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Authors

Bomyea, Jessica
Simmons, Alan N
Shenton, Martha E
et al.

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Neurocognitive markers of childhood abuse in individuals with PTSD: Findings from the INTRuST Clinical Consortium

Jessica Bomyea[a,b,*], **Alan N. Simmons**[a,b], **Martha E. Shenton**[c,d,e], **Michael J. Coleman**[c], **Sylvain Bouix**[c], **Yogesh Rathi**[c], **Ofer Pasternak**[c,d], **Raul Coimbra**[f], **Lori Shutter**[g], **Mark S. George**[h,i], **Gerald Grant**[j,k], **Ross D. Zafonte**[l], **Thomas W. McAllister**[m,n], **Murray B. Stein**[b,o]
INTRuST consortium

[a]Center of Excellence for Stress and Mental Health, VA San Diego Healthcare System, San Diego, CA, 92161, USA

[b]Department of Psychiatry, University of California San Diego, La Jolla, CA, 92093, USA

[c]Psychiatry Neuroimaging Laboratory, Department of Psychiatry, Brigham and Women's Hospital, Harvard Medical School, 1249 Boylston St, Boston, MA, 02215, USA

[d]Department of Radiology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, 02115, USA

[e]VA Boston Healthcare System, Brockton Division, Brockton, MA, 02301, USA

[f]Department of Surgery, University of California San Diego, La Jolla, CA, 92161, USA

[g]University of Pittsburgh School of Medicine, Pittsburgh, PA, 15261, USA

[h]Medical University of South Carolina, Ralph H. Johnson VA Medical Center, Charleston, SC, 29401, USA

[i]Ralph H. Johnson VA Medical Center, Charleston, SC, 29401, USA

[j]Stanford University Medical Center, Palo Alto, CA, 94305, USA

[k]Duke University, Durham, NC, 90586, USA

[l]Spaulding Rehabilitation Hospital, Massachusetts General Hospital, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, 02215, USA

[m]Geisel School of Medicine at Dartmouth, Hanover, NH, 03755, USA

[*]Corresponding author., 9500 Gilman Dr. MC 0855, San Diego, CA, 92137, USA. jbomyea@ucsd.edu (J. Bomyea).

Declaration of competing interest

The authors declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2019.11.012.

Note: WRAT-4 = Wide Range Achievement Test-4th edition; PCL-C= PTSD Checklist civilian version; PHQ9 = Patient Health Questionnaire-9; CTQ = Childhood Trauma Questionnaire; HC = healthy comparison; PTSD + M = PTSD with childhood maltreatment; PTSD = PTSD without significant childhood maltreatment; *p < .05. + indicates significant differences in the variable across site, p < .05.

Note: HC = healthy comparison; PTSD + A = PTSD with childhood maltreatment; PTSD = PTSD without significant childhood maltreatment.* significant with FDR correction for multiple comparisons. [a] = HC significantly different from PTSD-M, [b] = HC significantly different from PTSD + M, [c] = PTSD significantly different from PTSD + M.

[n]Indiana University School of Medicine, Indianapolis, IN, 46202, USA

[o]University of California, San Diego Department of Family Medicine and Public Health, La Jolla, CA, 92093, USA

Abstract

To date, few studies have evaluated the contribution of early life experiences to neurocognitive abnormalities observed in posttraumatic stress disorder (PTSD). Childhood maltreatment is common among individuals with PTSD and is thought to catalyze stress-related biobehavioral changes that might impact both brain structure and function in adulthood. The current study examined differences in brain morphology (brain volume, cortical thickness) and neuropsychological performance in individuals with PTSD characterized by low or high self-reported childhood maltreatment, compared with healthy comparison participants. Data were drawn from the INjury and TRaUmatic STress (INTRuST) Clinical Consortium imaging repository, which contains MRI and self-report data for individuals classified as PTSD positive (with and without a history of mild traumatic brain injury [mTBI]), individuals with mTBI only, and healthy comparison participants. The final sample included 36 individuals with PTSD without childhood maltreatment exposure (PTSD, n = 30 with mTBI), 31 individuals with PTSD and childhood maltreatment exposure (PTSD + M, n = 26 with mTBI), and 114 healthy comparison participants without history of childhood maltreatment exposure (HC). The PTSD + M and PTSD groups demonstrated cortical thinning in prefrontal and occipital regions, and poorer verbal memory and processing speed compared to the HC group. PTSD + M participants demonstrated cortical thinning in frontal and cingulate regions, and poorer executive functioning relative to the PTSD and HC groups. Thus, neurocognitive features varied between individuals with PTSD who did versus did not have exposure to childhood maltreatment, highlighting the need to assess developmental history of maltreatment when examining biomarkers in PTSD.

Keywords

PTSD; Childhood maltreatment; Cortical thickness; Morphology; MRI

1. Introduction

Posttraumatic stress disorder (PTSD) consists of four symptom clusters (re-experiencing, avoidance, negative cognitions and mood, and dysregulation in arousal (APA, 2013)). PTSD is associated with abnormal functioning and connectivity of limbic and prefrontal brain regions during affective processing (Akiki et al., 2017; Garfinkel and Liberzon, 2009; Lanius et al., 2015; Liberzon and Sripada, 2008). Moreover, reductions in volume and cortical thickness are observed in brain regions including the ventromedial prefrontal cortex (vmPFC), dorsolateral prefrontal cortex (dlPFC), anterior cingulate cortex (ACC), amygdala, and hippocampus (e.g., Akiki et al., 2017; Karl et al., 2006). Functional and structural integrity differences in these regions may underlie the cognitive and emotional dysregulation observed in PTSD (Garfinkel and Liberzon, 2009).

Presence of early maltreatment is thought to produce heterogeneity among individuals with psychiatric disorders (Teicher and Samson, 2013; Teicher et al., 2016). Childhood maltreatment refers to physical, emotional, or sexual abuse, and may also include neglect – failing to provide for physical, social, or emotional needs (Teicher and Samson, 2013). Childhood maltreatment is widespread, associated with significant socioeconomic costs, and linked to worse physical and affective outcomes (Anda et al., 2006; Chartrand and Bargh, 1999; Dube et al., 2009; Gould et al., 2012; Green et al., 2010; Hart and Rubia, 2012; Pechtel and Pizzagalli, 2011). Within psychiatric diagnoses there are clinically-relevant differences in individuals who have experienced childhood maltreatment, including earlier disorder onset and greater treatment resistance, relative to those who have not (Alvarez et al., 2011; Hovens et al., 2015; Nanni et al., 2012).

