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Interpersonal early life trauma is associated with increased cerebral perfusion and poorer memory performance in post-9/11 veterans

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ABSTRACT

Background: Cerebral blood flow (CBF) is critically important in the overall maintenance of brain health, and disruptions in normal flow have been linked to the degradation of the brain's structural integrity and function. Recent studies have highlighted the potential role of CBF as a link between psychiatric disorders and brain integrity. Although interpersonal early life trauma (IP-ELT) is a risk factor for the development of psychiatric disorders and has been linked to disruptions in brain structure and function, the mechanisms through which IP-ELT alters brain integrity and development remain unclear. The goal of this study was to understand whether IP-ELT was associated with alterations in CBF assessed during adulthood. Further, because the cognitive implications of perfusion disruptions in IP-ELT are also unclear, this study sought to investigate the relationship between IP-ELT, perfusion, and cognition. **Methods:** 179 Operations Enduring Freedom/Iraqi Freedom/New Dawn (OEF/OIF/OND) Veterans and military personnel completed pseudo-continuous arterial spin labeling (pCASL) imaging, clinical interviews, the Traumatic Life Events Questionnaire (TLEQ), and a battery of neuropsychological tests that were used to derive attention, memory, and executive function cognitive composite scores. To determine whether individuals were exposed to an IP-ELT, events on the TLEQ that specifically queried interpersonal trauma before the age of 18 were tallied for each individual. Analyses compared individuals who reported an interpersonal IP-ELT (IP-ELT+, n = 48) with those who did not (IP-ELT-, n = 131). **Results:** Whole brain analyses revealed that IP-ELT+ individuals had significantly greater CBF in the right inferior/middle temporal gyrus compared to those in the IP-ELT- group, even after controlling for age, sex, and posttraumatic stress disorder (PTSD). Further, perfusion in the right inferior/middle temporal gyrus significantly mediated the relationship between IP-ELT and memory, not attention or executive function, such that those with an IP-ELT had greater perfusion, which, in turn, was associated with poorer memory. Examination of other clinical variables such as current PTSD diagnosis and severity as well as the interaction between IP-ELT and PTSD yielded no significant effects. **Conclusions:** These results extend prior work demonstrating an association between ELT and cerebral perfusion by suggesting that increased CBF may be an important neural marker with cognitive implications in populations at risk for psychiatric disorders.

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1. Introduction[1]

Exposure to an interpersonal early life trauma (IP-ELT), such as physical, emotional, or sexual abuse before the age of 18, is one of the greatest risk factors for a range of negative health outcomes, including subsequent development of psychiatric disorders and poorer general health (Maschi et al., 2013). This is especially prevalent in the Veteran population, where studies have shown that exposure to and duration of IP-ELT is higher among Veteran than non-Veteran cohorts (McCauley et al., 2015; Schultz et al., 2006). This increased exposure to IP-ELT also appears to carry a heavier burden for Veterans, with a higher prevalence of posttraumatic stress disorder (PTSD) later in life (Bremner et al., 1993; Owens et al., 2009; Van Voorhees et al., 2012). In a *meta*-analysis examining military and civilian populations, Brewin et al. (2000) found that age at trauma and childhood adversity were greater risk factors for later PTSD development in military populations, further suggesting that IP-ELT may be especially important to examine in Veteran populations.

Studies have also pointed to the importance of ELT on brain health, with research suggesting disruptions to both brain structure and function. For example, studies have reported that healthy individuals with exposure to traumatic events during childhood and adolescence have significantly smaller volumes of the hippocampus and anterior cingulate cortex compared to those without ELT (Andersen et al., 2008; Cohen et al., 2006; Dannlowski et al., 2012). A more recent study has shown that both increases and decreases in 13 gray matter regions predicted childhood trauma severity (Clausen et al., 2019). Additional research has shown ELT negatively impacts brain function, with increased functional connectivity and activation in limbic structures during an emotional processing task (Jedd et al., 2015) as well as a sustained attention task (Fortenbaugh et al., 2017) and decreased functional connectivity between amygdalae and prefrontal regions at rest (Fan et al., 2014; Pagliaccio et al., 2015). Moreover, a recent *meta*-analysis reported structural and functional abnormalities in association with childhood trauma type (Cassiers et al., 2018), further implicating disruptions to both structure and function in association with ELT.

Despite the growing body of literature on brain morphologic and functional changes following ELT, little is known about the effect of ELT on perfusion, or cerebral blood flow (CBF). CBF is critically important in the overall maintenance of brain health and has been linked to the degradation of the brain's structural integrity (Bernbaum et al., 2015; Brickman et al., 2009; Promjunyakul et al., 2015, 2016). Thus, understanding the impact of ELT on CBF may be particularly important in understanding the neurobiological sequelae of ELT. Although prior studies of this topic are limited, a recent study examining perfusion in individuals with ELT found that scores on the childhood trauma questionnaire (CTQ) were positively associated with CBF in the bilateral hippocampus and negatively with CBF in the left prefrontal cortex in individuals at high risk for psychosis, providing preliminary evidence that ELT may be associated with long-term alterations in CBF (Allen et al., 2018). The notion that ELT may influence CBF is further supported by research showing that ELT elevates risk for obesity (Gunstad et al., 2006), cardiovascular disease (Dong et al., 2004) and metabolic syndrome (Franz et al., 2019) in adulthood, which are physical health problems known to have negative CBF implications (Birdsill et al., 2013; Dorrance et al., 2014; Pase et al., 2012; Selim et al., 2008). Together, these studies suggest that ELT may be an important factor in later cerebrovascular health.

Beyond the implications for overall brain health, CBF also plays a role in cognitive function. Research in healthy and pathological aging populations have shown that disruptions in CBF are associated with cognitive decline (Benedictus et al., 2017; Bertsch et al., 2009; Chao et al., 2010; Heo et al., 2010; O'Brien et al., 1992; Pearlson et al., 1992). For example, Benedictus and colleagues (2017) examined a group of 88 patients with Alzheimer's disease-related dementia over at least a one-year follow-up period and found that lower whole brain and parietal CBF at baseline was associated with faster rates of cognitive decline. ELT has also been separately linked to cognitive performance (Gould et al., 2012; Majer et al., 2010). Specifically, research suggests that the negative effects of ELT on cognition spans multiple domains, including memory and affective functions as well as sustained attention, and persist well into adulthood after ELT has ceased (Fortenbaugh et al., 2017; Hedges and Woon, 2011; Pechtel and Pizzagalli, 2011). Together, this work indicates that perfusion may have important cognitive implications in individuals exposed to ELT.

