Early Sexual Trauma Exposure and Neural Response Inhibition in Adolescence and Young Adults: Trajectories of Frontal Theta Oscillations during a Go/NoGo Task

RH = Trauma and Neural Response Inhibition

Editorial
Clinical Guidance

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ABSTRACT

Objective: Trauma, particularly when experienced early in life, may alter neurophysiological and behavioral development, thereby increasing risk for substance use disorders and related psychopathology. However, few studies have empirically examined this using well characterized developmental samples that are followed longitudinally.

Method: We examined the association of assaultive, non-assaultive, and sexual-assaultive experiences prior to age 10 with developmental trajectories of brain function during response inhibition, by measuring electrophysiological theta and delta oscillations during No-Go and Go conditions in an equal probability Go/No-Go task. Data were drawn from the Collaborative Study of the Genetics of Alcoholism (COGA) prospective cohort, comprising offspring from high-risk and comparison families who were aged 12-22 at enrollment, with follow ups at two-year intervals since 2004. Additionally, we investigated other important predictors of neurophysiological functioning (eg, substance use, impulsivity, parental alcohol use disorders). Finally, we examined associations of neurophysiological functioning with alcohol and cannabis use disorder symptom counts (AUDsx, CUDsx), and externalizing (EXT) and internalizing (INT) psychopathology.

Results: Individuals exposed to sexual assaultive trauma prior to age 10 had slower rates of change in developmental trajectories of No-go frontal theta during response inhibition. Importantly, effects remained significant after accounting for exposure to other traumatic exposures, parental history of AUD and participants' substance use, but not measures of impulsivity. Further, slower rates of changes in No-go frontal theta

adolescent and young adult development were associated with increased risk for AUDsx and INT, but not CUDsx or EXT.

Conclusion: Childhood sexual assault is associated with atypical frontal neurophysiological development during response inhibition. This may reflect alterations in frontal lobe development, synaptic pruning and/or cortical maturation involving neural circuits for inhibitory control. These same areas may be associated with increased risk for young adult AUDsx and INT. These findings support the hypothesis that changes in neurocognitive development related to early sexual trauma exposure may increase risk for mental health and substance use problems in young adulthood.

INTRODUCTION

Approximately 1 in 4 adolescents in the United States is exposed to a traumatic event prior to age 16[1]. Those who experience early life trauma have greater lifetime risk for substance use disorders and related mental health problems (ie, depression, anxiety[2–4]). Researchers have suggested that trauma, particularly when experienced early in life, may alter neurobiological and behavioral development, thereby increasing risk for later onset of psychopathology[5], including substance use disorders (SUD)[6,7]. Several cross-sectional studies have reported associations between childhood trauma exposure and neurobiological and cognitive alterations[8–10]. Further, many of these same neurocognitive alterations are also correlates of mental health and substance use disorders[6,7]. While it has been suggested that the links between early trauma exposure and later mental health and substance use problems are related to such neurocognitive alterations, few studies have empirically examined this. Therefore, the longitudinal effects of early trauma exposure on neurocognitive development, and the impact such effects may have on risk for later mental health and substance use disorders, remain largely unknown.

Advances in understanding typical brain development have begun to elucidate why early traumatic experiences may have such a profound influence on neurobiological and behavioral development[11,12]. The brain undergoes its greatest growth and development in the first years of life, with a second phase beginning in adolescence characterized by synaptic pruning, leading to anatomical and functional maturation[13–16]. This second

phase of development is most profound in frontal lobe regions of the brain involved in higher order cognitive functions, including top-down control functions, such as inhibition and other aspects of executive function. This phase is also accompanied by broader developmental changes, including pubertal development which has also been shown to influence cortical maturation and synaptic pruning throughout this period[17,18]. It is therefore important to understand whether early trauma exposure predicts differential patterns of brain development during this second maturational phase, a period of great susceptibility to environmental influences, and if such effects are associated with increased susceptibility to mental health and substance use problems.

Studies examining the effects of early life stress on brain development have mainly implicated neural stress reactivity and emotional processing/regulation pathways[5,19–23], indicating that those exposed to early life stress exhibit deficits in cognitive and behavioral control, selective attention, and reward processing [21,24–27]. Cognitive tasks such as the Go/No-Go (GNG) task, which requires selective attention and behavioral inhibition, may be particularly relevant to the assessment of neural functioning in individuals exposed to early trauma[28,29]. The GNG task requires activation of several brain networks including the executive network[29], which facilitates the detection, monitoring, and resolution of conflict between two competing response tendencies, execution (Go) and refraining from execution (No-go) of a motor response, therefore reflecting behavioral execution and inhibition[30–33]. Behavioral inhibition is an essential regulatory executive control undergoes substantial development during adolescence and persists through young adulthood[34]. This is one developmental process that may be

altered in those exposed to early life trauma[20,35]. To date, two functional magnetic resonance imagining (fMRI) studies have investigated response inhibition via the GNG task in adolescents exposed to different types of early trauma or adversity (eg, abuse, neglect, or witnessing parental violence[36]; neglect, maltreatment, or multiple foster placements prior to adoption[37]). In both studies, decreased behavioral inhibition, and activation differences in the pre-frontal cortex were observed among trauma exposed subjects.

Studies that have examined the influence of child maltreatment utilizing electroencephalography (EEG) have the advantage of temporal resolution on the order of milliseconds, a scale at which many relevant sensory, motor, and cognitive phenomena take place at the neural level[38–41]. Brain oscillations of different frequency bands are related to various cognitive functions[42–44], and task-related event-related oscillations (EROs) provide both time and frequency information for a specific sensory, motor, or cognitive event. Howells et al.[38] reported altered cortical arousal during GNG task performance among adults who retrospectively reported different types of childhood trauma exposures. Findings were dependent on the form of childhood trauma experienced; for example, child emotional abuse was correlated with increased theta activity during the GNG task. Other electrophysiological studies conducted in children exposed to psychosocial deprivation[39] or other severe forms of neglect also found increased resting-state theta activity, and decreased resting-state alpha and beta activity[40,45]. In one of the few longitudinal studies conducted in this area, McLaughlin and colleagues[40,41] reported lagged developmental trajectories of frontal resting-state

EEG from 9 months to age 8 among children reared in Romanian institutions, many of whom were exposed to severe neglect. Importantly, this study also demonstrated that these changes predicted hyperactivity, impulsivity, and internalizing symptoms at age ~4.5. Collectively, these findings have been interpreted as representing a maturational delay in cortical development associated with severe early life stress[39–41,46–52].

Previous research suggests that exposure to early childhood trauma is associated with a developmental lag in cortical arousal and relatedly behavioral inhibition, and that these neural responses may increase risk for later onset of psychopathology, including mood, anxiety disorders, and behavioral disorders[39–41,46–52]. However, no study to our knowledge has explicitly examined this prospectively through emerging adulthood, the period of highest risk for the onset of many of these disorders. The studies that have examined similar questions regarding the legacy of early trauma on neurodevelopment[21,40,41,49,50,53] have primarily relied on data from the Bucharest Early Intervention Study, which focuses on early development (ages 9 months through 8 years), but not thereafter. This leaves unknown whether early life stress influences adolescent and young adulthood neurodevelopment and/or increases risk for young adult mental health and substance use problems. Further, this literature has been limited by several methodological factors, including relatively small study sizes (N<200), cross-sectional and/or retrospective nature of most of these data, and the robustness of these associations to other confounding factors, including participants' psychopathology, substance use, family history, and several key socio-demographic characteristics. In addition, no study to our knowledge has incorporated information on

parents' psychopathology, which often co-occurs with adverse childhood experiences, and has been shown to influence neurodevelopment and risk for mental health problems[54,55]. These factors pose serious challenges when attempting to disentangle which neurobiological effects are due specifically to early traumatic experiences, and if those particular neurobiological changes influence risk for mental health and substance use problems.

