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Connectome gradient dysfunction in earthquake-induced posttraumatic stress disorder and its association with gene expression and neurotransmitter profiles

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Original Article

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Abstract

Background. Posttraumatic stress disorder (PTSD) exhibits disrupted functional organization of brain networks involving sensory and association cortices. Connectome studies reveal a principal unimodal-to-transmodal gradient in the brain functional network that supports the spectrum from sensation to cognition. However, the disruption of the connectome gradient in PTSD and its associated transcriptional and neurotransmitter patterns remains poorly understood.

Methods. Using resting-state functional magnetic resonance imaging data from a cohort of 86 non-comorbid adult patients with PTSD caused by an earthquake and 86 trauma-exposed non-PTSD (TENP) controls who experienced the same disaster, we examined PTSD-related changes in the principal connectome gradient, their links to symptom severity and sex/age interactions, and brain-wide associations between gradient changes and microscale transcriptomic and neurotransmitter maps and macroscale cognitive function.

Results. Compared with TENP controls, PTSD exhibited global topographic abnormalities in the principal unimodal-to-transmodal gradient, and focal aberrance mainly in the unimodal (visual network) and transmodal systems (limbic, ventral attention, and frontoparietal networks). Sex had no significant effects, while gradient decrease in the subcortical network is more prominent in adolescents with PTSD than adults. The PTSD-related gradients colocalized with brain-wide gene expression enriched in mitochondria and DNA/RNA metabolic process and corresponded with the distribution of dopamine, opioid, noradrenaline, and cholinergic neurotransmitter systems.

Conclusions. These findings highlight the dysfunctional connectome hierarchy in PTSD and its association with transcriptomic and molecular profiles, suggesting that early traumatization may more significantly impact the development of subcortical network. This work provides insight into the neurobiological basis of PTSD and indicates potential biomarkers for prediction and prevention.

Introduction

Posttraumatic stress disorder (PTSD) is a debilitating, heterogeneous mental disorder characterized by four symptom clusters: re-experience, avoidance, negative mood and cognition, and hyperarousal (Sarmiento & Lau, 2020). Research on PTSD neurobiology has identified abnormalities in emotional regulation, fear learning, threat detection, contextual processing, high-level cognitive functions (Shalev, Liberzon, & Marmar, 2017; Siehl et al., 2018), and low-level sensorimotor processes such as visual processing (Ju et al., 2020) and pain perception (Tesarz, Baumeister, Andersen, & Vaegter, 2020). How alterations in high-level cognitive activity and lower-level sensorimotor processing interact in the generation of the clinical manifestations of PTSD remains to be elucidated.

The hierarchical architecture of human brain directs low-level sensorimotor information through various cortical layers into high-level transmodal areas for processing abstract and complex information (Huntenburg, Bazin, & Margulies, 2018). The gradient decomposition framework identifies and analyzes brain functional hierarchies by mapping connectivity profiles into a continuous, low-dimensional space that places unimodal sensory and motor networks at one end and transmodal networks at the other (Margulies et al., 2016). More conventional methods such as functional connectivity (FC) or graph-theoretical analyses generally decompose the brain into a set of discrete

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networks consisting of interconnected regions Zuo et al., (2026), which makes it difficult to identify the continuous spatial transitions of connectivity profiles across brain regions. In contrast, by computing an inter-regional similarity matrix and applying dimensionality reduction, the gradient approach organizes the high-dimensional brain connectome into a small set of gradient axes that represent the dominant spatial trends of connectivity variation within a lower-dimensional manifold space (Huntenburg, Bazin, & Margulies, 2018; Vos de Wael et al., 2020). In short, the gradient-based framework captures continuous spatial patterns of connectivity beyond segregated networks, and its main dimensions yield a conveniently simplified characterization of the macroscale cortical hierarchy. This approach can be applied to both structural/morphological and functional data, and FC gradients are particularly promising for potential biomarker development due to their higher reproducibility, reliability, and superior accuracy in predicting phenotypic variations, compared to traditional parcellation-based connectivity measures (Hong et al., 2020). This gradient approach has been applied to healthy participants (Dong, Margulies, Zuo, & Holmes, 2021; Tian, Margulies, Breakspear, & Zalesky, 2020) and neuropsychiatric disorders such as autism spectrum disorder (Hong et al., 2019), schizophrenia (Dong et al., 2023), depression (Xia et al., 2022), and epilepsy (Caciagli et al., 2023).