In this study, we used pseudo-continuous arterial spin labeling (pCASL), a non-invasive perfusion magnetic resonance imaging (MRI) technique that directly quantifies CBF with magnetically labeled arterial blood water, a battery of neuropsychological tests, and the Trauma Life Events Questionnaire (TLEQ) to examine the association between perfusion, cognition, and IP-ELT in a sample of 179 Operations Enduring Freedom/Iraqi Freedom/New Dawn Veterans (OEF/OIF/OND). We hypothesized that IP-ELT would be associated with increases in perfusion in brain regions such as the temporal lobes, including the hippocampus, and decreases in the prefrontal cortex, which, in turn, would be associated with poorer cognitive performance. Additionally, because ELT is a known risk factor for subsequent development of PTSD (Bremner et al., 1993; Cougle et al., 2010; Lang et al., 2008), which in its own right has been associated with disruptions in perfusion (Bonne et al., 2003; Zhe et al., 2016), we also investigated (1) whether PTSD is associated with perfusion alterations and (2) whether PTSD exacerbates the effects of IP-ELT on perfusion.

2. Methods

2.1. Participants

Participants were 179 Veterans deployed to OEF/OIF/OND (n = 176) or active duty service members not yet deployed to OEF/OIF/OND serving in the Reserves or National Guard (n = 3) enrolled in the Translational Research Center for TBI and Stress Disorders (TRACTS) (McGlinchey et al., 2017) at the VA Boston Healthcare System, Jamaica Plain Campus. Participants were excluded if they reported a history of seizures or neurological illness (unrelated to head injuries), serious mental illness such as bipolar disorder or other psychotic disorders (unrelated to PTSD), unstable psychological diagnosis that would interfere with accurate data collection (determined by consensus of at least two doctorate-level psychologists), active suicidal or homicidal ideation, cognitive disorder due to a general medical condition, incompatibility with MRI due to ferromagnetic objects or pregnancy, a history of moderate or severe TBI at any epoch (pre-deployment, blast/military, or post-deployment), had poor MRI data quality that resulted in unusable data, or had unavailable data on MRI, clinical assessments, or covariates used in analyses. Participants were further excluded from neuropsychological analyses (n = 6) if they failed validity measures on the Medical Validity Symptoms Test (MVST) (Green, 2004), did not have available data on premorbid IQ, or had known factors to influence neuropsychological performance such as English as a second language or low IQ.

[1] Uncommon abbreviations to the field: ASL = arterial spin labeling; BAT-L = Boston Assessment of TBI -Lifetime; BMI = body mass index; CAPS = Clinician-Administered PTSD Scale; CBF = cerebral blood flow; CSF = cerebrospinal fluid; CTQ = Childhood Trauma Questionnaire; CVLT = California Verbal Learning Test; FTND = Fagerstrom Test of Nicotine Dependence; IED = Intra-Extra Dimensional Set Shift; IP-ELT = interpersonal early life trauma; LDH = Lifetime Drinking History; MVST = Medical Validity Symptoms Test; OEF/OIF/OND = Operations Enduring Freedom/Iraqi Freedom/New Dawn; pCASL = pseudo-continuous arterial spin labeling; PTSD = posttraumatic stress disorder; TBI = traumatic brain injury; TLEQ = Trauma Life Events Questionnaire; TOVA = Test of Variables of Attention; WTAR = Wechsler Test of Adult Reading.

All participants provided written and informed consent. The study was approved by the VA Boston Healthcare System Institutional Review Board and Research and Development and was conducted in accordance with the Declaration of Helsinki.

2.2. Clinical assessments

IP-ELT was assessed with the TLEQ (Kubany et al., 2000), which is a self-report measure that assesses exposure to 21 traumatic events that meet the DSM-IV PTSD criterion A1 definition. For each event endorsed, a follow-up question assessed whether the individual also met DSM-IV PTSD criterion A2. To determine whether individuals were exposed to an IP-ELT, events on the TLEQ that specifically queried interpersonal trauma before the age of 18 were tallied for each individual. Following previous published work by our group (Corbo et al., 2016, 2014), individuals were assigned to groups based on whether they endorsed an IP-ELT (IP-ELT+, n = 48) or not (IP-ELT-, n = 131). The IP-ELT- group did not preclude exposure to other events not of an interpersonal nature (e.g. natural disaster, motor vehicle accidents). Table 1 lists details about the type and number of IP-ELTs for the IP-ELT+ group. Further, to determine the effects of adult trauma exposure on the relationship between IP-ELT group and perfusion, items on the TLEQ that specifically queried trauma after the age of 18 were tallied for each individual. For consistency with analyses of IP-ELT, individuals were then assigned to groups based on whether they endorsed an adult trauma (yes, n = 130) or not (no, n = 49). Adult trauma exposure group (yes/no) was then used as a covariate in secondary analyses, which are detailed in the statistical analysis.

PTSD symptoms and severity were assessed with the Clinician-Administered PTSD Scale (CAPS) for DSM-IV (Blake et al., 1995) by doctoral level psychologists. The CAPS is currently the gold standard for assessment of PTSD and captures the presence of PTSD within the past 30 days. Total CAPS score and PTSD diagnosis (yes/no) based on DSM-IV criteria were used in analyses as a measure of current PTSD symptom severity and diagnosis respectively.

History of blast exposure and traumatic brain injury (TBI) was assessed by doctoral-level psychologists using the Boston Assessment of TBI-Lifetime (BAT-L) (Fortier et al., 2014). The BAT-L is a semi-structured interview based on Department of Defense TBI diagnostic criteria that queries participants about blast exposure and TBI pre, during, and post-military experience. The total number of blast exposures at distance ranges of 0–10 m, 11–25 m, and 26–100 m were summed for each individual to obtain a continuous measure. Mild TBI (mTBI) was defined as the presence of altered mental status < 24 h, posttraumatic amnesia < 24 h, and/or loss of consciousness < 30 min pre, during, or post-military experience (i.e., lifetime mild TBI [mTBI], yes/no). Moderate/severe TBI were exclusionary for this study and were not examined.

Table 1
Descriptive characteristics of the traumatic events in the IP-ELT+ group (n = 48).