The current study investigates the associations of non-assaultive, assaultive, and sexual-assaultive trauma exposure prior to age 10 with developmental trajectories of frontal theta oscillations and posterior delta oscillations during No-go (response inhibition) and Go conditions. Data are from a longitudinal, developmental sample of adolescents and young adults from the Collaborative Study of the Genetics of Alcoholism (COGA) prospective cohort. A second aim is to examine the role of parental history of alcohol use disorders, as well as participants' substance use, impulsivity, gender, and race/ethnicity, in these associations. A third aim is to assess whether trauma-associated neurophysiological trajectories influence risk for alcohol and cannabis use disorders (AUD, CUD), and/or related internalizing and externalizing psychopathology.

Method

Sample

COGA's prospective study began data collection in 2004 and is on-going. Details on

data collection and procedures have been published previously[56]. Briefly, offspring from families densely affected with alcohol use problems and comparison community families who were aged 12-22 at intake, and who had at least one parent interviewed in an earlier phase of the COGA study, were enrolled, with new subjects added as they reach the age of 12. Subjects were interviewed every two years with a comprehensive battery that includes the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA[57]) covering substance use problems as well as other psychiatric disorders and related behavior, personality questionnaires, family history of alcohol use problems, and a neurophysiological battery. An age appropriate SSAGA (cSSAGA[58]) was used for subjects under age 18. At the time of analysis, the current study presents data on 2,625 offspring from 2,413 nuclear families who had at least one follow-up interview; 1931 participants had a third assessment, 1324 a fourth assessment, 842 had a fifth assessment, 428 had a sixth assessment, and thus far 8 participants have had a seventh assessment (N.B., data collection is ongoing). Among the 2,625 offspring analyzed, the mean age at baseline was 17.1 (SD=3.6, Range=12-26), 50.7% were female, and self-reported race/ethnicity was 29.2% African American, 62.0% Caucasian, and 9.0% Asian, Pacific Islander, or “other”. Analytic sample details are provided in Table 1.

Experimental protocols were approved by each site's institutional review board, and informed consent was obtained from all participants. Participants were excluded from neurophysiological assessment if they had any of the following: (1) Positive breath-analyzer test and/or urine screen, (2) hepatic encephalopathy/cirrhosis of the liver, (3)

history of head injury, seizures or neurosurgery, (4) uncorrected sensory deficits, (5) history/symptoms of psychoses, (6) self-reported positive test for human immunodeficiency virus, (7) other acute/chronic medical illnesses that affect brain function, or (8) psychotropic medications that affect electrophysiological measurement.

Measures

Traumatic Exposures

Traumatic exposures were collected using the SSAGA[57] and have been described previously[56,59]. The SSAGA included 21 potentially traumatic events. Several events were excluded from the current study since they did not occur prior to age 10 (eg, combat related trauma). All events used in the current analysis are detailed in Table S1, available online. Based on evidence that interpersonal assaultive events have a stronger and more enduring effect on mental health/substance use than non-assaultive events[60–62], that traumatic events cluster together[63], and to remain consistent with prior studies[59], three composite variables were examined, representing report of one or more lifetime **assaultive** traumas (ie, stabbed, shot, mugged, threatened with a weapon, robbed, kidnapped, held captive), **non-assaultive** traumas (ie, life-threatening accident, disaster, witnessing someone seriously injured or killed, and unexpectedly finding a dead body), and **sexual assaultive** traumas (ie, rape or molestation by relative or non-relative). Importantly, age at occurrence of each event was recorded, and this information was utilized in the current study. We focused on traumatic events occurring prior to age 10, given the suggestion that trauma exposure at early stages of development may be more influential than later exposures for neurobiological

development and the onset of later psychopathology[23,64,65], as well as our desire to measure events that *preceded* measurement of neurophysiological and behavioral outcomes. Any trauma experienced after age 10 was combined into a binary measure that was used as a covariate in all models, since trauma exposure is known to re-occur throughout the lifecourse[66].

Parental AUD status

Parental AUD was a lifetime measure based on available parent SSAGA interviews (60.8% of fathers and 89.8% of mothers) as described previously[56,59]. For parents who were not interviewed, reports about the parent's alcohol problems obtained in earlier COGA waves from other relatives or, less commonly, from their offspring during the prospective study assessment, were used to code as affected parents with at least two positive family history reports based on the Family History Assessment Module[67]. Maternal and paternal variables were combined to represent lifetime AUDs in one or both parents.

Substance use and Psychopathology

Data from all offspring SSAGA and cSSAGA interviews were used to obtain lifetime reports of alcohol and cannabis use as previously detailed [56,59]. Participants' alcohol use disorder symptom count scores (AUD) and cannabis use disorder symptom count scores (CUD) were based on DSM-5 lifetime symptom counts. Internalizing psychopathology count scores (INT) included DSM-IV lifetime diagnoses for major depressive disorder, panic disorder, social phobia, and one additional item -- suicidal

ideation. Externalizing psychopathology count scores (EXT) included conduct disorder and oppositional defiant disorder diagnoses. Data from each individual's most recent interview was used.

Barratt Impulsiveness Scale (BIS)

The Barratt Impulsiveness Scale (Version 11) is a 30-item scale that measures three aspects of impulsivity: attentional impulsiveness, motor impulsiveness, and non-planning[68]. All items are answered 1 (never), 2 (occasionally), 3 (often), or 4 (always). Separate scales were developed for adolescents and adults. Total scores were computed by summing subscale items. Data from each individual's baseline interview were used.

Sensation Seeking Scale (SSS)

The SSS measures individual differences in stimulation and arousal[69] and assesses: boredom susceptibility, thrill and adventure seeking, experience seeking, and disinhibition. Total scores are computed by summing all 30 items. Data from each individual's baseline interview were used.

Theta ERO Power (Go/No-go)

Using the protocol described in Pandey *et al*., 2012 and 2015[70,71], each participant was presented with four types of visual stimuli consisting of white isosceles triangles pointing in either the up, down, right, or left direction. The stimuli were presented for 100 ms at the center of a computer screen (17″ diagonal, 75 Hz refresh rate, 1024 × 768

resolution) against a dark background that subtended a visual angle of approximately 1°. In the practice session, participants were inst ructed to press a key whenever a white triangle pointed either up or down (Go stimulus) and refrain from pressing the key whenever the triangle pointed towards the right or left (No-go stimulus). A dollar sign ($) appeared on the screen for 200 ms at 1200 ms after stimulus onset when participants responded correctly, whereas a cross sign (X) appeared on the screen for 200 ms at 1200 ms after stimulus onset when participants responded incorrectly. Participants were instructed that speed and accuracy were equally important for making a correct response. In the next phase, the experimental phase, EEG was recorded. Participants were informed that each correct response would earn a reward. However, each subject received a predetermined fixed amount at the end of the experiment without deductions for errors, although they were not informed of this while performing the task. The probabilities of occurrence of Go and No-go stimuli were equal (50/50), and the order of stimulus presentation was randomized. The inter-trial interval was 2400 ms. Go and No-go accuracy as well as Go reaction time at each of the assessments were also recorded and used in statistical analysis.