Maltreatment experiences are associated with a host of stress-related physiological sequelae, the long-term consequences of which could be reflected in neurobiological characteristics in adulthood (e.g., brain structure or function, Teicher and Samson, 2013). Exposure to early adverse events may alter neurodevelopmental trajectories by catalyzing hormonal and neurotransmitter changes (e.g., glucocorticoids, Heim and Nemeroff, 2001) that likely impact neurogenesis, pruning, and myelination processes involved in gray and white matter organization during development (de Graaf-Peters and Hadders-Algra, 2006; McEwen et al., 2012; Nemeroff, 2016; Teicher et al., 2002). As a result, individuals who experience childhood maltreatment may demonstrate abnormalities in stress-vulnerable brain structures and cognitive functions. Such abnormalities may be partially independent of diagnostic classification, representing a discernible subtype within a given patient population with distinct neurobiological, cognitive, and/or affective characteristics (Teicher et al., 2016).

Data from MRI and neuropsychological studies provide evidence for the lasting effects of childhood maltreatment exposure. Abnormalities in the PFC (e.g., Chaney et al., 2014; Fonzo et al., 2013; Tomoda et al., 2009b; van Harmelen et al., 2010), insula and ACC (Dannlowski et al., 2012), occipital cortex (Tomoda et al., 2009a, 2012), and the amygdala and hippocampus (Dannlowski et al., 2012; Gurvits et al., 1996), as well as network architecture across these brain regions (Ohashi et al., 2017), are documented in individuals with a history of childhood maltreatment. Two recent meta-analyses synthesized voxel-based morphology (VBM) studies on this topic and concluded that childhood maltreatment impacts brain regions including orbitofrontal and temporal regions, inferior frontal cortex, ACC, vmPFC, dlPFC, and postcentral gyrus (Lim et al., 2014; Paquola et al., 2016). Cognitive dysfunction has also been observed following childhood maltreatment - and in some cases linked to neural changes (Pechtel and Pizzagalli, 2011). The majority of evidence for deficits across cognitive domains come from data collected during childhood, temporally close to the onset of trauma (Beers and De Bellis, 2002; Bucker et al., 2012; De Bellis et al., 2009; Nolin and Ethier, 2007). However, impairments in memory, executive functioning, attention and working memory, and global cognitive functioning performance are also observed distally in adults with history of childhood maltreatment (Majer et al., 2010; Navalta et al., 2006; Nikulina and Widom, 2013).

Despite growing evidence for the neural impact of childhood maltreatment, the relative contribution of these experiences to neuroimaging and neuropsychological findings in PTSD

remains unclear. Structural brain regions identified as sensitive to childhood maltreatment tend to overlap with brain regions identified in PTSD (e.g., ACC, vmPFC), which may be a consequence of methodological features of existing studies. For example, some prior studies included patients with PTSD secondary to childhood maltreatment but did not include PTSD without maltreatment or maltreatment-only patient control groups (Landre et al., 2010; Thomaes et al., 2010). Also, studies have not routinely examined the possibility that within PTSD, maltreatment is associated with distinct neurocognitive features. One exception to this is a study by Fonzo and colleagues (Fonzo et al., 2013), who reported that severity of childhood maltreatment was correlated with functional and structural abnormalities in brain regions that included the insula, ACC, and precentral gyrus in a sample of women with PTSD secondary to intimate partner violence. To date, studies of cognitive sequelae of PTSD point to deficits in memory, executive functioning, and attention (Aupperle et al., 2012; Golier and Yehuda, 2002; Qureshi et al., 2011; Vasterling et al., 2002) and a recent meta-analysis in children suggested that maltreatment with PTSD was associated with worse performance than maltreatment alone across many cognitive domains, (Malarbi et al., 2017). Taken together, there remains a need to determine if neurobiological and cognitive features observed in extant studies are due to childhood maltreatment, psychiatric symptoms, or to their interaction (Hart and Rubia, 2012; Teicher et al., 2016).

The current study evaluated neurocognitive features in a sample of individuals with PTSD, with and without a history of childhood maltreatment (including abuse or neglect), compared to a non-exposed healthy comparison group. As part of the broader aims of the INjury and TRaUmatic STress Clinical Consortium (INTRuST; W81XWH-08-2-0159), individuals with PTSD with and without a history of mild traumatic brain injury (mTBI) were included, allowing us to also explore if mTBI history impacted the pattern of findings. Groups were compared on whole-brain structural metrics and brain regions of interests (ROIs) identified by prior reviews (Lim et al., 2014; Paquola et al., 2016; Teicher et al., 2016). Volume and cortical thickness were examined separately based on evidence that combining these measures provide distinct information (e.g., developmental trajectories, genetic correlates; Panizzon et al., 2009; Raznahan et al., 2011; Winkler et al., 2010) and greater sensitivity (Hutton et al., 2009). Group differences in neuropsychological functioning, which may be impacted by neurobiological or affective correlates of childhood maltreatment and PTSD (Dickerson et al., 2008), were also examined. It was hypothesized that groups would differ on brain volume, cortical thickness, and neuropsychological test performance such that individuals in the PTSD with childhood maltreatment group would demonstrate the worst neuropsychological and neuroimaging outcomes, followed by individuals with PTSD without childhood maltreatment, followed by healthy comparison participants.

2. Methods

2.1. Participants

Participants were 223 individuals from the INTRuST imaging data repository. Individuals completed a written informed consent, questionnaires, neuropsychological assessments, and a magnetic resonance imaging (MRI) scan. Participants were individuals who enrolled in

one of the INTRuST consortium parent trials and who agreed to participate in the repository or individuals who were recruited specifically for the repository (see Supplemental Materials, section 1 for details on inclusion and exclusion criteria). Analyses were conducted on a subset of individuals diagnosed with PTSD (including individuals with and without history of mTBI) or healthy comparison participants. Additionally, participants were further characterized based on the presence or absence of child maltreatment history (see Measures section below). Study procedures were carried out in accordance with the Declaration of Helsinki and approved by each site's institutional review board.

