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Investigating the Separate and Interactive Associations of Trauma and Depression on Brain Structure: Implications for cognition and aging

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Abstract

Objective—Trauma and depression are associated with brain structural alterations; their combined effects on these outcomes are unclear. We previously reported a negative effect of trauma, independent of depression, on verbal learning and memory; less is known about underlying structural associates. We investigated separate and interactive associations of trauma and depression on brain structure.

Methods—Adults aged 30–89 (N=203) evaluated for depression (D+) and trauma history (T+) using structured clinical interviews were divided into 53 D+T+, 42 D+T−, 50 D−T+, and 58 D−T−. Multivariable linear regressions examined the separate and interactive associations of depression and trauma with prefrontal and temporal lobe cortical thickness composites, and hippocampal volumes adjusting for age, sex, predicted verbal IQ, comorbid anxiety, and vascular risk. Significant results informed analyses of tract-based structural connectomics measures of efficiency and centrality.

Results—Trauma, independent of depression was associated with greater left prefrontal cortical (PFC) thickness, in particular the medial orbitofrontal cortex (OFC) and pars orbitalis. A trauma×depression interaction was observed for the right PFC in age-stratified analyses: older D+T+ had reduced PFC thickness compared to older D−T+ individuals. Regardless of age, trauma was associated with more left medial OFC efficiency and less pars orbitalis centrality. In the T+ group, left pars orbitalis cortical thickness and centrality negatively correlated with verbal learning.

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Conclusions—Trauma, independent of depression, associated with altered PFC characteristics, morphologically and in terms of structural network communication and influence. Additionally, findings suggest there may be a combined effect of trauma and depression in older adults.

Keywords

trauma; depression; neuroimaging; connectome; aging; prefrontal cortex

Introduction

Trauma increases risk for adverse outcomes including cognitive decline (Petkus et al., 2012; Ritchie et al., 2012) and depression (Brown et al., 2014). Depression is associated with cognitive alterations across learning, memory, executive functioning and information processing speed (Dotson et al., 2008; Elderkin-Thompson et al., 2011; Snyder, 2013). Likewise, trauma is associated with worse learning and memory (Karstens et al., 2017; Ritchie et al., 2012; Yehuda et al., 2005), executive functioning (Petkus et al., 2012), and information processing speed (Stein et al., 2002). We previously reported that trauma, independent of depression, was negatively associated with verbal learning and memory (verbal-L&M), especially in older adults (Karstens et al., 2017). Here, we address whether these cognitive results are accompanied by alterations in key brain structures involved with verbal-L&M for individuals with trauma independent of depression, or if there is a trauma×depression interaction at the brain structure level, especially in older adults.

Brain regions involved in verbal-L&M, i.e., the prefrontal cortex (PFC), temporal lobe, and hippocampus (Blumenfeld & Ranganath, 2007; Squire, 1992), are associated with trauma (Andersen et al., 2008; Lim et al., 2014; Lui et al., 2013; Stein et al., 1997; Teicher et al., 2012; van Harmelen et al., 2010; Vythilingam, et al., 2002) and depression (Zhao et al., 2014; Sexton et al., 2013). Trauma-exposed individuals exhibit reduced volume and, in some studies, cortical thickness within the PFC (e.g., medial PFC, orbitofrontal and inferior frontal gyri; Lim et al., 2014; van Harmelen et al., 2010), middle temporal and parahippocampal gyri (Lim et al., 2014) and hippocampus (Andersen et al., 2008; Lui et al., 2013; Teicher et al., 2012; Vythilingam, et al., 2002). Similarly, meta-analyses demonstrate that compared to controls, depressed young and middle-aged adults have reduced PFC (e.g. left inferior and right middle frontal gyri), parahippocampal and hippocampal volumes (Zhao et al., 2014) as well as reduced orbitofrontal (OFC) and temporal lobe cortical thickness (Schmaal et al., 2016). Many of these same regions are reduced in late life depression (LLD) (Sexton et al., 2013). While these studies provide a firm foundation for the structural associates of trauma and depression in isolation, and may shed light on previous cognitive results implicating verbal-L&M in these same populations, more work is needed to understand the interaction of trauma and depression on these brain regions given their high rate of comorbidity (Afzali et al., 2016).