Participants were comfortably seated in front of a computer monitor screen placed one meter away in a dimly lit sound-attenuated RF-shielded room (IAC, Industrial Acoustics, The Bronx, NY). The EEG was recorded on a Neuroscan System (Versions 4.1, 4.2, 4.3, 4.4 and 4.5; (Neurosoft, Inc., El Paso, TX) using a 61 channel electrode cap (Electro-cap International, Inc., Eaton, OH) that had electrode placements based on the extended 10–20 International System (Electrode Position Nomenclature, (Society,

1991)) with the notch filter off. The electrodes were referenced to the tip of the nose, and participants were grounded using an electrode placed on the forehead (frontal midline, 2 cm above nasion). Eye movements were recorded using a supraorbital vertical lead and a horizontal lead on the external canthus of the left eye. Electrode impedance was maintained below 5 kΩ throughout the recording. The continuous EEG signals were recorded marked with all stimulus, response, and feedback event codes at the sampling rates of 512 (16 bit A/D) or 500 Hz (32 bit A/D) depending on the amplifier version, with a band pass filter set at 0.02–100 Hz and were amplified 10,000 times using a set of amplifiers (SynAmps^2, Neuroscan, TX).

Given prior evidence indicating the importance of frontal theta oscillations during the No-go condition and posterior delta oscillations during the Go condition of the GNG task[38,70,71], and a preliminary analysis to determine time-frequency regions of interest, the current study utilized S-transformed frontal theta total power (4-7.5 Hz, 200-400 ms, Fz) during the No-go (response inhibition) and Go conditions, and for comparison, posterior delta total power (1-3.5 Hz, 200-500 ms, Pz), during the Go and No-go conditions at baseline and follow-up assessments 1-4. Further details about the ERO signal processing using S-transform method can be found in previous publications[72] (Note, previous study conducted in a different analytic sample) and in previous publications.[72]

Statistical Methods

We first estimated an unconditional growth model that predicted log transformed ERO

measures from baseline through the most recent assessment by age, incorporating individual participant's age at each follow up (Mplus option: time scores). This model specifies latent variables for the random intercept, the random slope for time (rate of change in ERO value by age), and a constant or individual deviation from these mean values. This approach allowed us to simultaneously estimate the variance in ERO both within and between individuals across time. The slope and residual variances were fixed to be equal across all available time points. Separate models were run for delta and theta ERO (total power) during the Go and No-go conditions.

We next examined time-invariant predictors of ERO trajectories. We simultaneously examined the association of three binary measures of trauma exposure prior to age 10 (non-assaultive, non-sexual assaultive, and sexual assaultive traumatic exposures) with ERO intercepts and slopes (linear change from baseline through follow-up 4). This is depicted in Figure 1. Initial results indicated no evidence of non-linear (ie, quadratic) effects. Modeling was conducted in Mplus version 7.4 (© Muthén and Muthén, 1998-2015), using full maximum likelihood estimation with robust standard errors. Age, gender (0: male, 1: female), and self-reported race/ethnicity (0: Non-Hispanic White, 1: Non-Hispanic Black/African American, 2: Other) were used as covariates in all analyses. In addition, we accounted for genetic relatedness among siblings. Subsequent models included participants' alcohol and cannabis use (0: Never used, 1: Ever used) at each interview, parental history of AUD, and participants' impulsivity as measured by baseline BIS and SSS. Finally, we evaluated whether residualized change in ERO from baseline to most recent follow-up was related to AUD, CUD, INT and EXT

at each participant's latest interview.

Results

Rates of traumatic exposure in COGA's prospective sample have been described previously[56,59]. When considering trauma experienced prior to age 10 (Table 1), 26.6% reported experiencing one or more type of trauma; 16.6% reported experiencing non-assaultive trauma, 4.5% reported experiencing assaultive trauma, and 6.6% reported experiencing sexual assault. Non-sexual assaultive trauma was more common among males ($p<0.05$), while sexual assaultive trauma was more common among females ($p<0.05$). Non-assaultive trauma exposure was higher among African-American participants as compared with Whites ($p<0.05$).

Individuals exposed to early trauma differed with respect to measures of impulsivity as measured by the BIS and SSS, substance use behavior and psychiatric symptoms (Table 2; note, associations were adjusted for gender, age of assessment, self-reported race, and parental history of AUD). Several associations withstood a Bonferroni multiple-test correction; sexual trauma prior to 10 was associated with cognitive impulsivity (BIS), AUD symptom count, CUD symptom count, INT and EXT. Assaultive trauma exposure was associated with INT, and non-assaultive trauma was associated with EXT symptoms (Table 2). Correlations among all variables are presented in Table S2, available online. Go and No-go accuracy, and Go reaction time on the GNG task did not differ significantly among participants (Table S3, available online).

Results from ERO models, including parameter estimates and fit statistics, are displayed in Table 3 and Table S4, available online. The only statistically significant effect observed involved sexual assaultive trauma prior to age 10 and No-go frontal theta. That is, when all three trauma exposures were examined simultaneously (Table 3), no statistically significant effects were observed for non-assaultive trauma, or non-sexual assaultive trauma, nor for oscillations in the Go condition. In models including gender, race/ethnicity, non-assaultive trauma, and non-sexual assaultive trauma as covariates, sexual assaultive trauma prior to age 10 was associated with decreased No-go frontal theta at baseline (Intercept, $p<.01$; Table 3) and a decreased rate of change in No-go frontal theta from baseline to follow-up 4 (Slope, $p<0.001$; Table 3). This is displayed in Figures 2 and 3. No significant effects were observed in the Go condition. Further, no statistically significant effects were observed for posterior delta ERO in either the Go or No-go condition (Table S4, available online).

Associations remained statistically significant when participants' alcohol and cannabis use were included in the model (Intercept, $p<.01$; Slope, $p<.001$; Table 3). However, when parental AUD was included in the model, only a decreased rate of change in No-go frontal theta from baseline to follow-up 4 was observed (Intercept, $p>0.05$; Slope, $p<.05$; Table 3). When cognitive impulsivity (BIS subscale, baseline assessment) was included in the model, associations were no longer statistically significant (Intercept, $p>0.05$; Slope>0.05). When additional pathways from the slope and intercept factors to INT, EXT, AUD sx, and CUD sx (age 18+) were included in the model, the rate of

change in No-go frontal theta was positively associated with INT and AUD sx at participant's latest follow-ups ($p<0.001$; Figure 2). In addition, models including intercepts as covariates were also examined and results remained largely unchanged (results available upon request).

Discussion

Although previous studies have reported associations among childhood trauma exposure and neurobiological alterations[9,10,21,41,74–76], it remains unclear to what extent childhood trauma influences adolescent and young adult neurodevelopment, and whether these effects influence risk for the onset of psychopathology in young adulthood. Findings from the current study suggest that individuals exposed to sexual assaultive trauma prior to age 10 have atypical developmental trajectories of neurophysiological functioning during response inhibition (No-go); the typical decrease in frontal theta oscillatory activity during response inhibition (No-go) observed throughout adolescence and young adulthood occurs at a slower rate among those who have been exposed to early sexual assault. Importantly, these effects remained significant after accounting for parental history of AUD and participants' substance use (note, intercept differences were no longer significant when parental AUD was included in the model, see Table 3, Model 3). However, effects were no longer significant when aspects of impulsivity were included in the model, suggesting that impulsivity may have an important role in the relation of early sexual trauma and frontal theta development during response inhibition. In addition, change in frontal No-go theta trajectories was

associated with AUD symptom count and internalizing psychopathology (depression, anxiety, and suicidal ideation) in young adulthood.