Patient inclusion and exclusion criteria were based on the individual INTRuST studies in which participants were enrolled (see Supplemental Materials section 1). Exclusions for participation in the repository were: 1) lifetime bipolar I, psychotic, or dementia disorders, delirium, current alcohol or substance dependence, 2) CNS disorders, 3) pregnant/lactating, 4) taking medications that affect brain function, 5) English as a second language after the age of 5, 6) history of a learning disability, 7) weight>300 pounds, and 8) other MRI-incompatible conditions (e.g., ferrous metal, pace maker, full dental braces). PTSD diagnosis for patients was determined based on the procedures of the parent study using a PCL-C cutoff of 50 and/or a diagnostic interview (Clinician Administered PTSD Scale (Blake et al., 1995) or MINI International Neuropsychiatric Interview (Sheehan et al., 1998)).

As part of participation in the repository, patients were also classified based on whether they had experienced a probable mTBI during their lifetime using a brief self-report questionnaire designed for the study. Individuals were considered probable mTBI positive if they endorsed a history of head injury with alteration or loss of consciousness and/or posttraumatic amnesia (n = 56). Analyses to examine the potential effect of mTBI on outcomes of interest are reported in the Supplemental Materials section 3. Because mTBI was evenly distributed across the patient groups and did not appear to influence the neural variables of interest, it was not included as a factor in the primary analyses.

Each study site also recruited healthy comparison participants between the ages of 18–65 by using media advertising and registries containing individuals interested in research participation. Exclusions for healthy comparison participants included: 1) CNS disorders, 2) medication exclusions, including more than one antihypertensive drug, psychotropic drugs within the last 90 days, herbal psychoactive substance use, or steroid use in the last 4 months, 3) pregnant/lactating, 4) history of mood, anxiety, psychotic, dementia, delirium, or substance dependence disorders in the past 12 months, 5) history of probable TBI, and/or, 6) MRI incompatibility. Those who initially met inclusion criteria based on a phone screen completed an in-person MINI interview to confirm eligibility.

Analyses were conducted on the subset of 181 individuals who completed the MRI scan (n = 41 excluded for data quality; 18.4%) and neuropsychological assessment (missing n = 18; 8.1%). There were no statistically significant differences between participants missing data on age, education, or PTSD or depression severity. However, men were more likely to have missing data than women, $\chi^2 = 4.54$, $p = .03$. Participants were divided into three sub-groups: healthy comparison (HC) participants with no/low childhood maltreatment scores (n = 114); PTSD patients with no/low childhood maltreatment scores (PTSD; n = 36); and

PTSD patients with elevated childhood maltreatment scores (PTSD + M; $n = 42$). Those who did not fall into one of the three categories (i.e., maltreatment experiences falling outside of the described range; $n = 31(13.9\%)$) were excluded from the analyses. Power calculations indicated that the sample size derived from these groupings was adequate (power > .80) for primary analyses assuming at least a medium effect size (f = 0.25).

2.2. Measures

2.2.1. Childhood maltreatment—The Childhood Trauma Questionnaire (CTQ; Bernstein et al., 2003) was used to classify history of childhood maltreatment. The CTQ assesses self-reported frequency of physical, sexual, and emotional abuse and physical and emotional neglect using a five-point rating scale from 1 (*never true*) to 5 (*very often true*). The PTSD + M group consisted of PTSD patients who endorsed at least "moderate" on one or more of the CTQ subscales using established cutoffs (Bernstein et al., 2003). The PTSD group consisted of PTSD patients who endorsed less than moderate ratings on all subscales. The HC group consisted of healthy comparison participants who endorsed less than moderate ratings on all subscales.

2.2.2. PTSD severity—The PTSD Checklist-Civilian Version (PCL-C; Weathers et al., 1993) is a 17-item self-report of PTSD symptom severity. Items correspond to diagnostic criteria for PTSD outlined in the DSM-IV and are rated on a scale from 1 (*not at all bothersome*) to 5 (*extremely bothersome*) to create a total sum score.

2.2.3. Depression severity—The Patient Health Questionnaire-9 (PHQ9; Kroenke et al., 2001) is a 9-item self-report assessing depressive symptoms. Items are rated on a scale from 0 (*not at all*) to 3 (*nearly every* day) and summed to create a continuous total severity score.

2.2.4. Neuropsychological tests—Neuropsychological tests assessed level of academic achievement (Wide Range Achievement Test-4th edition word reading (WRAT-4), Wilkinson and Robertson, 2006), visual and verbal learning and memory (Rey Auditory Verbal Learning Test-2 (RAVLT-2) total, short and long delay recall scores, (Schmidt, 1996; Strauss et al., 2006); Brief Visuospatial Memory Test-Revised (BVMT-R) total, learning, and long delay recall scores (Benedict, 1997)), attention and working memory (Wechsler Memory Scales-III (WMS-III) Letter Number Sequencing (LNS) (Wechsler, 1997); Paced Auditory Serial Addition Test (PASAT) number correct (Gronwall, 1977)), psychomotor processing speed (Trail Making Test-A, (Reitan and Wolfson, 1993); Wechsler Adult Intelligence Scale-III (WAIS-III) Digit Symbol Coding and Symbol Search (Wechsler, 1997)), and executive functioning (Trail Making Test-B (Reitan and Wolfson, 1993)). Standardized z, T, or scaled scores with demographically corrected norms were calculated using guidelines from the administration manuals, except the PASAT for which a residual score was calculated using an age and education-adjusted regression model. Composite z-scores were then created for verbal memory (RAVLT-2 subtests), visual memory (BVMT-R subtests), attention and working memory (PASAT and WMS-III LNS), processing speed (WAIS-III Processing Speed Index (PSI), Trail Making Test-A score), and a total cognitive functioning score with all variables. Embedded performance validity metrics included the

Trail Making Test (total time > 170), BVMT-R (recognition hits < 5), and RAVLT-2 recognition (< 10) (Denning, 2012; Shura et al., 2016; Whitney and Davis, 2015). Individuals were required to pass at least two of the three validity measures to be included in the neuropsychological analysis (n = 10 excluded).