Variable	*N (%)*	Frequency, *N*					
		1	2	3	4	5	> 5
Type of IP-ELT event							
Family violence	34 (70.8)	6	4	3	1	–	20
Physical abuse	30 (62.5)	2	3	–	–	–	25
Sexual abuse < 13 years old[1]	13 (27.7)	5	1	2	1	–	4
Sexual abuse < 13 years old from someone of the same age[1]	3 (6.4)	1	–	2	–	–	–
Sexual abuse 13–18 years old[1]	4 (8.5)	1	1	–	1	1	–
Number of different types of IP-ELT events							
One	27 (56.3)						
Two	17 (35.4)						
Three	3 (6.3)						
Four	1 (0.1)						
Five	0 (0.0)						

Note: [1]Sexual abuse data was unavailable for one participant (n = 47) and percentages for this data were determined with n = 47. Frequency indicates the number of times the IP-ELT was reported for participants. IP-ELT = interpersonal early life trauma.

The Fagerstrom Test for Nicotine Dependence (FTND) (Heatherton et al., 1991) was used to assess cigarette smoking status (yes/no). The FTND is a self-report questionnaire in which individuals answer various questions relating to nicotine dependence. For the purposes of this study, only cigarette smoking status was analyzed (yes/no).

The Lifetime Drinking History (LDH) (Skinner and Sheu, 1982) was used to asses alcohol use throughout the lifespan. The LDH is a retrospective interview that yields an estimate of total lifetime exposure to alcohol using the number of standard drinks consumed and a standard drink conversion (grams of absolute alcohol). For the current study, the LDH total score was then weight corrected to account for grams of absolute alcohol per kilogram of body weight. Additionally, the average and maximum number of drinks on a drinking day were also derived from the LDH. Total weight corrected LDH score was used in analyses. The average number of drinks on a drinking day and the maximum number of drinks on a drinking day are included in the demographics table to aid in interpretation.

All diagnoses were reviewed by a diagnostic team consensus of at least three Ph.D. or M.D.s for confirmation of TBI and DSM-IV diagnoses.

2.3. Neuropsychological assessments

Participants were administered the Wechsler Test of Adult Reading (WTAR) (Wechsler, 2001) as an estimate of premorbid IQ (WTAR standard score) as well as a battery of neuropsychological tests. Raw scores across neuropsychological test measures were converted to scaled, age-adjusted *z*-scores. For data reduction purposes, these neuropsychological *z*-scores were averaged to form three composite measures in domains of memory, attention, and executive function. This method was validated in an expanded set of the current sample (Riley et al., 2019). The memory composite was comprised of the California Verbal Learning Test-II (CVLT) short delay free recall, long delay free recall, and long delay recognition (Woods et al., 2006). The attention composite was comprised of the Test of Variables of Attention (TOVA) mean reaction time and *d'* (Henry, 2005; Leark et al., 2008), Digit Span Forward (Wechsler, 2008), and the Number Sequencing Subtest of the Trail Making Task (Trails-A) (Delis et al., 2001). The executive function composite was comprised of the Number/Letter Switching Subtest of the Trail Making Test (Trails-B) (Delis et al., 2001), Inhibition total time on the Stroop Test (Delis et al., 2001), the CANTAB Intra-Extra Dimensional Set Shift (IED; http://www.cantab.com), Verbal Fluency FAS (Delis et al., 2001), and Auditory Consonant Trigrams averaged across 9 s, 18 s, and 36 s delays (Stuss et al., 1985, 1987). The final sample for neuropsychological analyses was n = 173.

2.4. Image acquisition, processing, and analysis

2.4.1. Acquisition

The first 127 participants' neuroimaging data were collected on a Siemens 3-Tesla TIM Trio whole-body scanner at VA Boston Healthcare System, Jamaica Plain campus and 52 additional participants' neuroimaging data were collected after upgrading to a Siemens Prisma. The TIM Trio data were collected with a 32-channel head coil (12-channel for structural scans). Two Magnetization Prepared Rapid Gradient Echo (MP-RAGE) T1-weighted structural scans and one pseudo-continuous arterial spin labeling (pCASL) scan were acquired for each participant. The MP-RAGE T1-weighted parameters were as follows: TR = 2530 ms, TE = 3.32 ms flip angle = 7°, FOV = 256, Matrix = 256 × 256, voxel size = 1 mm^3. The pCASL sequence obtained for this research study was previously reported in Wu, Fernández-Seara, Detre, Wehrli, &

Wang (2007) and the parameters were as follows: TR = 4000 ms, TE = 11 ms, post-labeling delay = 1.5 s, labeling duration = 1.5 s, mean Gz × 10 = 6 mT/m, 30 tag-control pairs, Hanning window--shaped RF pulse with duration = 500 μs, RF gap = 360 μs, flip angle = 25°, slice-selective gradient = 6 mT/m, FOV = 220 mm, matrix = 64 × 64, 20 5 mm slices with 1 mm gap acquired sequentially inferior to superior, label placed at 9 cm below center of slices, no background suppression used, and a gradient echo planar imaging (EPI) sequence was used for image readout. The Siemens Prisma data were collected with a 20-channel head coil for structural and a 64-channel head coil for pCASL scans. Sequence specifications were kept the same after the upgrade from the Trio to Prisma, resulting in identical parameters for both structural and perfusion imaging except that the TE for the pCASL scan was changed from 11 ms to 12 ms. To account for potential scanner software differences, a scanner flag was included in analyses as a covariate. Individuals scanned with the Prisma were significantly older than those scanned with the Trio (Prisma, M (SD) = 36.5 (9.1); Trio, M(SD) = 32.6 (8.5); $t(177) = -2.71$, $p = 0.007$), but no other demographic variables were significantly different between scanners. MP-RAGE scans were averaged to create a single high contrast-to-noise image, although a second MP-RAGE was unavailable for three individuals and structural registration for those individuals were completed with a single MP-RAGE.