Associations of trauma and No-go Theta ERO

Gradual decreases in frontal theta oscillations during response inhibition across adolescence and young adulthood were observed among all study subjects. Previous developmental ERO studies[77–79] have observed similar decreases in oscillatory power globally, likely reflecting synaptic pruning (ie, fewer, but more efficient connections) which occurs rapidly during adolescence and continues through young adulthood[80–83]. This may also correspond with grey matter development and the progressive maturing of the prefrontal cortex as it assumes greater control over neural processing throughout adolescence and young adulthood[84–86].

Findings from the current study suggest that individuals exposed to sexual assaultive trauma prior to age 10 have atypical developmental trajectories of frontal theta oscillations during response inhibition; the decrease in frontal theta power throughout adolescent and young adult development occurs at a slightly slower rate. This perhaps suggests that children exposed to early sexual assault may have atypical frontal cortical development that may be characterized by altered rates of synaptic pruning and grey matter production, which in turn may impact the development of top-down control over neural processing throughout adolescence and young adulthood. Research conducted in rodent models found that the enduring effects of early isolation and maternal separation on brain development may be a consequence of an arrested phase of

synaptic overproduction[81]. This is in agreement with previous studies in humans which found maturational delay in cortical development associated with severe early life stress[39–41,46,48,50,52,76,87–91].

Further support comes from studies showing association between childhood sexual abuse, cognitive deficits and increased behavioral disinhibition[20,35,92]. In the current study, individuals exposed to early trauma also displayed higher rates of impulsivity as measured by the Barratt Impulsiveness Scale (BIS) and Zuckerman's sensation seeking scale (SSS). Interestingly, statistically significant differences in impulsivity and sensation seeking were most pronounced among those who had experienced sexual assault. When these measures of impulsivity were considered in the association of early sexual trauma and trajectories of frontal No-go theta power, effects of early sexual trauma were no longer statistically significant. There are at least two possible explanations for this. First, impulsivity may mediate the relation of early sexual trauma and frontal No-go theta development. Alternatively, impulsivity may be a shared risk factor for early trauma exposure and atypical neurodevelopment. Thus, participants in this study who had experienced sexual assault prior to age 10 show both atypical trajectories of frontal No-go theta power (possibly delayed frontal cortical maturation and synaptic pruning in neural circuits involved in response inhibition), as well as heightened levels of impulsivity and sensation seeking (ie, behavioral disinhibition). There is also the possibility that frontal No-go theta activity might mediate the relationship between early sexual abuse and impulsivity, which the timing of the assessment of trauma exposure, impulsivity (BIS and SSS), and No-go frontal theta preclude the testing of this

hypothesized mediation model in the current study. Future studies are needed to disentangle the influence of behavioral aspects of impulsivity with frontal theta oscillatory activity during response inhibition in the context of trauma exposure.

Results from the present study also indicated that sexual-trauma-related change in frontal No-go theta trajectories influenced risk for young adult AUD symptom count and internalizing psychopathology, but not CUD symptom count or externalizing psychopathology. Taken together, these findings support the hypothesis that early sexual trauma exposure may influence risk for psychopathology (ie, depression, anxiety, suicidal ideation, alcohol use disorders), in part through neurodevelopmental mechanisms. However, future longitudinal studies are needed to further characterize the potential moderating and/or mediating effects of neurodevelopmental trajectories in the associations of early trauma and later psychopathology. More research is needed to examine other aspects of neural functioning during response inhibition, and other aspects of stress-reactivity, including executive control and reward processing.

Interestingly, non-sexual assaultive trauma and non-assaultive trauma exposure prior to age 10 were not associated with developmental trajectories of theta ERO. This may indicate that while exposure to these traumas clearly has adverse mental and physical health consequences, exposure to early sexual abuse may be a particularly potent risk factor for neurocognitive development, behavioral disinhibition, and subsequent internalizing and alcohol use pathology. This is in agreement with prior evidence that interpersonal assaultive events have a stronger and more enduring effect on substance use and psychopathology than non-assaultive events[60,62]. In addition, GNG behavioral

data (ie, Go and No-go accuracy, and Go reaction time on the GNG task) did not differ among participants exposed to trauma (Table S4, available online). This is in agreement with previous work[71,93,94] that demonstrates that differences in neural oscillations during task performance (eg, No-go frontal ERO) may be observed even when behavioral differences are not (eg, no performance errors), suggesting that one major strength of ERO data is detection of extremely subtle effects occurring at the neural level, which have important implications for neurocognitive functioning and risk for psychopathology. It should be noted however, that No-go frontal ERO and performance on the GNG task are significantly correlated-- suggesting that frontal theta ERO is relevant to task performance, although this is not reflected in a statistically significant behavioral difference among the trauma exposure groups. In the context of the current study, the atypical frontal ERO during No-go observed in individuals who are trauma exposed may be a subtle index of risk for psychopathology, and suggests less efficient neural processing during response inhibition, necessitating the use of alternate neural strategies to as effectively inhibit their responses in the GNG task. Also of note is the effect of parental history of AUD on the associations of trauma exposure and No-go frontal theta ERO. Given previous evidence that decreased No-go frontal theta ERO is observed among individuals with a family history of AUD, this suggests that the association of sexual assaultive trauma exposure prior to age 10 with a slower rate of change in developmental trajectories of frontal oscillations during response inhibition (No-go frontal theta power) across adolescence and young adulthood remains after accounting for mean level differences in No-go frontal theta power due to familial risk for AUD. Future studies should investigate the extent of these findings among individuals

with a family history of AUD and among community control families.

These findings should be considered in light of several caveats. First, the sample consists of offspring primarily from high risk, densely AUD-affected families, and as such findings may not be generalizable to other populations. Second, although data across multiple waves of assessment were included in the analyses, some individuals who may have eventually developed AUD, CUD, internalizing or externalizing problems are treated here as unaffected. Third, effects of maternal AUD present in 45.3% of the analytic sample may reflect in part in utero exposure to alcohol (which is unknown for most offspring), which may impact neurodevelopment. Fourth, the current study did not have information on the frequency or duration of specific traumatic exposures. Fifth, given the relatively low number of participants meeting criteria for post-traumatic stress disorder (PTSD) in this sample, PTSD was not incorporated into the current study. Finally, attrition of the sample due to participants who did not return for follow-up assessments may have impacted the current study's findings. A non-response analysis indicated that individuals who did not return for follow-up were younger ($p<0.001$) and were more likely to have had a diagnosis of alcohol dependence ($p<0.001$), and that fewer non-responders were exposed to assaultive ($p<0.001$) and non-assaultive trauma ($p<0.001$) and had a diagnosis of cannabis dependence ($p<0.001$); no differences regarding gender, race/ethnicity, impulsivity, sexual trauma exposure, or ERO values were observed. In light of the absence of attrition effects for the primary findings for sexual trauma exposure and ERO power, we believe that inferences made in this manuscript are likely to be sound. Relatedly, decreased sample sizes available in

follow-ups 4 and 5 may limit the statistical power of some complex models examined in this study, leading to the possibility of Type I and Type II errors. Despite these limitations, this is the first study to our knowledge to examine associations of early trauma exposure, neurophysiological developmental trajectories in adolescence and young adulthood, and risk for later psychopathology. This is particularly important since this is the peak age range for the onset of substance use and mental health related problems, and has been previously understudied. Further, information provided on clinical, behavioral, and familial influences enables characterization of neuro-behavioral functioning among a relatively large and racially/ethnically diverse sample.