2.3. Image acquisition and processing

MRI scans were acquired across six participating institutions (Dartmouth, Duke, South Carolina, Spaulding-Brigham and Women's Hospital-Harvard, University of California San Diego, University of Cincinnati) on 3T scanners (Supplemental Materials section 2 details scan parameters). Brain volume and cortical thickness measurements were obtained using FreeSurfer image analysis suite Version 5.3 (Dale et al., 1999; Fischl and Dale, 2000). FreeSurfer implements a multistage, automated process to derive cortical and subcortical anatomical data, including volume registration with the Talairach atlas, bias field correction, initial volumetric labeling, non-linear alignment to the Talairach space, and final volume labeling from which a subgroup of ROIs was selected.

We examined hypotheses regarding group differences in brain volume and cortical thickness metrics using ROI analyses on a subset of regions derived from FreeSurfer. The following bilateral ROIs were identified based on prior meta-analyses and reviews exploring the effects of childhood maltreatment on brain structure with voxel-based morphometry (Lim et al., 2014; Paquola et al., 2016; Teicher et al., 2016): orbitofrontal/superior temporal cortex (pars oribitalis, superior temporal), inferior frontal cortex (pars opercularis, pars triangularis), dlPFC (superior frontal and rostral middle frontal), pre- and postcentral gyrus, cuneus, insula, rostral anterior cingulate, medial prefrontal cortex (medial orbitofrontal and lateral orbitofrontal), and - for volume data - the hippocampus and amygdala. We also examined the effect of group on global measures of brain structure (CSF volume, total gray matter volume, white matter volume, and intracranial volume).

2.4. Analytic plan

Univariate analysis of variance was conducted to examine group differences on continuous variables and chi-square analysis was used for categorical variables (SPSS v18.0). Neuropsychological tests were scored using demographically corrected norms and models controlled for sex. Missing data on individual tests were handled using case-wise deletion, such that each analysis was conducted on all individuals who had data for the specific variable of interest. Analysis of variance was conducted on volumetric and cortical thickness data with group (HC, PTSD, PTSD + M) as a between-subjects factor and hemisphere entered as a within-subjects factor to examine potential interaction effects of maltreatment group on lateralization. No significant group-by-hemisphere interaction effects were observed for any analyses. Given the potential for demographic variables to influence neural outcomes and variance across site in clinical variables, volume and cortical thickness analyses controlled for scanner, intracranial volume (ICV), age, and sex. A supplemental analysis of all outcome variables with groupings based on childhood maltreatment only (HC or PTSD versus PTSD + M) is also presented in the Supplemental Materials section 4. Spearman correlations were used to examine associations between cortical thickness and neuropsychological performance separately within the HC and the patient groups. To control

for multiple comparisons ($p < .05$), FDR correction was applied (Benjamini and Hochberg, 1995).

3. Results

3.1. Demographic and clinical variables

Table 1 presents a summary of demographic and clinical variables. Groups were significantly different on age, such that individuals in the HC group were younger than individuals in the PTSD + M group ($M_{diff} = -6.86$, SE = 2.44, $p = .005$), and gender, such that the HC group contained a higher proportion of women than either PTSD group (HC-PTSD $\chi^2 = 17.87$, $p < .001$; HC-PTSD + M $\chi^2 = 13.56$, $p < .001$). The HC group endorsed lower PTSD symptoms relative to the two PTSD groups (HC-PTSD $M_{diff} = -39.59$, SE = 1.55, $p < .001$; HC-PTSD + M $M_{diff} = -38.44$, SE = 1.64, $p < .001$). The HC group also endorsed lower depression symptoms relative to the two PTSD groups (HC-PTSD $M_{diff} = -11.0$, SE = 0.69, $p < .001$; HC-PTSD + M $M_{diff} = -11.70$, SE = 0.73, $p < .001$). The PTSD and PTSD + M groups did not significantly differ from each other on PTSD or depression symptoms.

3.2. Global and gray matter volumes

Values for global structural measures and gray matter volume in the ROIs are presented in Table 2 for each group. The three groups were not significantly different on brain volume outcomes after controlling for multiple comparisons.

3.3. Cortical thickness

The three groups significantly differed on cortical thickness in the orbitofrontal/superior temporal cortex, inferior frontal gyrus, dlPFC, cuneus, insula, rostral ACC, and medial PFC (Table 3). Compared to the HC and PTSD groups, the PTSD + M group was characterized by cortical thinning in the IFG (HC-PTSD $M_{diff} = 0.03$, SE = 0.04, $p = .34$; HC-PTSD + M $M_{diff} = 0.12$, SE = 0.03, $p = .001$; PTSD-PTSD + M $M_{diff} = 0.08$, SE = 0.04, $p = .04$) and ACC (HC-PTSD $M_{diff} = 0.01$, SE = 0.03, $p = .76$; HC-PTSD + M $M_{diff} = 0.10$, SE = 0.03, $p = .001$; PTSD-PTSD + M $M_{diff} = 0.09$, SE = 0.03, $p = .008$). The PTSD + M group differed from the HC group in the dlPFC (HC-PTSD $M_{diff} = 0.06$, SE = 0.04, $p = .10$; HC-PTSD + M $M_{diff} = 0.10$, SE = 0.04, $p = .007$; PTSD-PTSD + M $M_{diff} = .04$, SE = 0.04, $p = .40$) and insula (HC-PTSD $M_{diff} = 0.04$, SE = 0.03, $p = .16$; HC-PTSD + M $M_{diff} = 0.08$, SE = 0.02, $p = .001$; PTSD-PTSD + M $M_{diff} = 0.05$, SE = 0.03, $p = .11$). Compared to the HC group, both PTSD groups demonstrated cortical thinning in the OFG, (HC-PTSD $M_{diff} = 0.09$, SE = 0.04, $p = .037$; HC-PTSD + M $M_{diff} = 0.15$, SE = 0.04, $p < .001$; PTSD-PTSD + M $M_{diff} = 0.06$, SE = 0.05, $p = .21$), vmPFC, (HC-PTSD $M_{diff} = 0.05$, SE = 0.02, $p = .013$; HC-PTSD + M $M_{diff} = 0.07$, SE = 0.02, $p < .001$; PTSD-PTSD + M $M_{diff} = 0.02$, SE = 0.02, $p = .36$), and cuneus (HC-PTSD $M_{diff} = 0.07$, SE = 0.02, $p = .001$; HC-PTSD + M $M_{diff} = 0.09$, SE = 0.02, $p < .001$; PTSD-PTSD + M $M_{diff} = 0.01$, SE = 0.03, $p = .58$) (Fig. 1).