2.4.2. Processing

Data were processed with FMRIB's Software Library's (FSL, version 6.0.1, http://www.fmrib.ox.ac.uk/fsl/) Bayesian Inference for Arterial Spin Labeling (BASIL). First, structural images were pre-processed with fsl_anat, which is a general anatomical pipeline script that performs brain extraction, bias-field correction, segmentation, orientation to standard MNI space, and linear and non-linear registration. Next, Oxford ASL (oxford_asl), a command line utility within BASIL, was used to process pCASL data to produce a calibrated map of resting state perfusion (Chappell et al., 2008). PCASL data were motion corrected with MCFLIRT (Jenkinson et al., 2002), corrected for partial volume, (Chappell et al., 2011), and smoothed with adaptive spatial smoothing (Groves et al., 2009). The oxford_asl tool performed a tag-control subtraction and the resulting time series was used to calculate relative CBF by using a Bayesian model inversion technique (Chappell et al., 2008), an arterial transit time of 1.3 s, and a T_1 relaxation time of 1.65 s for arterial blood and 1.3 s for tissue. Relative CBF in scanner units was then converted to absolute physiological units (ml/100 g/min) with a calibration image, which was created using the mean of the unlabeled (control) images from the data, by calling asl_calib to model the M0 of cerebrospinal fluid (CSF) assuming 3 T default T1 CSF, T2 CSF, and T2 blood values (4.30 ms, 750 ms, and 150 ms, respectively). The calibration process computed and applied the calibration factor by measuring equilibrium magnetization of the CSF in the ventricles, which automatically generated a ventricle mask that was then transformed into ASL space and applied to the calibration image for conversion. Resulting calibrated CBF maps were visually inspected for data quality.

2.4.3. Analysis

Whole brain group-level analyses were conducted with flameo in FSL. The partial volume corrected and calibrated perfusion maps in standard space for each subject were combined into a single 4D image for further group-level processing. To determine voxel-wise perfusion correlates with variables of interest, group-level analyses were conducted using mixed effects model FLAME stage 1 (Beckmann et al., 2003; Woolrich, 2008; Woolrich et al., 2004). Age, sex, and scanner were entered into the model as regressors and group-level perfusion maps were generated for group contrasts (IP-ELT+ > IP-ELT- and IP-ELT+ < IP-ELT-). Analyses were repeated including total CAPS score (i.e., current PTSD symptom severity) and current PTSD diagnosis as additional covariates in separate models (along with age, sex, and scanner). Main effects of current PTSD symptom severity (positive and negative) and diagnosis (PTSD > No PTSD and No PTSD > PTSD) were also examined. Smoothness estimates were generated from the residuals using FSL's smoothest command line utility. Lastly, Z statistic images were thresholded using clusters determined by $Z >= 3.1$ ($p < = 0.001$) with a corrected cluster significance threshold of $p = 0.05$ using FSL's cluster tool.

2.5. Statistical approach

Statistical analyses were performed using SPSS version 26 (IBM Corp., Armonk, NY) or MPlus version 7.11 (Muthén and Muthén, 2013).

2.5.1. Demographics and clinical characteristics

IP-ELT group differences in demographic and clinical characteristics were examined using independent t-tests for continuous data or chi-square tests for categorical data. The number of total blast exposures variable was positively skewed and therefore was log transformed with log base 10 after adding a constant (to account for any zero values) and before it was entered into analyses.

2.5.2. Secondary follow-up analyses

The significant cluster that survived multiple comparison correction in the whole-brain IP-ELT analysis (that included age, sex, scanner and current PTSD symptom severity) was binarized to serve as a mask. Next, this cluster-derived mask was used to extract perfusion values in standard space from each individual's partial volume corrected and calibrated perfusion map. These cluster-extracted perfusion values were then used in all follow-up analyses.

2.5.2.1. The number of IP-ELTs. We performed a secondary follow-up analysis to confirm whether the implicated region in the whole-brain IP-ELT group analysis was also associated with the number of IP-ELTs. The number of IP-ELTs variable was positively skewed and therefore was log transformed with log base 10 after adding a constant (to account for any zero values) and before it was entered into the analysis. A follow-up hierarchical regression model was performed in which age, sex, scanner, and total CAPS score were included in the first step of the model followed by the log transformed number of IP-ELTs in the second step.

2.5.2.2. Other factors relevant to perfusion. To determine whether factors such as adult trauma exposure, the number of total blast exposures, the presence of a lifetime mTBI, body mass index (BMI), smoking status, or lifetime alcohol use influenced the relationship between IP-ELT and perfusion, separate follow-up hierarchical regression models were performed in which age, sex, scanner, total CAPS score, and adult trauma exposure group, the log transformed number of total blast exposures, lifetime mTBI, BMI, smoking status, or the weight corrected LDH total score were included in the first step of the model followed by IP-ELT group in the second step. Cluster-extracted perfusion values served as the dependent variable.

2.5.2.3. The interaction between IP-ELT and PTSD. To examine whether the effect of IP-ELT on perfusion was exacerbated by PTSD, a follow-up hierarchal regression analysis was performed in which the interaction between current PTSD symptom severity and IP-ELT group was included in the model. Age, sex, and scanner were included in the first step of the model, the main effects of total CAPS score and IP-ELT group were added in the second step, and the interaction between total CAPS score and IP-ELT group was included in the final step. Cluster-extracted perfusion values served as the dependent variable.

2.5.2.4. Mediation of cognitive function. To examine the potential mediating effects of perfusion on the relationship between IP-ELT and cognitive performance, we used direct maximum likelihood estimation and bootstrap mediation models as implemented in MPlus. In this

model, the independent variable was IP-ELT group and the dependent variables were memory, attention, and executive function composites scores, with the cluster-extracted perfusion values serving as the mediator. Age, sex, scanner, total CAPS score, and WTAR standard score (premorbid IQ) were included as covariates. The maximum percentage of missing data on any variable was 30.6% and all analyses proceeded with direct maximum likelihood estimation. Bootstrapping was used to estimate the sample distribution (n = 10000) and statistical significance for direct and indirect effects were set at $p < 0.05$ and 95% confidence intervals.

3. Results

3.1. Demographics and clinical characteristics

Table 2 lists the participant demographics and clinical characteristics. Groups did not significantly differ in scanner (Trio or Prisma), age, BMI, smoking status, lifetime alcohol use (weight corrected LDH total score and average or maximum number of drinks on a drinking day), current PTSD diagnosis, the presence of a lifetime mTBI, the number of total blast exposures, premorbid IQ, or memory and executive cognitive composite scores. However, the IP-ELT+ group had significantly fewer males, higher current PTSD symptom severity, and lower attention composite scores than the IP-ELT- group. Age, sex, and scanner were included as covariates in all analyses. Analyses were repeated including current PTSD symptom severity and PTSD diagnosis as additional covariates. Additionally, various follow-up analyses were conducted including other demographic variables as covariates.