In conclusion, findings from the current study suggest sexual assaultive trauma exposure prior to age 10 is associated with a slower rate of change in developmental trajectories of frontal oscillations during response inhibition (No-go frontal theta power) across adolescence and young adulthood, as well as increased levels of behavioral disinhibition. In addition, this atypical neurophysiological development, that may reflect delays in frontal cortical maturation and synaptic pruning, was associated with young adult internalizing and alcohol use problems. Taken together, these findings support the hypothesis that changes in neural development related to early sexual trauma exposure may increase later risk for mental health problems. These findings highlight the importance of developing effective prevention strategies to reduce exposure to childhood sexual assault and to increase treatment following trauma exposure, as this early experience significantly increases risk for a cascade of mental and physical health problems throughout the individual's life-course. Researchers, clinicians and policy

makers should build on ongoing work aimed at identifying interventions and therapeutic strategies to mitigate risk associated with early sexual assaultive trauma exposure.

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Table 1. Analytic Sample Descriptive Statistics

	All Participants (N: 2625)	**Male Participants (N: 1286)**	**Female Participants (N: 1339)**
Mean age at baseline interview	17.1 (12.0-26.2)	17.2 (12.0-29.2)	17.2 (12.0-28.7)
Mean age at follow-up 1 (N:1931)	19.5 (13.3-32.2)	19.2 (13.3-32.2)	19.7 (13.8-31.6)
Mean age at follow-up 2 (N:1324)	21.7 (15.3-32.2)	21.7 (15.3-31.8)	21.8 (15.8-32.2)
Mean age at follow-up 3 (N:842)	23.4 (17.4-32.3)	23.5 (17.4-32.3)	23.3 (17.7-31.7)
Mean age at follow-up 4 (N:428)	25.1 (19.6-32.2)	25.0 (19.6-32.2)	25.2 (19.8-31.9)
Mean age at follow-up 5 (N:8)	27.9 (22.1-31.9)	27.4 (22.3-31.8)	28.4 (22.1-31.9)
Mean age at most recent interview	22.4 (12-32.0)	22.1 (12.0-32.0)	22.7 (12.0-32.0)
Self-reported race/ethnicity (%)			
White/Caucasian	62.0	61.9	62.0
Black/African-American	29.2	29.6	28.7
Other	9.0	8.6	9.3
Non-assaultive <age10(%)	16.6	18.0	15.3
Assaultive <age10 (%)	4.6	5.6	3.5
Sexual assaultive <age10 (%)	6.6	4.0	8.9
Parental history of AUD (%)	41.1	41.6	40.7
Alcohol ever use (%)	94.7	95.8	93.7
Cannabis ever use (%)	77.4	82.4	72.5
DSM-5 *AUD symptoms (% any)*	64.6	65.4	64.0
Mean (SD)	3.0 (3.6)	2.1 (2.4)	1.6 (2.3)
DSM-5 *CUD symptoms (any) (%)*	72.2	53.0	75.2
Mean (SD)	1.5 (2.7)	2.5 (3.0)	1.3 (2.4)
DSM-5 *INT symptoms (any) (%)*	38.7	32.5	44.6
Mean (SD)	0.4 (0.5)	0.3 (0.5)	0.5 (0.5)
DSM-5 *EXT symptoms (any) (%)*	16.8	19.4	12.0
Mean (SD)	0.2 (0.4)	0.2 (0.4)	0.1 (0.3)

Note: Assaultive traumas (ie, stabbed, shot, mugged, threatened with a weapon, robbed, kidnapped, held captive), non-assaultive traumas (ie, life-threatening accident, disaster, witnessing someone seriously injured or killed, and unexpectedly finding a dead body), and sexual assaultive traumas (ie, rape or molestation) prior to age 10. Internalizing (INT) psychopathology count scores included *DSM-IV* lifetime symptoms for major depressive disorder, panic disorder, social phobia, and one additional item--suicidal ideation. Externalizing (EXT) psychopathology count scores included conduct disorder and oppositional defiant disorder symptoms. Data from each individual's most recent interview was used. AUD = alcohol use disorder; CUD = cannabis use disorder.

Table 2. Associations of Early Trauma Exposure with Impulsivity, Substance Use and Psychiatric Disorder Symptoms

	Non-Assaultive Trauma <age10 [N:418]			**Assaultive Trauma <age10 [N:111]**			**Sexual Assaultive Trauma <age10 [N:121]**		
	B	*SE*	*p*	*B*	*SE*	*p*	*B*	*SE*	*p*
BIS: Total Score	0.69	0.95	0.47	1.04	1.67	0.53	**3.03**	**1.40**	**0.03**
Non-Planning	-0.25	0.41	0.54	0.73	0.73	0.32	**1.12**	**0.56**	**0.05**
Motor Impulsive	0.32	0.35	0.35	0.31	0.62	0.66	0.82	0.48	0.09
Cognitive Impulsive[a]	**0.82**	**0.32**	**0.01**	**1.31**	**0.57**	**0.02**	**1.21**	**0.45**	**<0.001**[a]
Zuckerman Score	0.19	0.64	0.77	0.79	1.15	0.49	**1.71**	**0.82**	**0.04**
Disinhibition	-0.07	0.24	0.79	-0.57	0.44	0.19	0.44	0.31	0.15
Boredom Susceptibility	-0.16	0.19	0.41	-0.08	0.34	0.81	0.43	0.24	0.07
Thrill Seeking	0.04	0.29	0.19	0.98	0.52	0.06	0.26	0.37	0.48
Experience Seeking	0.02	0.21	0.92	0.46	0.37	0.22	**0.57**	**0.27**	**0.03**
Ever drinking	-0.01	0.01	0.39	0.01	0.03	0.73	**0.05**	**0.02**	**0.04**
Ever used cannabis	-0.04	0.03	0.15	0.03	0.05	0.63	0.07	0.05	0.15
DSM-5 *AUD sx*[a]	0.13	0.15	0.40	**0.55**	**0.29**	**0.05**	**0.91**	**0.25**	**<0.001**[a]
DSM-5 *CUD sx*[a]	0.24	0.16	0.14	**0.75**	**0.31**	**0.02**	**1.00**	**0.27**	**<0.001**[a]
DSM-5 *INT sx*[a]	**0.06**	**0.02**	**0.01**	**0.33**	**0.05**	**<0.001**[a]	**0.20**	**0.06**	**<0.001**[a]
DSM-5 *EXT sx*[a]	**0.09**	**0.03**	**<0.001**[a]	**0.13**	**0.06**	**0.02**	**0.19**	**0.05**	**<0.001**[a]

Note: All associations are adjusted for gender, self-reported race/ethnicity, age of assessment, and parental history of alcohol dependence. Comparison groups are participants who were not exposed to any trauma type prior to age 10. Bolded font denotes significance $p<.05$. AUD = alcohol use disorder; BIS = ??; CUD = cannabis use disorder; EXT = externalizing INT = internalizing.