This study aims to investigate functional connectome hierarchical alterations in PTSD patients using gradient-based analyses of resting-state FC at global, subnetwork, and voxel levels. Specifically, we hypothesized that (i) PTSD patients exhibit disruptions in the principal unimodal-to-transmodal gradient, involving the global gradient topography and focal gradient scores; and (ii) these alterations of the connectome gradient are associated with symptom severity, and meta-analytic maps of various cognitive functional domains. Given the high risk of developing PTSD in females (Tang et al., 2017), and the potential dependency of stress–brain associations on the timing of adverse experiences (Siehl et al., 2022), we (iii) analyzed interactions between sex/age and PTSD diagnosis. Finally, considering the heritability of PTSD (Stein et al., 2021), and the effect of genetic factors on brain connectome variations (Arnatkeviciute et al., 2021), we (iv) decoded the PTSD-related connectome gradient using published profiles of microscale transcriptomic and neurotransmitter architectures.

Methods

Subjects

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. The study protocol was approved by the Sichuan University Research Ethics Committee. All participants provided fully-informed written consent.

Between January and August 2009, survivors of a severe earthquake in Sichuan Province of China in 2008 were recruited and screened using the PTSD checklist-Civilian Version (PCL). As described elsewhere (Suo et al., 2022), at 8–15 months follow-up, the Structured Clinical Interview for DSM-IV Diagnosis (SCID) was used to confirm PTSD diagnosis, and the Clinician-Administered PTSD Scale (CAPS) to assess symptom severity. Survivors scoring PCL ≥ 35 and CAPS ≥50 were included as PTSD if confirmed by SCID; those scoring PCL < 35 without meeting SCID criteria for PTSD were included as trauma-exposed non-PTSD (TENP). Finally included were 86 untreated PTSD patients without psychiatric comorbidities, and 86 demographically matched TENP controls. This recruitment strategy ensured that individuals with and without PTSD had similar earthquake experiences and demographic characteristics. Notably, several other analyses of MRI data from these participants have been reported (Li et al., 2016a; Li et al., 2016b; Niu et al., 2018; Suo et al., 2023; Suo et al., 2024b), with the results described in the cited papers. The present study is distinguished from these by its specific focus on connectome gradient dysfunction and its transcriptomic/neurotransmitter correlates, with all hypotheses and analyses predefined accordingly.

Data acquisition

MRI data were obtained using a 3.0 T MRI system (Excite; GE Healthcare, Milwaukee, WI) with an eight-channel phased-array head coil. Participants were instructed to keep their eyes closed, minimize head movement, stay awake, and not think of anything in particular. Resting-state functional MRI (rs-fMRI) data were acquired using an echo-planar imaging sequence with the following parameters: repetition time 2000 ms, echo time 30 ms, matrix 64 × 64, field of view 240 × 240 mm^2, flip angle 90°, voxel size 3.75 × 3.75 × 5 mm^3, 30 axial slices (thickness/gap 5/0 mm), 200 volumes, and scanning time 400 s.