In addition to investigating brain structure, advances in neuroimaging analytics may allow for a more detailed investigation of the subtleties in structural network communication associated with trauma and depression. Graph theory combines neuroimaging techniques to investigate brain regions *as* brain networks defined as a set of ‘nodes’ (brain regions) with

'edges' (connections) between them (Bullmore & Sporns, 2009). Graph theory analytics quantify 'efficiency' of a node's communication within a network and the importance or 'centrality' of that node to a network. As applied to LLD, studies show less global efficiency, i.e., less average communication across all nodes and networks (Ajilore et al., 2014; Bai et al., 2012; Mak et al., 2016), and less temporal lobe local efficiency (Charlton et al., 2015) when compared to non-depressed controls. In the trauma literature, adults with early life trauma (ELT) exhibit less right middle frontal and left inferior temporal gyri centrality, and greater right anterior insula and precuneus centrality compared to controls (Teicher et al., 2014). While none of these studies associated their findings with cognition, many regions outlined above are integral to verbal-L&M.

Furthermore, despite investigations of depression and trauma in isolation, work capturing interactive effects of trauma and depression is limited. In studies of depression, ELT was negatively associated with OFC volume (Saleh et al., 2016) and right middle temporal gyrus cortical thickness (Jaworska et al., 2014). A study directly assessing joint trauma and depression effects found that depressed females with ELT had smaller hippocampal volumes than depressed females without ELT or non-depressed/non-ELT controls (Vythilingam, et al., 2002). Little to no work addresses structural connectivity in trauma and depression combined, and more work is needed investigating the interaction of trauma and depression on brain-behavior relationships.

This study examined separate and interactive associations of trauma and depression on brain composite regions of interest associated with verbal L&M (i.e., left hemisphere PFC, temporal lobe, and hippocampus). We hypothesize a trauma×depression interaction associated with reduced cortical thickness within the left PFC and temporal lobe and reduced hippocampal volume. We also hypothesize a main effect of trauma alone on these same regions given findings from our previous study in this sample (Karstens et al., 2017). Trauma and depression increase risk for adverse outcomes in later life. When combined with the fact that that aging is associated with increased bilateral PFC recruitment during L&M (Cabeza et al., 1997), we hypothesize that older adults with trauma will show reductions in the right and left PFC in stratified analyses. Significant results from these main analyses will inform connectomics analyses to explore the separate and interactive associations of trauma and depression on efficiency and centrality measures. Finally, we will determine if significant brain structures correlate with and/or mediate verbal-L&M performance.

Methods

Participants

The current study leveraged cross-sectional data from depression and diabetes studies conducted in a diverse population (N=319) at the Department of Psychiatry, University of Illinois at Chicago (UIC). Participants aged 30 and older were recruited through community outreach, fliers, and research registries. The study was approved by the UIC Institutional Review Board and conducted in accordance with the Declaration of Helsinki.

Telephone screen exclusion criteria consisted of current or past history of: Axis-I disorders other than major depression (e.g., PTSD); substance/ETOH dependence; current substance/

ETOH abuse or past abuse within 5 years of study entry; neurological disorders (e.g. stroke, dementia, seizure, etc.); prior head injury regardless of loss of consciousness; MRI contraindications; and current psychotropic medication use including anti-depressants. Thus, participants were free of anti-depressant medication for at least two weeks to study untreated depressed mood. Depressed participants were not excluded for generalized anxiety disorder, a common co-morbidity of depression (Hunt et al., 2004). Participants were not excluded for self-reported chronic medical conditions (e.g. hypertension).