[a] denotes associations that withstood a Bonferroni multiple test correction (0.05/45 tests conducted for a $p<.001$).

Table 3. Effects of Early Trauma Exposure on the Developmental Trajectory of No-Go Frontal Theta Power From Baseline Through Follow-Up 4

Trauma Exposure <age 10	Model 1	Model 2	Model 3	Model 4
Non-Assaultive				
Intercept	-0.29 (1.50)	-0.29 (1.50)	1.22 (1.98)	0.59 (2.37)
Slope	-0.01 (0.07)	-0.01 (0.07)	-0.08 (0.09)	-0.01 (0.09)
Assaultive				
Intercept	-2.58 (1.56)	-2.58 (1.56)	2.36 (1.99)	3.05 (2.09)
Slope	0.09 (0.07)	0.09 (0.07)	-0.08 (0.08)	-0.09 (0.09)
Sexually Assaultive				
Intercept	**-4.41 (1.59)****	**-4.41 (1.59)****	-3.11(1.99)	0.13 (1.89)
Slope	**0.22 (0.07)*****	**0.22 (0.07)*****	**0.17 (0.08)***	0.03 (0.07)

Note: All models include age modeled via time scores; Model 1 *(Free Parameters: 20; AIC: 39270.74; BIC: 39387.91)* includes gender, race/ethnicity, and age; Model 2 *(Free Parameters: 24; AIC: 21607.93; BIC: 21713.31*) adds to covariates in Model 1 alcohol use and cannabis use; Model 3 *(Free Parameters: 26; AIC: 21601.10; BIC: 21725.64*) adds to covariates in Model 2 parental alcohol use disorder; Model 4 *(Free Parameters: 28; AIC: 12627.05; BIC: 12748.28)* adds to covariates in Model 3 participants' impulsivity as measured using the BIS and SSS. AIC = ??; BIC = ??; SSS = ??.
p*<.05; ***p*<.01*; *p*<.001

Figure 1. Effects of Early Trauma Exposure on No-Go Frontal Theta Power From Baseline Through Follow-Up 4 and Associations With Substance Use Disorder and Psychopathology

Note: Parameter estimates (and standard errors) are only displayed for statistically significant pathways. Not pictured, but also included in this model are the following covariates: gender, race/ethnicity, and age, alcohol use and cannabis use and parental alcohol use disorder. Internalizing (INT) psychopathology count scores included *DSM-IV* lifetime symptoms for major depressive disorder, panic disorder, social phobia, and one additional item--suicidal ideation. Externalizing (EXT) psychopathology count scores included conduct disorder and oppositional defiant disorder symptoms. Data from each individual's most recent interview was used.
*p<.05; **p<.01; ***p<.001.

Figure 2. Adjusted Mean Trajectories of No-Go Frontal Theta by Sexual Assaultive Trauma Exposure

Note: Models are adjusted for gender, self-reported race/ethnicity, age of assessment, and parental history of alcohol dependence. Comparison group includes participants who were not exposed to sexual trauma type prior to age 10 (93.4% of the analytic sample).

Figure 3. No-Go Frontal Theta by Early Sexual Assaultive Trauma Exposure

Legend: This figure depicts the differences in frontal theta No-go power values at baseline, observed among (a) participants who have not been exposed to sexual trauma prior to age 10 and (b) participants who have been sexually trauma exposed prior to age 10. Note, the more focused frontal topography and more efficient neural synchronization (ie, higher theta ERO power values) during response inhibition (No-go condition of the GNG task) among participants who have not been trauma exposed. In contrast, the frontal topography indicates a less efficient neural synchronization (ie, lower ERO power values) during response inhibition (No-go condition of the GNG task) among participants who have been trauma exposed.

Early Sexual Trauma Exposure and Neural Response Inhibition in Adolescence and Young Adults: Trajectories of Frontal Theta Oscillations During a Go/NoGo Task

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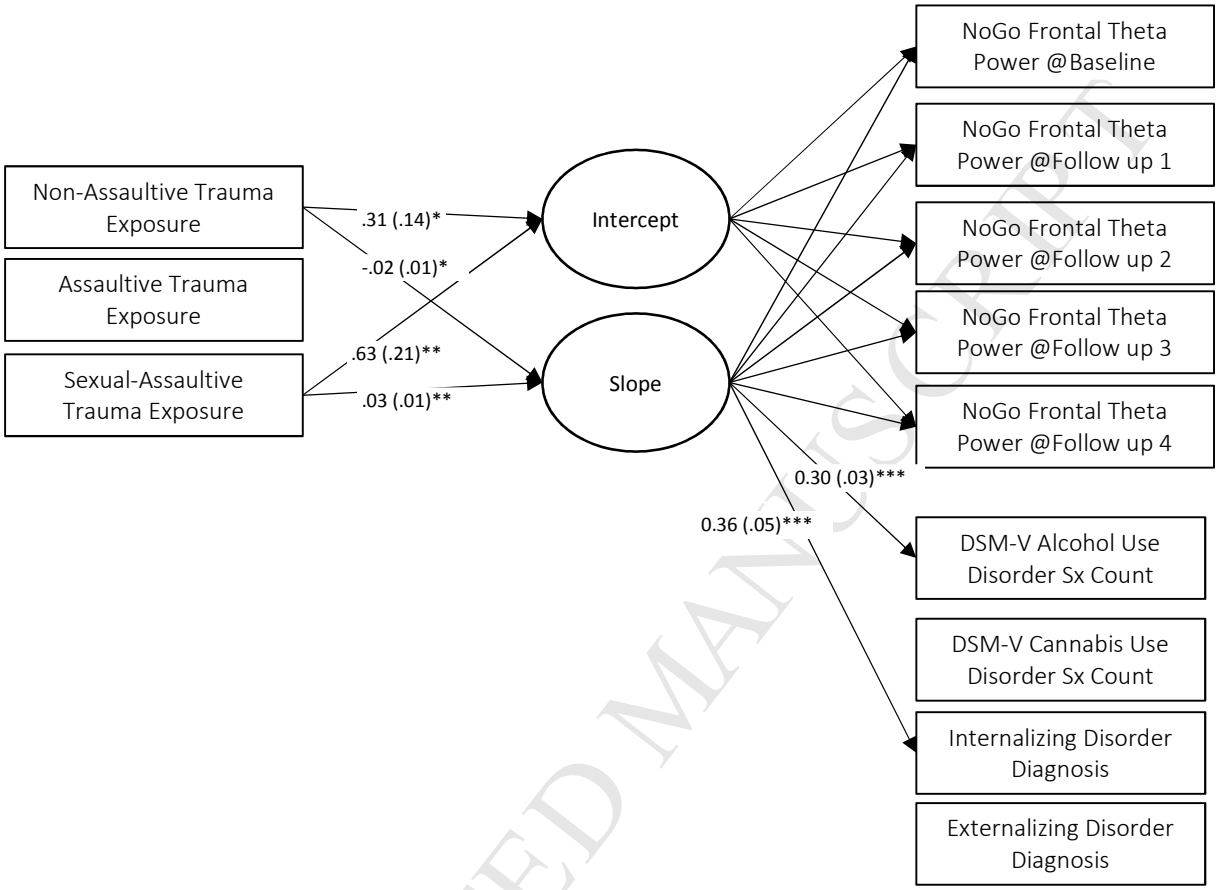
Disclosures:

Dr. Kuperman has served as a researcher of a double-blind placebo-controlled trial for Neurocrine. The medication is being tested as an alternative choice for adolescents with Tourette Syndrome. His involvement consisted of providing medical monitoring for two adolescent males, and the study is now over. There is no overlap with this study.