Data processing

Rs-fMRI data were preprocessed using the Data Processing Assistant for Resting-State fMRI (http://rfmri.org/DPARSF) based on Statistical Parametric Mapping software (SPM12, http://www.fil.ion.ucl.ac.uk/spm/) and the Data Processing and Analysis of Brain Imaging (http://rfmri.org/DPABI) toolbox. The initial 10 volumes were excluded to ensure signal stabilization. The remaining data were corrected for slice timing and realigned for head motion correction. Participants (7 PTSD and 3 TENP) with head motion exceeding 2.5 mm or 2.5° in any direction were excluded, and frame-wise displacement (FD) was calculated as a summary metric of head motion for subsequent analysis (Jenkinson, Bannister, Brady, & Smith, 2002). After normalization to Montreal Neurological Institute space, the images were resampled to 3 × 3 × 3 mm^3, smoothed with a 6 mm full-width at half-maximum Gaussian kernel, regressed out linear trends, Friston's 24 head motion parameters (Friston et al., 1996), white matter, cerebrospinal fluid and global signal, and band-pass filtered with 0.01–0.08 Hz to reduce low-frequency drift and high-frequency noise.

Functional connectome gradient mapping

We constructed the voxel-wise functional network for each individual and estimated the connectome gradient using diffusion map embedding, a nonlinear dimensionality reduction approach. The preprocessed rs-fMRI data were resampled to 4 × 4 × 4 mm^3 to reduce computational complexity. Subsequently, the individual FC matrix was constructed using Pearson correlation coefficients between each pair of gray matter nodes (that is 18933 voxels); as in previous work (Hong et al., 2019; Margulies et al., 2016; Xia et al., 2022), we included only the top 10% connections of each node, to minimize spurious connectivity originating from noise effects and capture the most typical connection characteristics. The individual similarity matrix was constructed by calculating the cosine similarity between the thresholded connectivity profiles of each pair of nodes and scaling them into a normalized angle matrix to avoid negative values (Paquola et al., 2019). We applied diffusion map embedding with the alpha parameter of 0.5 to identify the gradient compoents explaining the

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variance in the functional connectome's connectivity pattern (Coifman et al., 2005; Margulies et al., 2016), consistent with prior research (Hong et al., 2019; Larivière et al., 2020; Margulies et al., 2016). Next, iterative Procrustes rotation aligned the individual gradient maps across all participants (Hong et al., 2019; Larivière et al., 2020). In line with prior research (Xia et al., 2022), we focused on the principal unimodal-to-transmodal gradient, which accounts for the majority of variance and is closely linked to neuronal microstructure and cognitive functions (Huntenburg, Bazin, & Margulies, 2018). Three global metrics of the principal gradient were calculated: *gradient explanation ratio*, the proportion of total connectome variance captured by the principal gradient; *gradient range*, the difference between the maximum and minimum gradient scores across all voxels, reflecting the extent of functional differentiation between the two extremes of the unimodal-to-transmodal axis; and *gradient variation*, the standard deviation of gradient values across the whole brain, indicating the overall dispersion of connectivity patterns across brain regions.

Identification of PTSD–TENP gradient differences

Statistical analyses were conducted at three different spatial resolutions: the global level, the macroscale functional subnetwork level, and the regional (voxel) level. Nonparametric permutation tests (10000 iterations) were used to examine PTSD–TENP differences in global gradient metrics, controlling for age, sex, education years, time since trauma, and mean FD. PTSD–TENP differences in connectome gradient scores were evaluated using a general linear model (GLM) with age, sex, education years, time since trauma, and mean FD as covariates. Subnetwork-level connectome gradient scores were determined using a canonical whole-brain partition into 8 functional subnetworks: a 7-system cortical parcellation (visual, sensorimotor, dorsal and ventral attention, limbic, frontoparietal, and default mode network) (Yeo et al., 2011) and the subcortical system from the Anatomical Automatic Labeling atlas (Tzourio-Mazoyer et al., 2002). Statistical significance for global and subnetwork differences was set to $P < 0.05$, with the false discovery rate (FDR) controlling false positives. Voxel-wise gradient score map comparisons were considered significant at voxel-level $P < 0.001$ and cluster-level $P < 0.05$ with Gaussian random field (GRF) correction (Friston et al., 1994; Xia et al., 2022).