After passing the telephone screen, participants underwent an in-person evaluation including the Mini Mental State Examination (MMSE; Folstein et al., 1975) and the Structured Clinical Interview for the DSM-IV-TR Disorders (SCID; Spitzer et al., 1992) for final inclusion/exclusion determination. Trained RAs administered these measures followed by an evaluation by a board certified or board eligible psychiatrist using the 17-item Hamilton Depression Rating Scale (HDRS; Hamilton, 1960). All raters were blind to telephone screen information.

All subjects had an MMSE score ≥24 and were native English speakers. Final inclusion criteria for adults with depression included a current diagnosis of major depressive disorder based on the SCID and HDRS scores>15. The SCID, a valid trauma assessment compared to the Stressful Life Event Questionnaire (Elhai et al., 2008), also quantified trauma. Described in more detail in Table 1 and elsewhere (Karstens et al., 2017), individuals with trauma had to meet both traumatic event SCID Criterion A. Final inclusion criteria for healthy controls included an absence of current and past history of any form of trauma or depression or other psychiatric disorders based on the SCID and HDRS scores<8. Subsequently, participants were divided into four groups: depressed with trauma history (D+T+;n=53), depressed without trauma history (D+T−;n=42), non-depressed with trauma history (D−T+;n=50), and non-depressed without trauma history (D−T−;n=58).

Participants received a cardiovascular risk assessment including an electrocardiogram and non-fasting blood draw. A modified Framingham Stroke Risk Profile (mFSRP) was calculated using systolic blood pressure, hypertension medication, diabetes mellitus, current cigarette smoking, cardiovascular disease, atrial fibrillation, and left ventricular hypertrophy, but not age (Wolf et al., 1991). We also quantified hemoglobin A1c levels.

Measures previously found to be associated with trauma in our cohort include Trials 1–5 (learning), and long delay free recall (memory) from the California Verbal Learning Test-II (CVLT-II; Delis et al., 1987). The Wechsler's Test of Adult Reading (Wechsler, 2001), often used to quantify educational quality in racially/ethnically diverse samples (Manly et al., 2002), estimated premorbid verbal intelligence (pVIQ).

Neuroimaging

Data Acquisition—Whole brain MRI was acquired on a Philips Achieva 3T scanner (Philips Medical Systems, Best, The Netherlands) using an 8-channel SENSE (Sensitivity Encoding) head coil. High resolution three-dimensional T_1-weighted images were acquired with a MPRAGE sequence (field of view/FOV=240mm; 134 contiguous axial slices; TR/TE=8.4/3.9ms; flip angle=8°; voxel size=1.1×1.1×1.1mm^3). DTI images were acquired

using single-shot spin-echo EPI sequence (FOV=240mm; TR/TE=6,994/71ms; flip angle=90°; voxel size=0.83×0.83×2.2mm^3). Sixty-seven contiguous axial slices aligned to the AC-PC line were collected in 32 gradient directions with b=700s/mm^2. Parallel imaging technique was utilized with a factor of 2.5, reducing scan time to ~4 minutes.

Image Analysis—T_1-weighted images were used to generate label maps using FreeSurfer (http://surfer.nmr.mgh.harvard.edu/) for cortical thickness (the average distance between white matter and pial surfaces) and subcortical structure segmentation (hippocampal volume); processing includes motion correction, removal of non-brain tissue, transformation into Talairach space, registration of image to an atlas and parcellation of the cerebral cortex into 87 region of interest (ROI) units based on gyral and sulcal structures (Desikan, et al., 2006; Destrieux et al., 2010; Fischl, et al., 2004).

Composite brain regions within the left hemisphere associated with verbal-L&M included the PFC, temporal lobe, and hippocampus. Cortical thickness composite regions for the left PFC and temporal lobe were calculated using individual ROIs, adjusted for total intracranial volume: PFC—medial and lateral OFC, inferior frontal gyrus (pars opercularis, pars triangularis and pars orbitalis) and the rostral division of the middle frontal gyrus; Temporal lobe—entorhinal cortex, parahippocampal and middle temporal gyri (Lamar et al., 2012). FreeSurfer hippocampal volumes were extracted. Identical right hemisphere ROIs were calculated for age-stratified analyses.