3.2. Whole brain IP-ELT analyses

Whole brain results revealed an effect of IP-ELT such that individuals in the IP-ELT+ group had significantly greater perfusion in the right inferior/middle temporal gyrus (peak MNI coordinates = 54 –24 –32, *Z* Max = 4.51, cluster size = 286 voxels) than those in the IP-ELT- group (Fig. 1). There were no significant perfusion reductions in the IP-ELT+ group compared to the IP-ELT- group. The pattern of results did not change when current PTSD symptom severity and PTSD diagnosis were separately included as covariates in the model along with age, sex, and scanner (current PTSD symptom severity as covariate in model: peak MNI coordinates = 54 –24 –32, *Z* Max = 4.10, cluster size = 207 voxels; current PTSD diagnosis as covariate in model: peak MNI coordinates = 54 –24 –32, *Z* Max = 4.51, cluster size = 295 voxels). Further, when we examined the number of IP-ELTs rather than IP-ELT group in a post-hoc, secondary analysis examining the significant cluster of the whole brain IP-ELT group analysis, the pattern of results did not change such that with more IP-ELTs, there was greater perfusion in the right inferior/middle temporal gyrus ($\Delta R^2 = 0.078$, $\Delta F(1,173) = 16.775$, $p < 0.001$, unstandardized B = 20.796, β = 0.292, $p < 0.001$). We also re-ran the whole brain analysis with the number of IP-ELTs rather than IP-ELT group and the pattern of results did not change such that with a greater number of IP-ELTs, there was increased perfusion in right inferior/middle temporal gyrus (see the Supplementary materials for more details of this analyses). Details relating to the main effects of age, sex, and scanner are also reported in the Supplementary Materials (Tables S1-S3).

3.3. Whole brain PTSD analyses

Separate examination of the wholebrain main effects of current PTSD symptom severity and PTSD diagnosis (controlling for age, sex, and scanner) revealed neither significant positive nor negative associations with current PTSD symptom severity nor group differences between those with and without PTSD after correction for multiple comparisons.

3.4. Other factors relevant to perfusion

To confirm that the effect was associated with IP-ELT and not with underlying effects of other factors also relevant to perfusion, we ran several follow-up hierarchal regression models that included adult trauma exposure group, the number of total blast exposures, the presence of a lifetime mTBI, BMI, smoking status, or lifetime alcohol use as an additional covariate. The pattern of results did not change, such that individuals in the IP-ELT+ group had significantly greater perfusion in the right inferior/middle temporal gyrus than the IP-ELT- group even after including these additional covariates in separate models (IP-ELT group unstandardized B ranged from 7.944 to 9.008 and β ranged from 0.281 to 0.310, all *p*'s < 0.001; covariates of interest unstandardized B ranged from −9.822E-5 to 2.017 and β ranged from 0.005 to 0.111, all *p*'s > 0.1; see Supplementary Tables S4-S9).

3.5. The interaction between IP-ELT and PTSD

To examine whether the effect of IP-ELT on perfusion was exacerbated by PTSD, we performed a follow-up hierarchal regression analysis in which the interaction between current PTSD symptom severity and IP-ELT group was included in the model. There was no change in the model when the interaction term was added ($\Delta R^2 = 0.00$, $\Delta F(1,172) = 0.00$, $p > 0.9$) and the interaction between current PTSD symptom severity and IP-ELT group was not significantly associated with perfusion of the right inferior/middle temporal gyrus (B = -0.001, SE(B) = 0.069, β = -0.001, $p > 0.9$).

3.6. Mediation of cognitive function

To examine whether IP-ELT group was associated with cognitive performance through its effect on perfusion, a mediation analysis that included memory, attention, and executive function composite scores was performed. The mediation analysis revealed that IP-ELT group indirectly influenced memory performance through its effect on perfusion in the right inferior/middle temporal gyrus, even after accounting for age, sex, scanner, current PTSD symptom severity, and premorbid IQ and when including all three cognitive composites in the model (Fig. 2). Individuals who had experienced an IP-ELT had greater perfusion in the right inferior/middle temporal gyrus than those without an IP-ELT (B = 8.907, $p < 0.001$) and, in turn, perfusion was negatively associated with memory performance (B = -0.018, $p = 0.009$). The direct effect of IP-ELT group on memory was not significant, although it just missed the threshold for significance (B = 0.359, $p = 0.061$). A bias-corrected bootstrap confidence interval for the indirect effect of memory (B = -0.156) based on 10,000 bootstrap samples did not encompass zero (95% CI [−0.277, −0.045], $p = 0.026$). There were no significant indirect and direct effects with executive function (indirect: B = 0.008, $p = 0.822$; direct: B = -0.119, $p = 0.365$), and there was no significant indirect effect with attention (B = 0.016, $p = 0.728$). However, there was a significant direct effect of IP-ELT group on attention (B = -0.419, $p = 0.002$), such that the IP-ELT+ group had significantly worse performance in attention than those in the IP-ELT- group. The total amount of variance explained by the mediator and dependent variables were: $R^2 = 0.209$ for perfusion in the right inferior/middle temporal gyrus, $R^2 = 0.132$ for the memory composite score, $R^2 = 0.200$ for the attention composite score, and $R^2 = 0.195$ for the executive function composite score. The residual correlations of the cognitive composites were minimal: attention and executive R = 0.444, $p < 0.001$; attention and memory R = 0.099, $p = 0.244$, executive

Table 2
Demographic and clinical participant characteristics.