3.4. Neuropsychological performance

The three groups were significantly different on performance on verbal memory, processing speed, executive functioning, and total cognitive score (Table 4). The PTSD and PTSD + M

groups performed worse than the HC group on verbal memory (HC-PTSD M_{diff} = 0.39, SE = 0.20, p = .048; HC-PTSD + M M_{diff} = 0.64, SE = 0.18, p = .001; PTSD-PTSD + M M_{diff} = 0.45, SE = 0.22, p = .27) and processing speed (HC-PTSD M_{diff} = 0.47, SE = 0.18, p = .010; HC-PTSD + M M_{diff} = 0.55, SE = 0.17, p = .001; PTSD-PTSD + M M_{diff} = 0.08, SE = 0.20, p = .69), and the PTSD + M group performed worse than the PTSD and HC groups on executive functioning (HC-PTSD M_{diff} = −0.83, SE = 2.53, p = .74; HC-PTSD + M M_{diff} = 6.08 SE = 2.42, p = .013; PTSD-PTSD + M M_{diff} = 6.92, SE = 2.95, p = .020). Individuals in the HC and PTSD + M group differed on total cognitive score (HC-PTSD M_{diff} = 0.14, SE = 0.12, p = .22; HC-PTSD + M M_{diff} = 0.35, SE = 0.11, p = .001; PTSD-PTSD + M M_{diff} = 0.21, SE = 0.13, p = .12). A set of supplemental analyses were undertaken to explore the potential effect of mTBI on results, given that a subset of individuals in the PTSD groups had history of mTBI (Supplemental Materials section 3). Evidence did not suggest that individuals with PTSD with and without mTBI significantly differed on neuropsychological performance. However, compared to HC, a subsample of repository participants selected based on having mTBI only (no PTSD) differed on verbal memory and processing speed domains (Supplemental Materials section 3). Results raise the possibility that observed effects between the HC and PTSD groups on these variables could be attributable to head injury. The supplemental analysis did not provide evidence that mTBI status impacted the executive functioning domain. There were no statistically significant associations between neuropsychological performance and cortical thickness data (all ps > .05).

4. Discussion

The current study evaluated whether individuals with PTSD and a history of childhood maltreatment demonstrate brain structure and cognitive performance differences compared to individuals with PTSD without childhood maltreatment and/or healthy comparison participants without childhood maltreatment. The HC, PTSD, and PTSD + M groups did not statistically differ on global brain structural metrics (e.g., total gray matter volume), or brain volume in predetermined ROIs. However, the PTSD + M group demonstrated cortical thinning in the IFG and ACC as compared to the other two groups. The PTSD + M group also performed worse on a measure of executive functioning than the other two groups. Both PTSD groups demonstrated relative impairments in memory and processing speed domains compared to the HC group. However, results of a supplemental analysis comparing healthy participants to a group of individuals with mTBI only (without PTSD) showed differences in memory and processing speed domains. Because a subset of individuals in the patient groups had experienced mTBI, it is possible that mTBI contributed to the lower performance in these groups. Neuropsychological variables were not correlated with the neural structure measures. Despite limitations inherent in these secondary data analyses (e.g., retrospective report of childhood experiences, heterogeneity of trauma history, lack of additional psychiatric control groups), results provide preliminary support for models suggesting that earlier traumatic experiences impact neuropsychological and neuroanatomical variables in adulthood.

Childhood maltreatment experiences are theorized to influence stress-vulnerable brain development in ways that are partially distinct from consequences of psychiatric disorders (Teicher et al., 2016), yet to date relatively little research has directly tested whether

individuals with PTSD but differing in early maltreatment histories are neurobiologically distinct. Though large-scale morphological differences spanning affective and cognitive processing networks have been reported in PTSD studies, variability exists in findings (Akiki et al., 2017; Karl et al., 2006; Scott et al., 2015). Our data demonstrated reduced cortical thickness in PFC, temporal, and occipital regions in PTSD, which are considered critical to anxiety-related processes (e.g., interoception, fear extinction memory, Khalsa et al., 2018; Milad et al., 2014). This pattern may imply that PTSD diagnosis adversely impacts neural size, cellular functioning, or cytoarchitecture of gray matter beyond the normal lifespan changes (Bajaj et al., 2017; Bing et al., 2013). Childhood maltreatment experiences commonly co-occur with PTSD (De Bellis, 2001; Koola et al., 2013; MacMillan et al., 2001) and may thus be one factor accounting for the variability in findings from existing studies of brain structure in PTSD.

Those with PTSD and childhood maltreatment history had abnormalities in the PFC (IFG, dlPFC), insula, and rostral ACC. Observed group differences converge with earlier data showing that early life experiences affect stress-sensitive brain structures in the prefrontal cortex and cingulate (Dannlowski et al., 2012; van Harmelen et al., 2010), which may contribute to the cognitive and affective clinical presentation of these individuals. For example, the IFG is implicated in a host of affective processing functions including emotion regulation (Ochsner et al., 2012; Wager et al., 2008), responding to others' emotions (Grecucci et al., 2013), and cognitive and behavioral inhibition (Aron et al., 2014). Similarly the ACC is thought to be a "top down" control region associated with multiple critical affective functions ranging from emotion regulation (Ochsner et al., 2012) to fear extinction memory (Milad et al., 2014).

Unlike prior studies of brain structure in individuals with childhood maltreatment, there was no evidence of significantly reduced hippocampal or amygdala volumes across the three groups. There are a number of potential explanations for these discrepant findings (for other examples see Cohen et al., 2006; Landre et al., 2010; Paquola et al., 2016). First, the neural effects of early stress likely depend on the type and chronicity of stressors, age at which the event(s) occur, and availability of enriching experiences to facilitate neural "catch up" (Andersen et al., 2008; Nelson et al., 2007; Pechtel et al., 2014; Teicher et al., 2006). Heterogeneity in these experiences in the current sample may have impacted findings. Second, sample differences between the PTSD patients in the current and prior studies could also have impacted the observed effects. For example, some previous studies recruited combat veterans, who experience a unique type of traumatic event and are predominantly male, in contrast to participants in the current dataset, which included individuals with substantial heterogeneity in history of trauma and severity and duration of PTSD. Third, the majority of studies in the literature have examined the amygdala and hippocampus using VBM or manual segmentation procedures, which do not fully correspond to data derived from FreeSurfer analyses as used here (Grimm et al., 2015). Future research is needed to elucidate these and other variables that may impact volume in these areas and contribute to observed heterogeneity.