To generate connectome data using graph theory analyses, a pipeline was constructed that integrates multiple image analysis techniques, i.e., the FreeSurfer label map consisting of 87 grey matter ROIs, and DTI-derived white matter tractography. DTI was eddy current corrected using the automatic image registration tool in DTI-Studio (http://www.mristudio.org) by registering all diffusion-weighted images to their corresponding b_0 images. An eddy current correction technique using affine transformation was performed (rotation, translation, scaling and shear, 12-parameters). This was followed by the computation of diffusion tensors then deterministic tractography using Fiber Assignment by Continuous Tracking (FACT) algorithm built into the DTI-Studio program. For each subject, tractography was first performed by tracking the whole brain, initiating tracts at each voxel. Fiber tracking was stopped when FA value fell below 0.15 or a turning angle became larger than 60°. Weighted streamline count matrices were used as they may be the most natural formulation in defining connectivity matrices (van den Heuvel and Sporns, 2011).

Briefly, we generated brain structural networks by counting the number of reconstructed streamlines resulting from DTI-Studio white matter tractography data described above that connected every pair of grey matter ROIs defined by FreeSurfer's parcellation atlas; this in-house developed pipeline has been previously described (Gadelkarim et al., 2012; Gadelkarim et al., 2014). The resulting matrices were analyzed using Brain Connectivity Toolbox (BCT; Rubinov & Sporns, 2010). Graph theory tract-based structural connectomics measures included local efficiency and centrality (Table 2; Rubinov & Sporns, 2010).

Statistical Approach

Analyses of Variance (ANOVA) and Chi-Square measured group differences across participant characteristics. A series of multivariable linear regression analyses were conducted to examine the separate and interactive associations of trauma and depression on our brain composites using SAS (version 9.4) adjusting for known confounders: age (Raz et al., 2005) and sex (Ruigrok et al., 2014). It should be noted that composite outliers falling 3 standard deviations from the interquartile range were windsorized. Significant composite analyses ($p<.05$) were followed-up by regressions of individual ROIs. A similar series of analyses were conducted stratified by age. We focused on older adults (60–89 years) and bilateral composite regions given trauma and depression increase risk for adverse outcomes in later life and older adults exhibit bilateral PFC activation during cognitive tasks compared to younger adults (Cabeza et al., 1997). Given our hypothesis driven approach, we did not correct for multiple comparisons.

Multivariate regression analyses tested separate and interactive associations of trauma and depression on efficiency and centrality of significant brain regions (as defined by the above analyses) using SPSS-v22. Partial correlations tested associations between significant brain regions and verbal-L&M, while multivariable linear regressions tested mediation of significant brain regions on previously reported association between trauma and verbal-L&M.

Results

Sample characteristics are shown in Table 3. An ANOVA revealed a main, albeit non-significant, effect of depression on age such that D+ participants were younger than D− participants [$F(3, 198)=3.44$, $p=.07$]. There was a significant trauma×depression interaction on pVIQ [$F(3, 193)=4.27$, $p=.04$] with lower scores in the D+T+ versus the D+T− group. Chi-square analysis revealed that 0% of T- individuals versus 3.9% of T+ individuals reported past substance abuse, [$X^2(2, 203)=3.96$, $p=.05$]. As expected, there were main effects of depression on depressive characteristics and comorbid anxiety (D+>D− participants; *p-values*<.001). T+ individuals had higher, albeit non-significant, mFSRP scores than T− individuals, [$F(3, 192)=3.00$, $p=.09$]. D+ individuals had significantly higher hA1c levels than D− individuals, [$F(3, 198)=6.48$, $p=.01$] although diabetes presence did not differ between groups. No other comparisons were significant.

Based on these results, we included pVIQ and comorbid anxiety (44.3% of D+ individuals) as covariates. Given the high collinearity of mFSRP and hA1c, [$r(195)=.45$, $p<.001$] and to be consistent with prior work, we covaried for mFSRP. Given the low frequency of past substance abuse (3.9%), the low threshold to meet DSM-IV substance abuse criteria (Hasin et al., 2013), and the fact that no participant met criteria for past substance dependence or current substance abuse, we did not control for past substance abuse. Thus, unless otherwise specified, all models covaried for age, sex, pVIQ, comorbid anxiety, and mFSRP.