Variable	Total (n = 179)	IP-ELT+ (n = 48)	IP-ELT- (n = 131)	Group Difference
Demographic				
Scanner (Trio), *n(%)*	127 (70.9)	35 (72.9)	92 (70.2)	$\chi^2(1) = 0.123$, $p = 0.73$
Sex (male), *n(%)*	167 (93.3)	41 (85.4)	126 (96.2)	$\chi^2(1) = 6.511$, $p = 0.01$*
Age, *M(SD)*	33.8 (8.8)	34.5 (8.9)	33.5 (8.8)	$t(177) = -0.714$, $p = 0.48$
BMI[1], *M(SD)*	28.1 (3.9)	27.7 (4.2)	28.2 (3.8)	$t(175) = 0.823$, $p = 0.41$
Smoking status (cigarette smoker)[2], *n(%)*	31 (19.1)	11 (25.6)	20 (16.8)	$\chi^2(1) = 1.572$, $p = 0.21$
LDH total weight corrected, *M(SD)*[3,4]	2446.3 (5122.3)	3540.7 (8841.2)	2056.1 (2757.4)	$t(48.2) = -1.120$, $p = 0.27$
Average # drinks on drinking day, *M(SD)*[4]	6.1 (3.8)	6.0 (3.8)	6.2 (3.8)	$t(173) = 0.361$, $p = 0.72$
Maximum # drinks on drinking day, *M(SD)*[4]	10.6 (6.2)	10.3 (6.4)	10.7 (6.2)	$t(173) = 0.302$, $p = 0.76$
Clinical				
CAPS total score, *M(SD)*	48.9 (29.0)	57.3 (29.8)	45.9 (28.1)	$t(177) = -2.365$, $p < 0.02$*
Current PTSD diagnosis, *n(%)*	132 (73.7)	37 (77.1)	95 (72.5)	$\chi^2(1) = 0.378$, $p = 0.54$
Adult trauma exposure group (yes), *n(%)*	130 (72.6)	39 (81.3)	91 (69.1)	$\chi^2(1) = 2.454$, $p = 0.12$
Presence of a lifetime mTBI, *n(%)*	124 (69.3)	38 (79.2)	86 (65.6)	$\chi^2(1) = 3.016$, $p = 0.08$
Number of total blast exposures[5], *M(SD)*	0.9 (0.7)	0.8 (0.6)	0.9 (0.8)	$t(177) = 0.689$, $p = 0.49$
Non-log-transformed, *M(SD)*	41.4 (141.1)	16.8 (33.0)	50.4 (163.0)	—
Neuropsychological[6]				
WTAR premorbid IQ, *M(SD)*[7]	104.6 (11.7)	105.2 (13.8)	104.3 (10.7)	$t(171) = -0.454$, $p = 0.65$
Attention composite, *M(SD)*	0.07 (0.7)	−0.2 (0.7)	0.2 (0.6)	$t(118) = 3.266$, $p = 0.001$*
Memory composite, *M(SD)*	−0.4 (1.0)	−0.2 (0.9)	−0.4 (1.0)	$t(156) = -0.962$, $p = 0.34$
Executive function composite, *M(SD)*	0.1 (0.6)	−0.07 (0.7)	0.2 (0.6)	$t(145) = 0.777$, $p = 0.44$

Note: [1]BMI data were unavailable for two participants (n = 177, IP-ELT+ = 47, IP-ELT- = 130) and [2]smoking status (cigarettes) were unavailable for 17 participants (n = 162, IP-ELT+ = 43, IP-ELT- = 119). [3]LDH total score was weight corrected (grams of pure alcohol per kilogram of body weight). Because equal variances were not assumed, a Welch *t*-test was conducted. [4]Data were unavailable for 4 participants (n = 175, IP-ELT+ = 46, IP-ELT- = 129). [5]Because the number of total blast exposures variable was positively skewed, we used the log transform (with log base 10) of this variable in the regression model and in comparing groups; the values here represent the log transform (log base 10) of this variable. [6]Sample size varied on neuropsychological variables based on missing data: attention n = 120 (IP-ELT+ = 35, IP-ELT- = 85), memory n = 158 (IP-ELT+ = 42, IP-ELT- = 116), and executive function n = 147 (IP-ELT+ = 38, IP-ELT- = 109). Although neuropsychological data were limited to conduct t-tests, neuropsychological mediation analyses included anyone with at least one predictor variable and used full information likelihood estimation (n = 173). [7]WTAR scores reflect the standard score (n = 173, IP-ELT+ = 48, IP-ELT- = 125). BMI = body mass index; IP-ELT = interpersonal early life trauma; LDH = lifetime drinking history; mTBI = mild traumatic brain injury; PTSD = posttraumatic stress disorder; WTAR = Wechsler Test of Adult Reading. *$p < 0.05$.

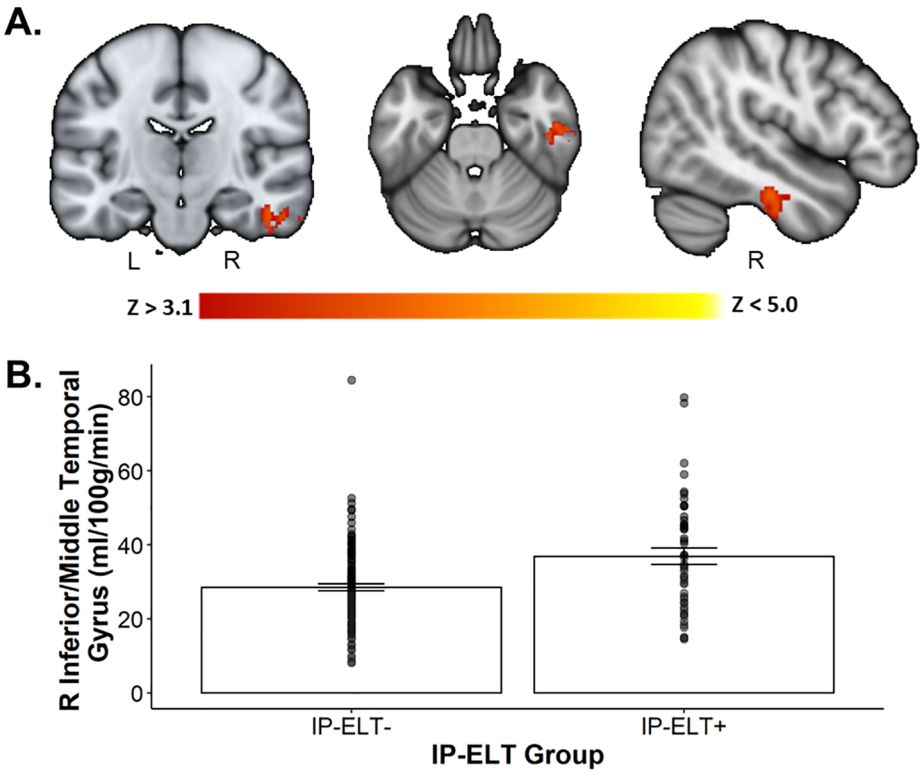

Fig. 1. IP-ELT+ > IP-ELT- in a whole brain analysis of perfusion. (A) There was significantly greater perfusion in the right inferior/middle temporal gyrus in the IP-ELT+ group compared to the IP-ELT- group, even after controlling for age, sex, and scanner (this effect held even after additionally controlling for PTSD). Color scale indicates *Z*-score threshold. **(B)** Corresponding bar graph with data points overlaid showing group differences in perfusion of the right inferior/middle temporal gyrus. Error bars reflect standard error of the mean. IP-ELT = interpersonal early life trauma; L = left; R = right.

and memory R = 0.179, p = 0.015. There were several significant covariate effects: age was significantly associated with perfusion (B = -0.232, p = 0.011); scanner was significantly associated with memory (B = -0.425, p = 0.02), perfusion (B = -7.822, p < 0.001), and just missed the threshold for significance for attention (B = -0.233, p = 0.052); and premorbid IQ was significantly associated with attention (B = 0.018, p < 0.001), executive function (B = 0.021, p < 0.001), and memory (B = 0.015, p = 0.032).

