 [−0.168, 0.084]	0.026 [−0.085, 0.154]
	Childhood Adversity	0.027 [−0.072, 0.130]	0.033 [−0.071, 0.124]	0.012 [−0.091, 0.111]	0.021 [−0.077, 0.117]	0.030 [−0.076, 0.138]
Interactions: PSS-I DSM 5*Life Events	Intrusions*Trauma Events	–	–	–	−0.168* [−0.316, −0.034]	−0.183 [−0.393, 0.012]
	Intrusions*Aggression Events	–	–	–	0.109 [−0.011, 0.230]	0.193* [0.012, 0.367]
	Avoidance*Trauma Events	–	–	−0.112* [−0.217, −0.004]	–	–
	Hyperarousal*Trauma Life Events	–	0.238*** [0.111, 0.356]	0.197*** [0.095, 0.298]	0.240** [0.130, 0.356]	0.253** [0.062, 0.427]
	Hyperarousal*Aggression Life Events	0.120** [0.037, 0.205]	–	–	–	−0.165* [−0.300, −0.043]
	Hyperarousal*Childhood Adversity	–	–	–	–	−0.091 [−0.208, −0.010]
	Negative Cognition & Mood*Trauma Life Events	–	−0.123* [−0.250, 0.007]	–	–	–
	Negative Cognition & Mood*Childhood Adversity	−0.156* [−0.277, −0.018]	−0.131*** [−0.254, −0.008]	−0.212*** [−0.317, −0.107]	−0.179** [−0.296, −0.093]	–
R² (Adj-R²)		9.1% (7.1%)	10.5% (8.2%)	9.8% (7.5%)	9.3% (6.7%)	5.1% (2.2%)

Significant values, as defined by p-value, highlighted in bold.

* p < 0.05.
** p < 0.01.
*** p = 0.001.

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neural lateralization may reflect some qualitative difference between people with current depression symptoms and a history of early childhood adversity. For example, in women, there are apparently long-term cortisol-mediated effects on frontal-amygdala connectivity as a result of childhood adversity, which are not related to current psychopathology (Burghy et al., 2012).

One of the robust predictors of PTSD onset is the building block effect (Neuner et al., 2004; Wilker et al., 2015), where the likelihood of PTSD increases with the number of different types of traumatic events. In this experiment, this has been related to stronger right relative power across delta, theta, and alpha bands. This is congruent with the notion that there is a lateralized frontal regulation of HPA axis response. Baeken, Vanderhasselt et al. (2011), showed that right-sided stimulation of frontal regions increased salivary cortisol in people with high anxiety levels. Chronic exposure to traumatic events could naturally potentiate right up-regulation of the HPA axis. This interpretation is supported by the consistent interaction of hyperarousal and number of trauma events in predicting stronger relative right-sided frontal activity in theta, alpha and beta bands. In this view, repeated exposure to traumatic events across the lifespan increases the probability of being in a constant state of readiness against external threat. Stronger relative right left-right imbalance would reflect this. Although we did not measure cortisol directly, given the fact that cortisol secretions alters throughout the day (Fries, Dettenborn, & Kirschbaum, 2009), it is possible that there is a systematic relationship between frontal activity and time of EEG measurement. Tests of this did not yield significant results.

A higher number of Aggressive Life Events predicted both increased relative right theta power and, in interaction with hyperarousal, increased relative right delta power. The interpretation of these differences is difficult, as the functional meaning of these frequency bands is not clear, nevertheless the difference between traumatic and Aggressive Life Events in soldiers supports the notion that aggressive acts are not necessarily equivalent to traumatic events in experienced soldiers (Elbert et al., 2017). This is in accord with a previous experimental study of male students, provoking appetitive aggression, which also showed an increased left desynchronization in the delta band (Moran, Weierstall, & Elbert, 2014). Though this earlier study also showed a left desynchronized alpha band, which was not found in this sample.

The interpretation of the above results for the main effects and interactions have, for the sake of simplicity, equated higher relative oscillatory power in one hemisphere with greater activity there. The opposite could also be true, where desynchronization in a given frequency band actually reflects greater activity in the relevant region. It is in fact conventionally understood in the case of alpha band oscillations, that greater power in one hemisphere represents a relative inhibition of that hemisphere (Harmon-Jones & Gable, 2017). Future experiments examining PTSD subsymptoms and life events should triangulate methods to make oscillatory power in a given band more interpretable, e.g. with fMRI, or rTMS.