Of the 203 participants with FreeSurfer data, 144 had connectome data: 35 D+T+, 30 D+T−, 38 D−T+, and 41 D−T− (Supplemental Table). Similar to the larger sample, there was a main effect of depression on age, [(D+:$M=56.1$, $SD=11.9$<D−:$M=60.6$, $SD=14.2$; $F(3,$

139)=3.86, p=.05]; a main effect of trauma on pVIQ, [(T+:M=103.1 SD=13.7<T−:M=108.0, SD=11.8; F(3, 139)=6.10, p=.02]; a non-significant main effect of trauma on past substance abuse, [0% T− versus 4.2% T+, X^2(2, 144)=2.98, p=.08]; significant main effects of depression on depressive characteristics and comorbid anxiety (p-values<.001) and a non-significant main effect of trauma on mFSRP, [(T+: M=6.8, SD=4.2<T−: M=5.5, SD=3.6; F(3, 135)=3.68, p=.06]. Although hA1c was not significantly different between groups, presence of diabetes was greater in the T−D+ than all other groups. No other group comparisons were significant. Based on these results and to be consistent with our overall sample covariates, we adjusted for age, sex, pVIQ, comorbid anxiety and mFSRP in all analyses (capturing presence of diabetes as well as other cardiovascular risk factors).

FreeSurfer Analyses

Independent of depression, multivariable regressions (Table 4) revealed that T+ individuals exhibited greater left PFC cortical thickness than T− individuals, [β(1.32), t(182)=2.19, p=.03]. Specifically, T+ individuals had significantly greater left pars orbitalis cortical thickness, [β(.17), t(182)=2.18, p=.03], and marginally greater, albeit non-significant, left medial OFC cortical thickness [β(.14), t(182)=1.83, p=.06] compared with T− individuals. Neither the temporal composite nor hippocampal volume analyses were significant (p-values>.2, data not shown).

Stratified multivariable regressions focusing on older adults (Table 5) adjusting for sex, pVIQ, comorbid anxiety, and mFSRP, revealed a significant trauma×depression interaction for the right PFC, [β(−3.31), t(95)=−2.14, p=.03]: D+T+ had reduced right PFC cortical thickness compared to D−T+, [β(−2.20), p=.03]. No one PFC ROI reached significance despite reductions in the right middle frontal gyrus, [β(−.30), t(93)=−1.72, p=.09], and lateral OFC, [β(−.31), t(92)=−1.81, p=.07] for older adults with D+T+. There were no main effects of trauma or depression.

Connectome Analyses

Using FreeSurfer results as a guide, the left pars orbitalis and medial OFC became ROIs in tractography-based structural connectome analyses. Multivariate regressions revealed that T+ individuals had less left pars orbitalis centrality [F(4,123)=4.68, p=.03], and greater left medial OFC local efficiency [β(−9.22), t(126)=−2.01, p=.04], compared to T− individuals.

Brain-Behavior Analyses

Partial correlations in the T+ group revealed a negative association between both left pars orbitalis cortical thickness [r(85)=−.23, p=.03] and centrality [r(60)=−.40, p=.001] with CVLT-II Trials 1–5 (Table 6). No other correlations were significant (p-values>.12). Separate multivariable regression analyses did not suggest that the left PFC composite or significant connectome measures mediated the relationship between trauma and verbal-L&M (data not shown).