Findings from this study partially converge with findings of worse neuropsychological functioning in individuals with history of childhood maltreatment (Pechtel and Pizzagalli,

2011). Earlier work suggests that individuals who experience childhood maltreatment may demonstrate deficits in memory, executive functioning, processing speed, and working memory in adulthood (Gould et al., 2012; Navalta et al., 2006). Results from the current study similarly found an effect of childhood trauma on the test of executive functioning. Additional domains of memory and processing speed were lower in both PTSD groups, rather than being specifically lower in the PTSD + M group. Moreover, there was evidence that presence of mTBI (which only occurred in the patient groups) was associated with neuropsychological performance in these domains, so it is not possible to fully disentangle the effect of PTSD versus mTBI (see also Bomyea et al., 2019 for results from this dataset in relation to mTBI). Given the high potential for comorbidity of childhood maltreatment, PTSD, and mTBI, this topic warrants future study. Discrepancies in neuropsychological findings may be attributable to methodological differences, including the specific patient and control groups used (e.g., specific types of abuse versus deprivation or general early life stress, healthy versus psychiatric comparator), and the analytic and assessment methods utilized.

The lack of correlation between neuropsychological and neuroimaging variables suggest the potential for diverging outcomes along neural and cognitive levels of analysis. Cognitive performance may not necessarily be rooted in the anatomical makeup of isolated regions of the brain, and while some studies find links between brain structure and neuropsychological outcomes (Bauer et al., 2009), a number of studies found that brain structure in regions implicated in specific cognitive domains did not correspond to performance on tests within those domains (see for example Woodward et al., 2009). Lower cognitive performance in maltreated individuals could instead be accounted for by complex interactive and functional differences during task performance. Exposure to early life experiences involving negative emotion and interpersonal stress may correspond to multiple ecophenotypes within PTSD (i.e., phenotypes derived as a result of environmental experience (Teicher and Samson, 2013)), characterized by executive dysfunction or neural alterations in brain regions important for social information processing and affective self-regulation.

There are a number of study limitations. First, because participants were drawn from an existing repository the information collected was necessarily restricted. Given that neurodevelopmental effects of the environment vary across childhood and could be influenced by duration of illness, the impact of developmental onset should be evaluated in future research. The dataset also did contain a sufficiently large group of individuals without PTSD but with childhood maltreatment histories to use as an alternate comparison group. Second, participants experienced symptoms related to a range of index trauma events (violence, accidents), making the nature of the PTSD diagnoses quite heterogeneous. Third, the patient and healthy control groups differed on clinical features in addition to PTSD, including level of functional impairment and potential comorbid conditions such as anxiety, depression, and history of head injury. Group differences between the HC and PTSD + M/PTSD groups may thus be partially accounted for by other symptoms. Fourth, reports of childhood maltreatment events were collected cross-sectionally and retrospectively with self-report measures, which may result in recall biases. Additional research is also needed to examine hypotheses regarding the impact of maltreatment experiences on specific proposed mechanisms (e.g., neurogenesis, myelination, pruning; Gogtay and Thompson, 2010).

In summary, we investigated associations between PTSD and childhood maltreatment history on brain structure and neuropsychological performance. These data advance existing literature by distinguishing neurocognitive effects of PTSD with and without childhood maltreatment and by separately examining cortical thickness and volume. PTSD with childhood maltreatment was associated with specific cortical thickness and neuropsychological performance reductions. These findings suggest that at least some of the heterogeneity of findings in PTSD may be addressed by separating individuals with PTSD with and without child maltreatment history.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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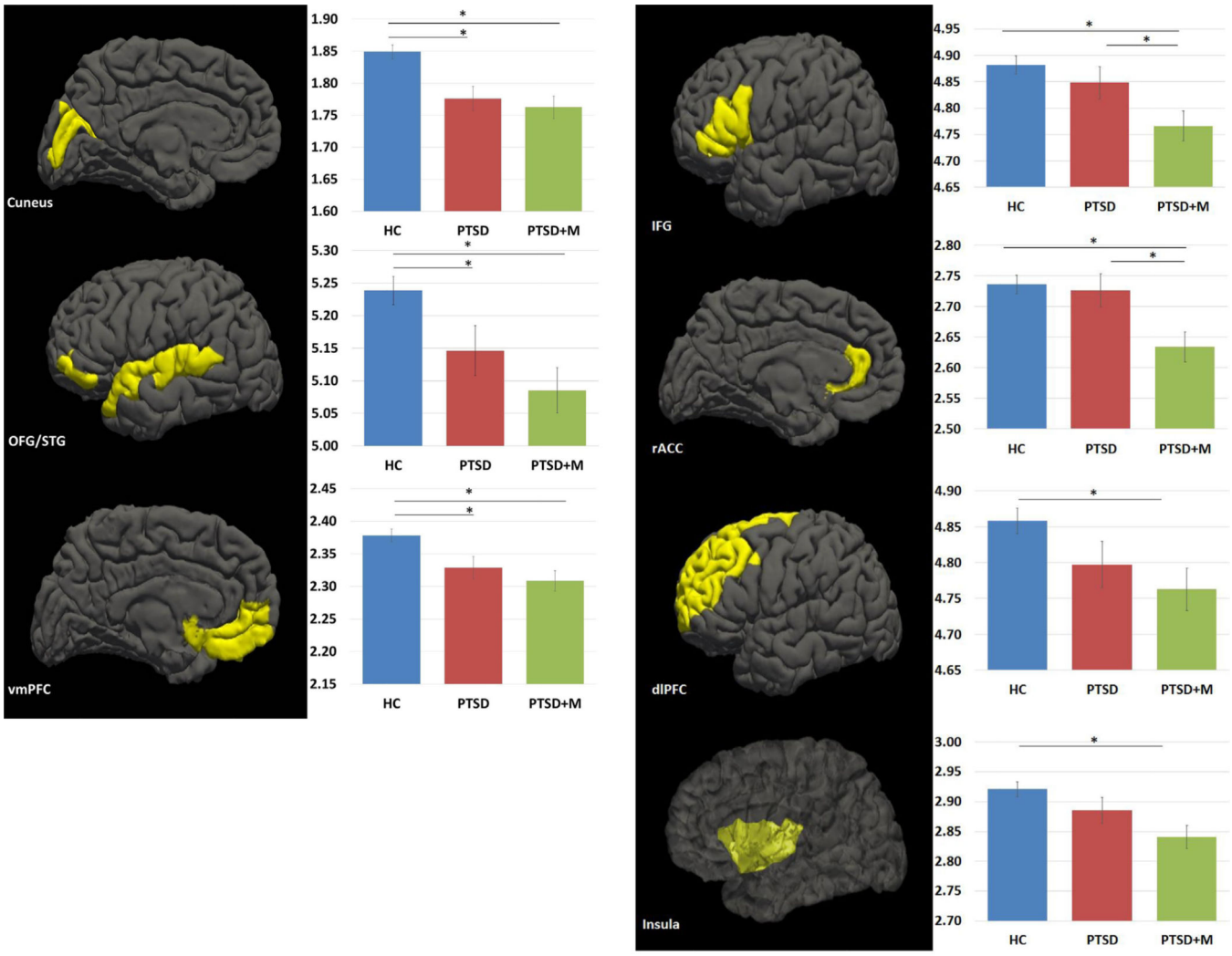