Dr. Bucholz reports that her spouse has a consulting relationship with a medical device company and holds several patents, but these are not related to the work presented here.

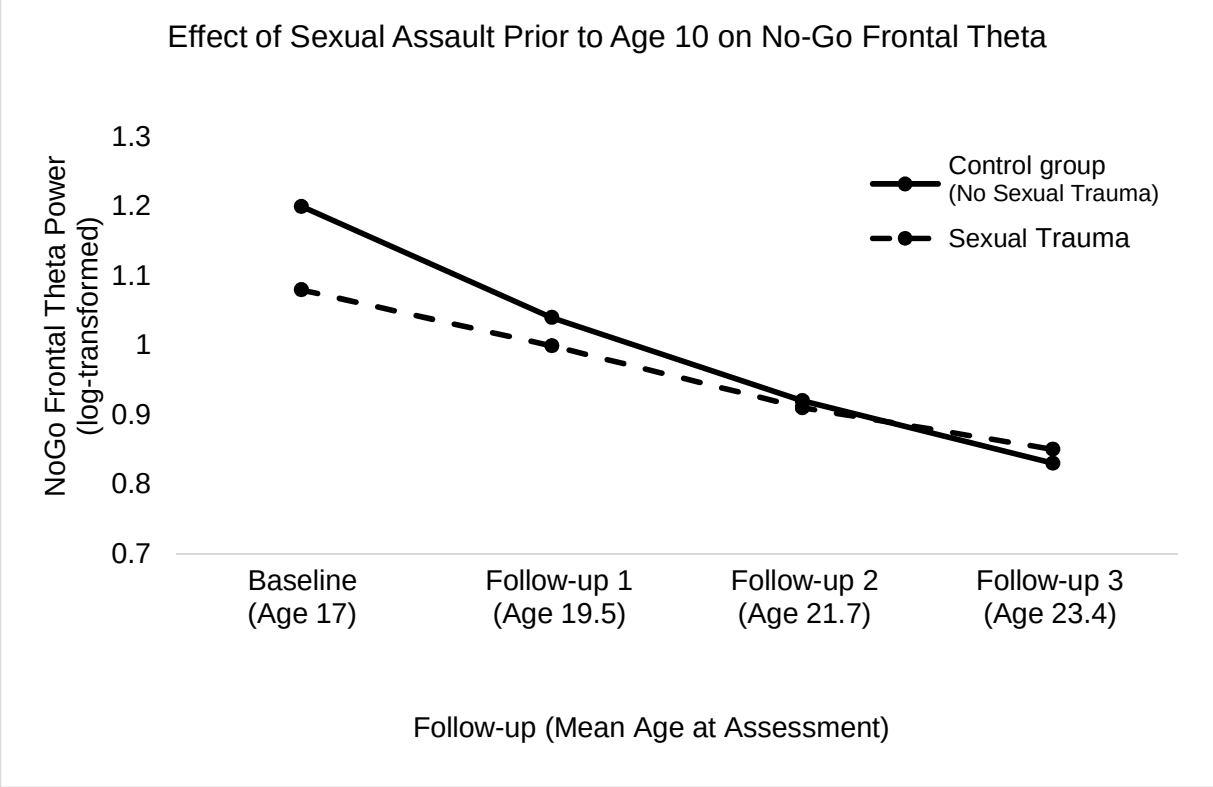
Drs. Meyers, McCutcheon, Pandey, Kamarajan, Salvatore, Pandey, Almasy, Anokhin, Bauer, Bender, Dick, Edenberg, Hesselbrock, Kramer, Agrawal, and Porjesz, Ms. Subbie, and Mr. Chorlian report no biomedical financial interests or potential conflicts of interest.

Figure 1. Effects of early trauma exposure on NoGo frontal theta power from baseline through follow-up 4 and associations with substance use disorder and psychopathology.



Note: *p<0.05, **p<0.01, ***p<0.001; Parameter estimates (and standard errors) are only displayed for statistically significant pathways. Not pictured, but also included in this model are the following covariates: gender, race/ethnicity, and age, alcohol use and cannabis use and parental AUD. Internalizing psychopathology count scores (INT) included DSM-IV lifetime symptoms for major depressive disorder, panic disorder, social phobia, and one additional item--suicidal ideation. Externalizing psychopathology count scores (EXT) included conduct disorder and oppositional defiant disorder symptoms. Data from each individual's most recent interview was used.

Figure 2. Adjusted Mean Trajectories of No-Go frontal theta by Sexual Assaultive Trauma Exposure



Footnote: Models are adjusted for gender, self-reported race/ethnicity, age of assessment, and parental history of alcohol dependence; Comparison group includes participants who were not exposed to sexual trauma type prior to age 10 (93.4% of the analytic sample).

Figure 3. No-Go frontal theta by Early Sexual Assaultive Trauma Exposure

Legend: This figure depicts the differences in frontal theta NoGo power values at baseline, observed among (a) participants who have not been exposed to sexual trauma prior to age 10 and (b) participants who have been sexually trauma exposed prior to age 10. Note, the more focused frontal topography and more efficient neural synchronization (i.e., higher theta ERO power values) during response inhibition (NoGo condition of the GNG task) among participants who have not been trauma exposed. In contrast, the frontal topography indicates a less efficient neural synchronization (i.e., lower ERO power values) during response inhibition (NoGo condition of the GNG task) among participants who have been trauma exposed.