Discussion

Independent of depression, trauma was associated with left PFC alterations, particularly the pars orbitalis and medial OFC. Greater cortical thickness in the left PFC as well as greater efficiency of, i.e., communication to the left medial OFC from surrounding network structures, are consistent with other studies showing associations between trauma and greater OFC volume (Chaney et al., 2014; Lui et a., 2013) and cerebral blood flow (Bremner et al., 1999). Together with studies showing that larger OFC volumes are positively associated with fear extinction and resiliency within human (Milad et al., 2005) and non-human primates (Parker et al., 2005), results may suggest that a larger OFC provides enhanced communication among local network structures to support fear extinction in trauma-exposed individuals. In contrast, trauma – independent of depression – was associated with less left pars orbitalis centrality. This is consistent with studies showing that individuals with ELT and depression have reduced connectivity in the ventromedial PFC including the pars orbitalis when compared to healthy controls (Wang et al., 2014). As seen in other conditions with psychiatric sequelae (Roberts et al., 2013), reduced left pars orbitalis influence to local network communication may release select inhibitory control mechanisms and allow for enhanced processing of depressive thoughts or emotions associated with trauma. While subtle distinctions between risk-resilience networks of depressive symptom processing and fear extinction may be intimated from our and others' work (Brown et al., 2012), additional empirically support is needed.

In contrast to our main effect of trauma, we did not see independent associations of depression on brain structure nor an interactive effect as originally hypothesized. This may be due, in part, to the fact that despite using stringent HDRS cut-offs to satisfy depressed (M=18.9, SD=3.2) and non-depressed (M=1.4, SD=1.7) criteria, given we recruited through the community as opposed to mental health clinics depressed participants may have had a more manageable form of depression. Additionally, none of our participants were on anti-depressant medications, another indication of the nature of the depression in our sample that may help explain our lack of a depression main effect and trauma×depression interaction.

We did, however, find a significant trauma×depression interaction in older adults. Analyses revealed significantly reduced right PFC cortical thickness for older adults with trauma and depression compared to trauma alone. Results are consistent with the larger literature documenting an age by depression effect in these same regions (Mak et al., 2016; Saleh et al., 2017; Schmaal et al., 2016; Lim et al., 2012; Du et al., 2014). Together with our previous cognitive findings of a main effect of trauma on verbal-L&M in older adults (Karstens et al., 2017), current results suggest greater brain *structural* vulnerability in LLD with a history of trauma not captured by cognition alone. Future work is needed to decipher if and how trauma and depression in combination may accelerate structural brain aging.

Despite revealing a significant relationship between PFC, trauma and verbal learning, there were no significant results for temporal or hippocampal regions. Previous trauma and depression work has found null findings for the temporal lobe (Arnone et al., 2012; Chen et al., 2012; Lui et al., 2013; van Harmelen et al., 2010) and hippocampus (Chen et al., 2012; van Harmelen et al., 2010). This may be due, in part, to a focus on hippocampal volume

instead of specific regions within the hippocampus, e.g., the cornu ammonis (Teicher et al., 2012), more sensitive to proposed mechanisms of brain atrophy following trauma (Heim et al., 2010) including overproduction of glucocorticoids related to an altered hypothalamic-pituitary axis.

Study strengths include the 2×2 model to determine separate and interactive associations of trauma and depression on brain structure, and isolating brain regions based on previous cognitive findings in our cohort; however, limitations do exist. The cross-sectional nature of our study prevents us from determining causality or directionality of our findings. Additionally, though the SCID is a reliable assessment of trauma, a gold-standard trauma measure could have provided more comprehensive data (e.g. age at trauma). Participants had an average of 3 years of college education, which may have provided a form of cognitive reserve (Stern et al., 2002) that countered possible negative associations of trauma and/or depression. Though sensitive MRI techniques were used, our neuroimaging sample was relatively small, potentially limiting power.

Conclusion

If replicated, our findings suggest that independent of depression, trauma is associated with brain-behavioral alterations related to the PFC and verbal learning. Additional investigation may shed light on possible risk-resilience networks within the PFC associated with trauma (Nilsen et al., 2016). Longitudinal work is also needed to address how separate and interactive associations of trauma and depression on brain structure may contribute to accelerated brain aging in affected individuals given the significant trauma×depression effect seen in older adults. Thus, our findings provide support for increased work to understand both the cross-sectional and longitudinal effects of brain-behavior relationships related to trauma exposure.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key points

1. Trauma and depression are associated with brain structural alterations but their combined effects are unclear.
2. In adults aged 30–89, trauma was associated with prefrontal structural and tract-based connectomic alterations independent of depression.
3. Specific morphological and network communication/influence may be negatively impacted by trauma exposure.