Fig. 1.

Group based differences in cortical thickness regions of interest.

Note: HC = healthy comparison; PTSD + M = PTSD with childhood abusemaltreatment; PTSD without significant childhood abusemaltreatment. Model adjusted values presented, * = FDR-corrected $p < .05$.

Table 1

Demographic and clinical characteristics.

Variable	HC	PTSD	PTSD + M	Omnibus test statistic, *p*-value, effect size
Mean Age (SD) +	33.40 (13.45)	35.69 (8.55)	38.60 (9.48)	F(2,189) = 3.01, $p = .05$, $\eta 2 = 0.03$
Mean WRAT-4 score (SD)	63.65 (4.90)	64.11 (4.49)	62.00 (5.32)	F(2,186) = 2.16, $p = .12$, $\eta 2 = 0.02$
Gender % female +	57.0	16.7	23.8	$X^2 = 26.76$, $p < .001$
Race*				$X^2 = 13.75$, $p = .19$
Native American/Alaskan Native	0	0	1	
Asian	8	0	0	
Hawaiian/Pacific Islander	0	1	1	
Black/African American	15	8	11	
Caucasian	83	25	26	
Unknown	1	1	3	
Mean PCL-C (SD) +	18.91 (3.86)	58.50 (12.83)	56.14 (12.43)	F(2,189) = 466.76, $p < .001$, $\eta 2 = 0.83$
Mean PHQ9 (SD) +	0.75 (1.25)	11.75 (5.68)	12.14 (5.79)	F(2,189) = 205.29, $p = .00$, $\eta 2 = 0.68$
Mean CTQ total (SD) +	28.52 (3.93)	32.69 (5.26)	66.43 (16.73)	F(2,189) = 300.93, $p = .00$, $\eta 2 = 0.76$

Table 2

Global brain structure and gray matter volume in each group.

Variable	HC	PTSD	PTSD + M	Test statistic, *p*-value, effect size
Cerebrospinal Fluid vol mm^3	267781.15 (37081.65)	285989.42 (38419.84)	290295.14(41405.19)	F(2,185) = 1.93, p = .15, $\eta 2$ = .02
Gray Matter vol mm^3	602001.65 (55583.82)	617182.86 (61858.34)	602224.48(57940.53)	F(2,185) = 0.55, p = .58, $\eta 2$ = .006
White Matter vol mm^3	529737.39 (54759.57)	555845.36 (70622.11)	542489.36(55211.23)	F(2,185) = 0.31, p = .73, $\eta 2$ = .003
Intracranial volume	991204.22 (122180.47)	1023385.53 (117965.96)	1015703.49(96110.80)	F(2,185) = 0.01, p = .99, $\eta 2$ < 0.001
Amygdala				F(2,184) = 2.36, p = .10, $\eta 2$ = .03
Left	1496.58 (189.51)	1596.58 (229.18)	1494.98(199.80)	
Right	1601.18 (214.90)	1685.80 (310.41)	1567.29(265.03)	
Hippocampus				F(2,184) = 2.19, p = .12, $\eta 2$ = .02
Left	4012.83 (396.70)	4181.52 (574.72)	4002.91(449.84)	
Right	4139.19 (362.98)	4323.02 (586.44)	4076.92(433.87)	
Orbitofrontal/Superior temporal				F(2,184) = 4.66, p = .01, $\eta 2$ = .05
Left	14171.39 (1718.82)	14155.92 (1784.75)	13745.38(1732.01)	
Right	14031.48 (1603.96)	14264.19 (1548.03)	13484.86(1632.93)	
Inferior frontal cortex				F(2,184) = 4.05, p = .02, $\eta 2$ = .04
Left	8464.72 (1180.76)	8632.75 (1386.19)	8192.90(1461.23)	
Right	8258.02 (1113.82)	8504.08 (1547.66)	7925.38(1421.05)	
Dorsolateral prefrontal cortex				F(2,184) = 1.63, p = .20, $\eta 2$ = .02
Left	37491.46 (4713.92)	37369.56 (4297.68)	36973.48(4370.55)	
Right	37072.53 (4653.62)	37043.78 (4414.21)	36430.02(4609.76)	
Insula				F(2,184) = 2.25, p = .11, $\eta 2$ = .02
Left	6694.21 (722.00)	6971.86 (1095.56)	6586.43(785.88)	
Right	6865.16 (852.24)	7066.39 (891.80)	6802.02(834.24)	
Rostral anterior cingulate				F(2,184) = 2.11, p = .12, $\eta 2$ = .02
Left	2261.63 (449.15)	2179.75 (506.95)	2158.02(440.77)	
Right	2802.53 (478.56)	2750.56 (445.75)	2673.69(583.46)	
Ventromedial prefrontal cortex				F(2,184) = 3.10, p = .05, $\eta 2$ = .03
Left	6283.07 (735.67)	6250.31 (686.83)	6160.11(693.80)	
Right	6099.86 (646.94)	6165.43 (673.56)	5978.38(693.50)	

Variable	HC	PTSD	PTSD + M	Test statistic, *p*-value, effect size
Precentral gyrus				F(2,184) = 0.63, *p* = .53, η2 = .01
Left	13362.96 (1448.74)	13446.36 (1585.49)	13315.98(1432.15)	
Right	13200.27 (1353.80)	13198.00 (1673.94)	12993.83(1479.07)	
Postcentral gyrus				F(2,184) = 0.01, *p* = .99, η2 < .001
Left	9677.12 (1408.89)	9723.03 (1190.46)	9862.45(1213.06)	
Right	8995.20 (1306.88)	9257.86 (1328.42)	8950.12(976.18)	
Cuneus				F(2,184) = 4.91, *p* = .01, η2 = .05
Left	2940.23 (410.12)	2824.69 (471.72)	2924.10(528.78)	
Right	3093.76 (473.03)	3056.83 (451.92)	3007.31(515.98)	

Note: HC = healthy comparison participants; PTSD + M = PTSD with childhood maltreatment; PTSD = PTSD without significant childhood maltreatment.