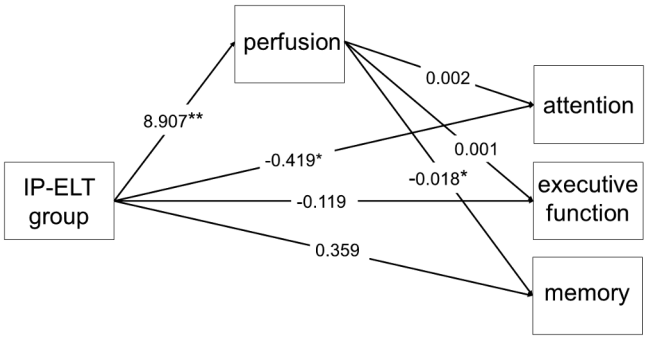

Fig. 2. Mediation model of cognitive function. IP-ELT group indirectly influenced memory performance through its effect on perfusion in the right inferior/middle temporal gyrus (B = -0.156, p = 0.026), even after accounting for age, sex, scanner, current PTSD symptom severity, and premorbid IQ (WTAR standard score) and when including all three cognitive composites in the model. There were no significant indirect or direct effects with executive function (indirect: B = 0.008, p = 0.822; direct: B = -0.119, p = 0.365) and no significant indirect effect with attention (indirect: B = 0.016, p = 0.728). However, there was a significant direct effect of IP-ELT group on attention (direct: B = -0.419, p = 0.002). The residual correlations of the cognitive composites were: attention and executive R = 0.444, p < 0.001; attention and memory R = 0.099, p = 0.244, executive and memory R = 0.179, p = 0.015. There were significant effects of covariates throughout the model: age was significantly associated with perfusion (B = -0.232, p = 0.011); scanner was significantly associated with memory (B = -0.425, p = 0.02), perfusion (B = -7.822, p < 0.001), and just missed the threshold of significance for attention (B = -0.233, p = 0.052); and premorbid IQ was significantly associated with attention (B = 0.018, p < 0.001), executive function (B = 0.021, p < 0.001), and memory (B = 0.015, p = 0.032). Estimates shown are unstandardized. **p < 0.001; *p < 0.05. IP-ELT = interpersonal early life trauma; WTAR = Weschler Test of Adult Reading.

4. Discussion

This study investigated the association of IP-ELT on perfusion in a cohort of 179 OEF/OIF/OND Veterans. Using pCASL imaging, we found that individuals exposed to an IP-ELT had increased perfusion in the right inferior/middle temporal gyrus. This relationship was not apparent in other clinical or CBF-relevant factors including PTSD, the interaction between PTSD and IP-ELT, the number of total blast exposures, the presence of a lifetime mTBI, BMI, smoking status, or lifetime alcohol use. Additionally, we found that increased perfusion in the right inferior/middle temporal gyrus mediated the relationship between IP-ELT and memory composite scores, such that those with an IP-ELT had greater perfusion, which, in turn, was associated with worse memory performance. There were no significant mediating effects for performance in attention or executive function domains, although attention performance was significantly worse in those with IP-ELT+ . Together, these results add to the growing literature that suggests a putative role of early adversity on brain health and cognition (Andersen et al., 2008; Cohen et al., 2006; Dannlowski et al., 2012; Fan et al., 2014; Fortenbaugh et al., 2017; Gould et al., 2012; Jedd et al., 2015; Majer et al., 2010; Pagliaccio et al., 2015).

Our finding that IP-ELT is associated with increased perfusion is consistent with previous work by Allen and colleagues (2018) who reported a positive association between CTQ scores and CBF. However, the brain regions that were reported to have increased perfusion differed across the studies: in the current study, we found increases in the right inferior/middle temporal gyrus while Allen et al. (2018) reported increases in the bilateral hippocampus. Interestingly, this same study also found decreased CBF in the left prefrontal cortex in those with higher CTQ scores, which we were unable to replicate in the current

study. However, it is important to note that our study included a Veteran sample without a history of serious mental illness, which is different from Allen et al.'s (2018) study that examined individuals who were at high risk for psychosis. Instead, our results point to increased perfusion in the right inferior/middle temporal gyrus, which is a region commonly associated with the default mode network (Gusnard et al., 2001b; Raichle et al., 2001).

The default mode network is a network of brain regions that is engaged primarily at rest or during internally directed tasks such as mind-wandering, future thinking, self-mentalizing, autobiographical memory, and social processing of the self and others (Andrews-Hanna et al., 2010, 2014; Gusnard et al., 2001a, 2001b; Kucyi et al., 2016; Raichle et al., 2001; Spreng and Grady, 2010). Within default mode network function, the middle temporal gyrus has been implicated in the dorsomedial prefrontal cortex subsystem of the default mode network, which is primarily involved in self-referential judgements, the present mental state, story comprehension and semantic memory processing and language (Andrews-Hanna et al., 2010; Spreng and Andrews-Hanna, 2015). Interestingly, disruptions in self-referential processing is a common clinical presentation of many psychiatric disorders such as major depressive disorder, PTSD, and schizophrenia (Bora et al., 2009; Frewen et al., 2011; Harvey et al., 2011; LeMoult et al., 2017; Mor and Winquist, 2002; Nejad et al., 2013), which commonly present in individuals exposed to an ELT (Bremner et al., 1993; Cougle et al., 2010; Lang et al., 2008; McLaughlin et al., 2010; Read et al., 2001, 2005). Thus, it is possible that perfusion alterations in a region important for self-referential processing may act as a mechanism for ELT-associated development of psychiatric disorders in adulthood. This is consistent with the notion that ELT interferes with the development of the DMN and its associated functions, which may, in turn, underly the proliferation of psychiatric processes (Daniels et al., 2011). However, this is a cross-sectional study and longitudinal research is needed to confirm this hypothesis.

Our finding that increased perfusion in the right inferior/middle temporal gyrus mediates the relationship between IP-ELT and memory performance suggests that perfusion in this region may be particularly important in IP-ELT-associated cognitive outcomes. Previous work has found that ELT is associated with a range of cognitive deficits in memory, attention, executive function, and affective processing (Fortenbaugh et al., 2017; Gould et al., 2012; Hedges and Woon, 2011; Majer et al., 2010; Pechtel and Pizzagalli, 2011).