Table 1

Inclusion and Exclusion Criteria for Trauma and Depression Group Status

Depressed	**Trauma**
• At least moderate depression symptoms (HDRS ≥ 15) • Diagnosis of MDD or Dysthymic (SCID) • No history of psychosis or mania (SCID) • No current or past Axis 1 Disorders other than depression (e.g., PTSD) with the exception of comorbid generalized anxiety disorder and past history of alcohol or substance abuse	• Meet SCID traumatic event Criterion A: 1) experienced, witnessed, or was confronted with an event or events that involved actual or threatened death or serious injury, or a threat to physical integrity of self or others 2) response involved intense fear, helplessness, or horror
Non-depressed	**No Trauma**
• No depression (HDRS ≤ 8) • No current or past Axis 1 Disorders (e.g., PTSD, depression) with the exception of past history of alcohol or substance abuse	• Did not report traumatic event(s) • Reported traumatic event(s) did not meet SCID Criterion A for a traumatic event

Table 2

Graph Theory Metrics.

Efficiency
Local efficiency, is a measure of network segregation defined as the efficiency of a subnetwork containing a particular node and its neighboring network nodes. Local efficiency is measured by the average inverse shortest path length, i.e. distance, between the node and other nodes in the network. Greater local efficiency indicates greater communication to the node from the surrounding network nodes.
Centrality
Centrality is a measure of how important or central a node is with respect to the entire network, or how influential it is to the communication between other nodes. Betweenness centrality is the fraction of all shortest path lengths in the network that pass through the node.

Table 3

Participant Characteristics Across Trauma/Depression Groups

	D+T+ (*n*=53)	D+T− (*n*=42)	D−T+ (*n*=50)	D−T− (*n*=58)
Age, *M*(SD) *a	53.8(11.7)	58.7(13.0)	60.2(14.0)	59.3(14.2)
pVIQ, *M*(SD) *c	99.7(13.2)	108.5(11.3)	105.0(14.3)	105.7(13.6)
MMSE, *M*(SD)	28.8(1.3)	29.2(1.3)	28.8(1.3)	28.9(1.1)
Female, %	56.6	57.1	44.0	48.3
Race, %				
Black	50.9	33.3	34.0	41.4
White	32.1	54.8	48.0	50.0
Other	17.0	11.9	18.0	8.6
CESD, *M*(SD) *a	31.4(10.0)	33.0(8.3)	6.2(5.4)	6.0(4.8)
No. Depressive Episodes, *M*(SD) *a	5.9(8.9)	3.5(4.5)	0.0(0.0)	0.0(0.0)
Comorbid Anxiety, % *a	35.8	54.8	0.0	0.0
Hx of Alcohol Abuse, %	9.4	9.5	8.0	5.2
Hx of Illicit Substance Abuse, % *b	3.8	0.0	4.0	0.0
mFSRP, *M*(SD) †b	7.0(4.0)	6.1(4.2)	6.8(4.7)	5.6(3.4)
Current Smoker, %	17.0	9.5	20.0	13.8
Diabetes, %	37.7	31.0	40.8	31.0
hA1c, *M*(SD) *a	6.6(1.6)	6.6(1.9)	6.1(0.9)	6.1(1.2)

Note. D+T+=depression with trauma history, D+T−=depression without trauma history, D−T+=non-depressed with trauma history, D−T−=non-depressed without trauma history; *M*(SD)=mean and standard deviation; pVIQ = predicted verbal intelligence quotient from the Wechsler Test of Adult Reading; MMSE = Mini Mental Status Examination; %=percent; CESD=Center for Epidemiologic Studies Depression Scale; No.=number; Hx=history; mFSRP=Framingham Stroke Risk Profile score modified without age included; hA1c=Hemoglobin A1c. Number of depressive episodes, comorbid anxiety, and history of alcohol or substance abuse were all taken from the SCID.