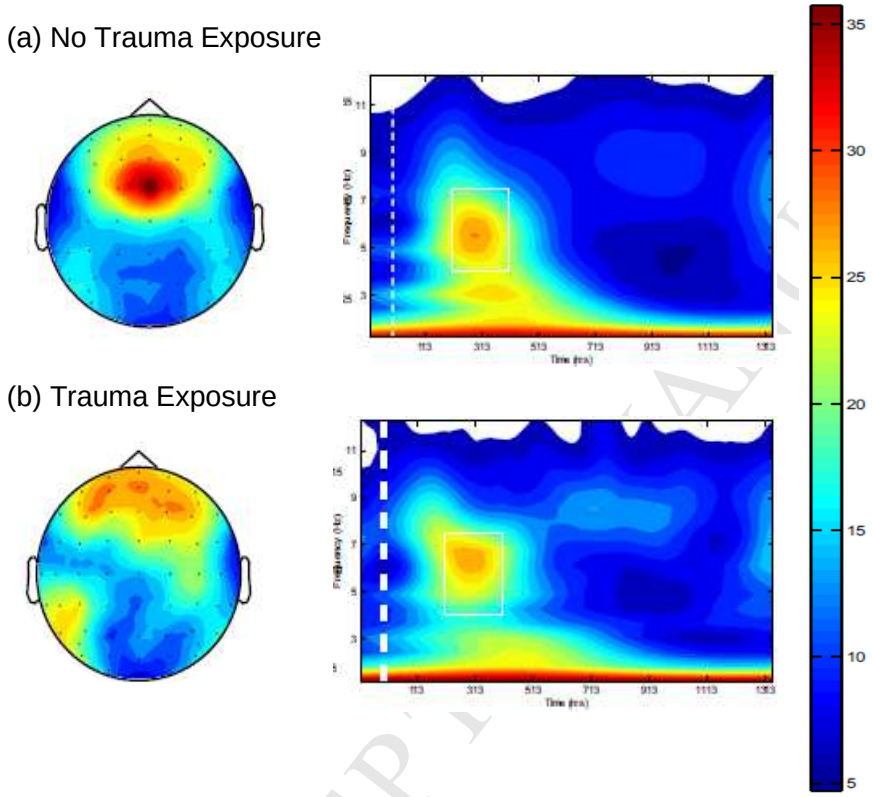


Table S1. Traumatic exposures Assessed in Current Study

1. Have you ever been shot?
2. Have you ever been stabbed?
3. Have you ever been mugged or threatened with a weapon, or experienced a break-in or robbery?
4. Have you ever been raped or sexually assaulted by a relative?
5. Have you ever been raped or sexually assaulted by someone not related to you?
6. Have you ever been in a natural disaster like a fire, flood, earthquake, tornado, mudslide or hurricane?
7. Have you ever been held captive, tortured, or kidnapped?
8. Have you ever been diagnosed with a life threatening illness?
9. Have you ever been in a serious accident?
10. Have you ever seen someone being seriously injured or killed?
11. Have you ever unexpectedly discovered a dead body?

Note: Several traumatic exposures (eg, combat related exposure) were excluded since they did not occur prior to age 10. Importantly, age at occurrence of each event was recorded, and this information was utilized in the current study.

Table S2. Pearson Correlation Coefficients

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)
(1) *Any Trauma*	1	0.81**	0.39**	0.44**	0.02	0.05*	0.13**	0.15**	0.11**	0.06*	0.08**	0.08**	0.04	0.05*
(2) *Non-Assaultive*	0.81**	1	0.07**	0.06**	0.01	0.03	0.04*	0.10**	0.00	0.01	0.04	0.03	0.03	0.04
(3) *Assaultive*	0.39**	0.07**	1	0.07**	0.03	0.04*	0.09**	0.10**	0.03	0.01	0.09**	0.08**	0.03	-0.01
(4) *Sexual Assaultive*	0.44**	0.06**	0.07**	1	0.07**	0.09**	0.17**	0.13**	0.04*	0.02	0.07*	0.06*	0.02	-0.15
(5) *DSM5 AUD Sx*	0.02	0.01	0.03	0.07**	1	0.48**	0.23**	0.30**	0.28**	0.36**	0.24**	0.28**	0.31**	-0.09*
(6) *DSM5 CUD Sx*	0.05*	0.03	0.04*	0.09**	0.48**	1	0.20**	0.33**	0.23**	0.43**	0.21**	0.27**	0.25**	-0.06**
(7) *INT*	0.13**	0.04*	0.09**	0.17**	0.23**	0.20**	1	0.20**	0.10**	0.14**	0.13**	0.10**	0.09**	-0.02
(8) *EXT*	0.15**	0.10**	0.10**	0.13**	0.30**	0.33**	0.20**	1	0.11**	0.18**	0.19**	0.15**	0.14**	-0.05*
(9) *Drink Ever*	0.11**	0.00	0.03	0.04*	0.28**	0.23**	0.10**	0.11**	1	0.49**	0.19**	0.02**	0.16**	-0.17**
(10) *MJ Ever*	0.06*	0.01	0.01	0.02	0.36**	0.43**	0.14**	0.18**	0.49**	1	0.30**	0.24**	0.32**	-0.10**
(11) *Parent AUD*	0.08**	0.04	0.09**	0.07*	0.24**	0.21**	0.13**	0.18**	0.19**	0.30**	1	0.14**	0.08*	-0.03
(12) *BIS Total Score*	0.08**	0.03	0.08**	0.06*	0.28**	0.27**	0.10**	0.15**	0.02**	0.24**	0.14**	1	0.35**	-0.03
(13) *SSS Total Score*	0.04	0.03	0.03	0.02	0.31**	0.25**	0.09**	0.14**	0.16**	0.32**	0.08*	0.35**	1	-0.04
(14) *No-Go frontal theta ERO*	0.05*	0.04	-0.01	-0.15	-0.09**	-0.06**	-0.02	-0.05*	-0.17**	-0.10**	-0.03	-0.03	-0.04	1

Note: *p<.05, **p<.01

Table S3. Early Trauma exposure and Go/No Go Task Performance and Behavior

	Non-Assaultive Trauma <age10 [N:418]			**Assaultive Trauma <age10 [N:111]**			**Sexual Assaultive Trauma <age10 [N:121]**		
	B	*SE*	*p*	*B*	*SE*	*p*	*B*	*SE*	*p*
Go Accuracy	0.01	0.01	0.50	-0.01	0.02	0.63	0.00	0.02	0.77
No-Go Accuracy	-0.01	0.00	0.06	0.00	0.01	0.91	0.00	0.01	0.68
Go Reaction Time	-2.83	2.00	0.16	-6.73	3.61	0.06	0.399	3.37	0.91

Note: Comparison groups are participants who were not exposed to any trauma type prior to age 10. SE = standard error.

Table S4 Associations of Early Trauma Exposure, Go/No-Go Event-Related Oscillations (ERO) (Frontal Theta and Posterior Delta Power) from Baseline Through Follow-Up Four

	Intercept			Slope		
	B	*S.E.*	*p-value*	*B*	*S.E.*	*p-value*
Condition: No-Go frontal theta						
Female Gender	-2.60	1.55	0.093	-0.03	0.07	0.696
Race/ethnicity (ref: White)	-1.59	1.53	0.299	0.01	0.07	0.926
Non-Assaultive	-0.29	1.50	0.847	-0.01	0.07	0.932
Assaultive	-2.58	1.56	0.099	0.09	0.07	0.198
Sexual Assaultive*	**-4.41**	**1.59**	**0.005**	**0.22**	**0.07**	**0.001**
Condition: Go frontal theta						
Female Gender	-0.02	0.12	0.873	-0.00	0.01	0.866
Race/ethnicity (ref: White)	-0.15	0.10	0.124	-0.01	0.01	0.048
Non-Assaultive	0.10	0.16	0.507	0.01	0.01	0.219
Assaultive	0.32	0.33	0.336	-0.02	0.02	0.254
Sexual Assaultive	0.32	0.23	0.174	-0.01	0.01	0.203
Condition: No-Go posterior delta						
Female Gender	0.02	0.33	0.948	0.00	0.02	0.972
Race/ethnicity (ref: White)	-0.29	0.27	0.097	0.00	0.01	0.842
Non-Assaultive	0.33	0.44	0.756	-0.02	0.02	0.348
Assaultive	-0.63	0.87	0.715	0.02	0.04	0.550
Sexual Assaultive	-0.35	0.73	0.483	0.02	0.04	0.609
Condition: Go posterior delta						
Female Gender	0.00	0.35	0.992	0.00	0.02	0.914
Race/ethnicity (ref: White)	-0.31	0.28	0.270	0.00	0.33	0.744
Non-Assaultive	0.94	0.44	0.051	-0.05	-2.07	0.052
Assaultive	-0.07	0.92	0.941	0.01	0.16	0.875
Sexual Assaultive	0.41	0.67	0.547	-0.02	-0.57	0.570

Note: All models include age modeled via time scores, gender, and self-reported race/ethnicity.

*$p<.05$