Nonetheless, our results extend previous findings by showing that the relationship between IP-ELT and memory was statistically mediated by perfusion in the right inferior/middle temporal gyrus. The inferior/middle temporal gyrus has been implicated in language and semantic memory processing, including the storage of object information (Cabeza and Nyberg, 2000; Chao et al., 1999; Maguire et al., 2000; Spreng and Andrews-Hanna, 2015) as well as episodic encoding across a spectrum of Alzheimer's patients and controls (Leube et al., 2008). Here, we report that *increased*, rather than decreased, perfusion may have negative cognitive implications in IP-ELT exposed individuals. This is consistent with work in the pathological aging literature that has shown that mild cognitive impairment patients also have increased perfusion in temporal regions, which may be a potential first step in neurodegenerative processes (Alexopoulos et al., 2012; Alsop et al., 2008; Luckhaus et al., 2008). Taken together, these results raise the possibility that increased perfusion in temporal regions is a marker of metabolic stress on the system that thereby propagates tissue dysfunction and associated negative behavioral outcomes (Bakker et al., 2012; Beason-Held et al., 2013; Kapogiannis and Mattson, 2011; Sojkova et al., 2008). However, more research is needed to confirm these hypotheses. Interestingly, we did not find that perfusion served as a mediator of the link between IP-ELT and other cognitive domains such as attention or executive function, although we did report a main effect of IP-ELT on attention. Importantly, the residual correlations of the cognitive composites were minimal, which is consistent with the differential pattern of mediation results and the notion that these composites are different constructs. Nonetheless, one possible explanation for our differential pattern of mediation findings is that the inferior/middle temporal gyrus is more heavily involved in memory than attention or executive function processes (Cabeza and Nyberg, 2000; Spreng and Andrews-Hanna, 2015). Another possibility is that other neuroimaging metrics not measured in the current study such as functional connectivity or brain structure may play a larger role than perfusion in mediating the relationship between IP-ELT and attention and executive function (Corbo et al., 2016; Lu et al., 2017). It will be important for future research to investigate other potential factors that may mediate the link between IP-ELT and cognition.

Contrary to our initial hypothesis, we did not find an effect of PTSD on perfusion. This contrasts with previous work that has shown alterations in perfusion at rest in PTSD (Bonne et al., 2003; Zhe et al., 2016). One possible explanation for this discrepancy is that this previous work examined acute civilian-related PTSD (e.g. motor vehicle accidents), in which imaging took place within 6 months after trauma, and compared them to non-traumatized healthy controls. In the current study, PTSD was deployment-related and in the chronic phase (i.e., the trauma occurred years prior to imaging) and controls were trauma-exposed. Interestingly, in the only other study to investigate Veterans with chronic PTSD using the CAPS, Schuff and colleagues (2011) reported increased resting CBF in the right parietal, superior temporal, inferior frontal, and superior frontal cortices in PTSD patients. However, the sample size of that study (n = 17 with PTSD) was significantly smaller than the current study (n = 132 with PTSD), which might have contributed to the disparity in findings. Nonetheless, it will be important to continue to investigate PTSD-associated effects on CBF to understand these inconsistencies. Further, we did not find that PTSD exacerbated the effect of IP-ELT on perfusion. Interestingly, Corbo and colleagues (2014) found a significant interaction between IP-ELT and PTSD on cortical thickness in an overlapping sample of the current study. One possible explanation for the inconsistency in findings is that gray matter perfusion may be more sensitive to IP-ELT than other brain metrics such as cortical thickness, which may require the additive effects of PTSD for discernable consequences. However, more work is needed to investigate this hypothesis further.

The limitations of this study should be noted. First, this study assessed IP-ELT with the TLEQ, which is a trauma questionnaire that assesses trauma across the lifespan. Future studies should re-examine these research questions with questionnaires specifically focused on childhood trauma such as the CTQ. Second, this study is cross-sectional, and we cannot make causal inferences about trauma, perfusion, and cognition. Third, we were unable to examine other potentially relevant cardiometabolic factors such as blood pressure and cholesterol in relationship to the association between IP-ELT and perfusion. However, given that our finding was increased perfusion rather than decreased perfusion in association with IP-ELT, it is unlikely that cardiometabolic factors underlie this effect (Muller et al., 2010; Nobili et al., 1993). This is further supported by our finding that BMI (a cardiometabolic factor that was available in the current study) was neither significantly associated with perfusion nor impacted the relationship between IP-ELT and perfusion. Fourth, our memory cognitive composite measure was derived from one instrument (CVLT-II) while the attention and executive function composites were derived from multiple instruments. Thus, it is possible that nuances in performance on a single measurement could have introduced undue influence on our findings and thereby contributed to the differential mediation findings with regards to memory verses other forms of cognition. More research with a variety of memory instruments is needed to confirm our findings. Finally, our sample was predominately male combat Veterans, which limits our ability to generalize our results to non-military groups or women.

5. Conclusion

In summary, we report that IP-ELT is associated with disruptions in cerebrovascular health, even after accounting for other relevant clinical factors such as PTSD, blast exposure, mTBI, BMI, smoking status, and lifetime alcohol use. Specifically, our results point to increased perfusion in the right inferior/middle temporal gyrus in individuals with an IP-ELT, which, in turn, mediates the relationship between IP-ELT and memory performance and suggest that IP-ELT-associated disruptions in perfusion may have negative cognitive consequences. The current findings extend prior work demonstrating an association between ELT and cerebral perfusion by suggesting that increased CBF may be an important neural marker with cognitive implications in populations at risk for psychiatric disorders.

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CRediT authorship contribution statement

Danielle R. Sullivan: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Writing - original draft, Writing - review & editing. **David H. Salat:** Methodology, Writing - original draft, Writing - review & editing. **Erika J. Wolf:** Methodology, Writing - original draft, Writing - review & editing. **Mark W. Logue:** Writing - review & editing. **Catherine B. Fortier:** Data curation, Methodology, Writing - review & editing. **Jennifer R. Fonda:** Data curation, Methodology, Writing - review & editing. **Joseph DeGutis:** Data curation, Methodology, Writing - review & editing. **Michael Esterman:** Data curation, Methodology, Writing - review & editing. **William P. Milberg:** Funding acquisition, Methodology, Writing - review & editing. **Regina E. McGlinchey:** Funding acquisition, Methodology, Writing - review & editing. **Mark W. Miller:** Funding acquisition, Methodology, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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