*$p<.05$,

†$p<.10$

a Main effect of Depression

b Main effect of Trauma

c Interactive effect of Trauma and Depression

Table 4

Associations of Trauma and Depression on Left PFC Cortical Thickness

	Trauma	Depression	Trauma×Depression		
	β(SE)	**β(SE)**	**Adjusted R^2**	**β(SE)**	**Adjusted R^2**
Left PFC Composite	1.32(.60)*	−.76(.70)	.003	−1.35(1.20)	.005
Left PFC ROIs					
medial OFC	.14(.01)+	−.04(.01)	.02	−.03(.02)	.02
lateral OFC	.08(.01)	−.01(.01)	.003	−.17(.02)	.001
pars opercularis	.02(.01)	−.09(.01)	.02	−.02(.02)	.01
pars triangularis	.05 (.01)	−.02(.01)	.01	−.21(.02)	.02
pars orbitalis	.17(.01)*	−.07(.02)	.003	.03(.03)	.01
middle frontal gyrus	.10(.01)	−.13(.01)	.13	−.20(.01)	.14

Note: β(SE)=Standardized beta weight and standard error; PFC=Prefrontal Cortex; ROIs=regions of interest; OFC=orbitofrontal cortex. Analyses adjusted for age, sex, predicted verbal IQ, comorbid anxiety, and modified Framingham Stroke Risk Profile score modified without age included.

*$p<.05$,

+$p<.10$

Table 5

Associations of Trauma and Depression on PFC Cortical Thickness: Older Adult Sample Only

	PFC Composites				
	Trauma	**Depression**	**Trauma×Depression**		
	β(SE)	**β(SE)**	**Adjusted R^2**		**Adjusted R^2**
Left PFC Composite	1.38(.88)	−.62(1.02)	.02	−2.40(1.80)	.01
Right PFC Composite	.55(.77)	−.87(.89)	.01	−3.31(1.55)*	.03
Right PFC ROIs					
medial OFC	.17(.02)	−.07(.02)	.03	−.26(.04)	.02
lateral OFC	.15(.01)	−.01(.02)	.02	−.31(.03)†	.05
pars opercularis	.001 (.01)	−.09(.01)	.03	−.20(.02)	.04
pars triangularis	−.01(.01)	.02(.01)	.03	−.23(.02)	.02
pars orbitalis	−.08(.02)	−.03(.02)	.03	−.02(.04)	.04
middle frontal gyrus	.06(.01)	−.24(.01)*	.02	−.30(.02)†	.04

Note: β(SE)=Standardized beta weight and standard error; PFC=Prefrontal Cortex; ROIs=regions of interest; OFC=orbitofrontal cortex. Analyses adjusted for age, sex, predicted verbal IQ, comorbid anxiety, and modified Framingham Stroke Risk Profile score modified without age included.

*$p<.05$,

†$p<.10$

Table 6

Correlations Between Brain Structure and Cognition in the Trauma Group

	Cortical Thickness Composite Regions					
	CVLT-II Trials 1–5			CVLT-II Long Delay		
	r	***df***	***p***	***r***	***df***	***p***
Left medial orbitofrontal gyrus	−.05	85	.65	−.11	85	.32
Left pars orbitalis	**−.26**	**85**	**.01**	−.17	85	.12
	Connectome Efficiency and Centrality Regions					
	CVLT-II Trials 1–5			CVLT-II Long Delay		
	r	*df*		*r*	*df*	
Left medial orbitofrontal efficiency	−.13	60	.33	−.17	60	.19
Left pars orbitalis centrality	**−.40**	**60**	**.001**	−.18	60	.17

Note: CVLT-II=California Verbal Learning Test-II. All analyses were two-tailed partial correlations adjusted for depression, age, sex, predicted verbal IQ, comorbid anxiety, and modified Framingham Stroke Risk Profile score modified without age included. Significant results are bolded.