Table 3

Cortical thickness in each group.

Variable	HC	PTSD	PTSD + M	Test statistic, *p*-value, effect size
Orbitofrontal/Superior temporal*, [a,b]				F(2,184) = 7.18, $p < .001$, $\eta 2 = 0.07$
Left	5.32 (0.30)	5.21 (0.21)	5.08(0.28)	
Right	5.31 (0.32)	5.16 (0.26)	5.05(0.30)	
Inferior frontal cortex*, [b,c]				F(2,184) = 6.01, $p < .001$, $\eta 2 = 0.06$
Left	4.96 (0.28)	4.89 (0.22)	4.74(0.23)	
Right	4.95 (0.29)	4.88 (0.26)	4.74(0.25)	
Dorsolateral prefrontal cortex *, [b]				F(2,184) = 4.02, $p = .02$, $\eta 2 = 0.04$
Left	4.94 (0.25)	4.85 (0.21)	4.79(0.19)	
Right	4.88 (0.28)	4.79 (0.25)	4.68(0.23)	
Insula*, [b]				F(2,184) = 5.84, $p < .001$, $\eta 2 = 0.06$
Left	2.94 (0.14)	2.90 (0.15)	2.85(0.14)	
Right	2.90 (0.17)	2.88 (0.17)	2.81(0.14)	
Rostral anterior cingulate*, [b,c]	2.75 (0.21)	2.74 (0.26)	2.58(0.21)	F(2,184) = 6.53, $p < .001$, $\eta 2 = 0.07$
Left				
Right	2.79 (0.18)	2.77 (0.22)	2.69(0.16)	
Ventromedial prefrontal cortex*, [a,b]				F(2,184) = 7.76, $p < .001$, $\eta 2 = 0.08$
Left	2.41 (0.13)	2.37 (0.12)	2.33(0.10)	
Right	2.37 (0.15)	2.34 (0.12)	2.30(0.11)	
Precentral gyrus				F(2,184) = 2.35, $p = .10$, $\eta 2 = 0.02$
Left	2.52 (0.12)	2.48 (0.11)	2.45(0.13)	
Right	2.50 (0.11)	2.46 (0.10)	2.41(0.14)	
Postcentral gyrus				F(2,184) = 0.34, $p = .71$, $\eta 2 < 0.001$
Left	2.06 (0.11)	2.04 (0.09)	2.03(0.09)	
Right	2.04 (0.12)	2.02 (0.10)	2.01(0.11)	
Cuneus*, [a,b]				F(2,184) = 10.6, $p < .001$, $\eta 2 = 0.10$
Left	1.83 (0.12)	1.78 (0.13)	1.76(0.12)	
Right	1.84 (0.14)	1.79 (0.11)	1.77(0.13)	

Table 4

Neuropsychological performance in each group.

Variable	HC	PTSD	PTSD + M	Omnibus test of group, *p*-value, effect size
Academic achievement				F(2,158) = 0.98, *p* = .38, η2 = .01
WRAT-4 score	63.65 (4.94)	64.53 (4.03)	62.79 (4.66)	
Total cognitive score* *b*	0.23 (0.57)	0.12 (0.52)	−0.09 (0.50)	F(2,178) = 5.35, *p* = .01, η2 = .06
Verbal learning and memory* *a,b*				F(2,178) = 6.74, *p* = .002, η2 = .07
RAVLT-2 Total z-score	0.54 (1.11)	−0.01 (0.96)	−0.24 (1.01)	
RAVLT-2 Short Delay z-score	0.35 (1.04)	0.11 (1.00)	−0.13 (1.05)	
RAVLT-2 Long Delay z-score	0.36 (0.96)	0.04 (0.97)	−0.24 (1.05)	
Visual learning and memory				F(2,158) = 0.98, *p* = .38, η2 = .01
BVMT-R Total t-score	52.60 (10.29)	54.96 (8.69)	50.06 (11.81)	
BVMT-R Learning t-score	49.19 (10.96)	48.73 (10.05)	50.61 (12.54)	
BVMT-R Long delay t-score	52.40 (9.99)	55.00 (8.84)	53.36 (8.98)	
Attention and working memory				F(2,178) = 0.74, *p* = .48, η2 = .01
WMS-III letter number sequencing scaled score	11.71 (3.07)	11.60 (2.58)	10.72 (2.93)	
PASAT z-score	−0.12 (1.06)	0.17 (0.89)	0.01 (0.86)	
Processing speed*, *a,b*				F(2,177) = 6.97, *p* = .001, η2 = .07
WAIS-III PSI	111.57 (13.99)	103.31 (16.29)	101.00 (11.26)	
Trail making test A t-score	54.53 (11.52)	49.50 (14.18)	50.18 (13.72)	
Executive function*, *b,c*				F(2,162) = 3.77, *p* = .03, η2 = .04
Trail making test B t-score	55.55 (11.71)	57.57 (9.63)	50.52 (13.46)	

Note: WRAT-4 = Wide Range Achievement Test-4th edition; RAVLT-2 = Rey auditory verbal learning test; BVMT-R = Benton visuospatial memory test; WMS-III = Wechsler memory scales-III; PASAT = Paced auditory serial attention test; WAIS-III PSI = Wechsler adult intelligence scales-III processing speed index. HC = healthy comparison; PTSD + M = PTSD with childhood maltreatment; PTSD = PTSD without significant childhood maltreatment

*significant with FDR correction for multiple comparisons

a= HC significantly different from PTSD

b= HC significantly different from PTSD + M

c= PTSD significantly different from PTSD + M.