Other studies have found differences between PTSD and controls in beta band activity (Begić et al., 2001; Cohen et al., 2013; Jokić-Begić & Begić, 2003). In our data, soldiers who have a history of traumatic experiences, and a currently higher level of intrusions were also more likely to have a relatively stronger beta band activity in left as opposed to right frontal regions. This could be related to memory, as regulation of memory encoding has been shown to take place in higher alpha/beta frequency bands in left prefrontal regions (Hanslmayr et al., 2014; Rossi et al., 2011). Conversely, right DLPFC has been related to recall (Turriziani et al., 2012). Of additional relevance to PTSD, specifically recall of emotional memory is specifically associated with right prefrontal regions (Bisby et al., 2015). In contrast to our results in the beta band, another oscillatory study found only right theta activity associated with recall (Waldhauser et al., 2012). Insofar as PTSD can be conceptualized as a disorder of memory (Elbert et al., 2006), one would predict dysfunction in both aspects of memory. The fact that our results show stronger left activity in beta bands would therefore indicate a

consistent problem with the encoding aspect of memory in people with PTSD, and an adaptation of experimental paradigm using these oscillatory landmarks to a PTSD sample could help to understand problems in memory processing of people with PTSD.

Since different frequency bands have different functions (Buzsáki, 2009; Knyazev, Slobodskoi-Plyusnin, Savost'yanov, Levin, & Bocharov, 2010), the fact that overall activity is similar across frequency bands requires comment. This may be a function of the resting state task, where there is no external stimulation to perturb the resting rhythms of the brain. With a provocation, one might see more variety across different frequency bands. Indeed, many researchers looking at frontal alpha asymmetry as a biomarker for clinical disorders contrast resting state activity with response to a stimulation (Allen & Reznik, 2015) e.g. an emotional challenge task distinguishes alpha asymmetry in depression (Stewart, Coan, Towers, & Allen, 2011), and PTSD showed similar changes in response to emotional pictures (Rabe et al., 2006).

The present study has several limitations and unanswered questions. One factor requiring explanation is the consistent right-lateralized influence of brain injury. Given that brain injury encompasses head injury, concussion, meningitis and epilepsy, there is no reason to expect these disorders to consistently target one side of the frontal lobes. It is possible that certain resting state networks are by their nature lateralized, and that any injury generally strengthens or weakens it. Another interpretive issue is the assumption that oscillatory activity measured at the scalp taps primarily stable dorsolateral prefrontal cortical activity, based on previous source analysis (Spielberg et al., 2011), and TMS manipulation of DLPFC (Baeken, Van Schuerbeek et al., 2011; Baeken, Vanderhasselt et al., 2011; Baeken et al., 2014), nevertheless, we cannot rule out alternative interpretations of the activity origins. A measure of dissociation as a PTSD subsymptom was not present in this study. Dissociation is a complex concept, encompassing many phenomena (e.g. depersonalization to out-of-body experiences), with many theoretical interpretations (Schauer & Elbert, 2010). It has been operationalized as a breakdown in the integration of consciousness, with delta as a candidate marker of functional deafferentiation. For example, Ray et al. (2006) interpret stronger delta band activity found in left frontal regions as a functional deafferentiation. They found a preponderance of slow wave activity in an area important for memory encoding and executive function is held to reflect the inability of people with PTSD to verbally articulate traumatic memories. Future studies of functional activity in PTSD groups should include some measures of dissociation in addition to the canonical symptoms outlined in DSM 5. The relatively low rates of PTSD reported in clinical interviews were unexpected, given the high trauma load. It is possible that this reflects resilience, alternately, the soldiers were recently returned from a relatively peaceful campaign in Somalia, and this may have influenced their momentary perspective. Being a soldier confers high social status, good pay, and the benefits of social support via camaraderie, the latter act as a bulwark against PTSD development (Feder et al., 2013). These present no problems for the statistical analyses, which were chosen to be robust to skewed data. Some measure of fatigue, e.g. number of hours of sleep, over the previous few days would have provided extra control in the EEG measures. Additionally, we did not quantify illiteracy levels, which are generally high in the population of the country. This may add an extra source of confounding in the EEG data, as this has been shown to affect functional brain activity (Dehaene, Cohen, Morais, & Kolinsky, 2015).

Our results highlight the necessity of considering PTSD symptom clusters individually, as they predict different oscillatory patterns in frontal regions, and also the importance of integrating lifetime trauma- and aggression-related events as well as type and timing effects of childhood adversity. It is apparent that people with early childhood adversity who currently manifest stronger symptoms and mood, have a stronger left left-right imbalance in frontal activity across delta, theta, alpha and beta bands. In contrast, those who have a lifetime history of trauma events and concurrent higher hyperarousal symptoms show a

stronger right left-right imbalance across theta, alpha, beta, and gamma bands. People who have a history of lifetime trauma events and current intrusion symptoms more likely have a stronger left left-right imbalance specifically in higher frequency beta bands. These differences can be related to the different roles that frontal regions play in both stress regulation and memory encoding and retrieval. Future research could examine frontal modulation of memory encoding/retrieval and stress response with respect to the differential impact of different sub-symptoms and life events.

Disclosure statement

The authors have no conflict of interest to declare.

Author contributions

JKM, RW, TE, and CW designed the study; JKM, CW, AC, CN, UL, and MB collected the data, JKM, RW, TE, CW analysed the data, all authors contributed to the written article.

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