A GLM was applied to investigate sex-by-group interactions. To explore age effects, we included a previously reported adolescent dataset (26 PTSD and 25 TENP, Table 1) using the same participant recruitment strategies and MRI pipeline (Suo et al., 2024a) to examine age-by-diagnosis interactions. We examined the clinical relevance of altered connectome gradients by correlating symptom severity with the abnormal gradient scores, using partial correlation with age, sex, education years, time since trauma, and mean FD as covariates. The averaged gradient score was extracted from subnetworks or brain regions showing altered principal gradients.

Cognitive terms relevant to PTSD–TENP gradient differences

To investigate cognitive items associated with functional connectome gradient alterations, the Z-statistic map derived from the between-group gradient differences was charted against the cognitive maps from the Neurosynth database (https://neurosynth.org/), using the "decoder" function in Neurosynth to analyze spatial correlations between the Z maps and the meta-analytic map of each term in the database.

Transcriptomic analysis

The Allen Human Brain Atlas (AHBA) dataset (Hawrylycz et al., 2012) (https://human.brain-map.org/) was used to explore the relationship between PTSD-related functional gradient alterations and the transcriptome. Transcriptome data obtained from 6 postmortem subjects in the AHBA database were mapped to 246 parcellated brain regions based on the Brainnetome 246 atlas using the abagen toolbox (https://github.com/rmarkello/abagen) (Markello et al., 2021). The processing steps included gene annotation reannotation, intensity-based filtering, probe selection, and sample-to-region matching (Qin et al., 2024). Due to the incomplete availability of matched tissue samples for all regions, the resulting gene expression matrix comprised 15632 genes and 224 regions.

Partial least squares (PLS) regression was conducted to explore the association between gene expression and PTSD–TENP differences in the principal gradient map, an approach widely used in imaging-transcriptomic integration studies (Abdi & Williams, 2013; Ma et al., 2023). The Z-map of PTSD–TENP differences in the principal gradient was the response variable, and the normalized gene expression matrix of brain regions (224 regions × 15632 genes) was the predictor variable. The first PLS component (PLS1), representing the linear combination of weighted gene expression values most strongly associated with the principal gradient's Z vector, was evaluated for its association with PTSD–TENP differences using Pearson's correlation coefficient. To correct for spatial autocorrelation, we tested the statistical significance of variance explained by randomizing the response variables 5,000 times using the Moran spectral randomization (Li et al., 2024a; Wagner & Dray, 2015). A bootstrapping method was used to estimate each gene's weighting coefficient in the PLS analysis (Whitaker et al., 2016). The 15632 genes, correctly weighted, were ranked to evaluate their contributions to the principal PTSD *vs* TENP differences in PLS1. Enrichment analysis was then conducted to elucidate the underlying biological mechanisms. Gene Ontology (GO) analysis, including cellular component, molecular function, and biological process, and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis were performed on the PLS1+/− gene lists using Metascape (https://metascape.org/) (Li et al., 2021; Zhou et al., 2019). Enriched terms were clustered based on pairwise similarity using the Kappa test (Niu et al., 2026), and the resulting pathways were filtered at an FDR-corrected significance threshold of 0.001. We categorized PLS1 genes into cell types by overlapping the PLS1 gene lists with gene sets from seven cell-type categories (Seidlitz et al., 2020): astrocytes, endothelial cells, excitatory and inhibitory neurons, microglia, oligodendrocyte precursors, and oligodendrocytes. The statistical significance of overlapping genes in each cell type was assessed using a permutation test (10000 times) and corrected for multiple comparisons using FDR, with $P < 0.05$ considered significant.

Neurotransmitter receptors and transporters analysis

JuSpace toolbox (v1.5, https://github.com/juryxy/JuSpace) was used to identify neurotransmitter systems linked to brain connectome gradient alterations by calculating the spatial correlation between the Z-map of PTSD *vs* TENP and positron emission tomography (PET)-based neurotransmitter receptor/transporter density maps (Dukart et al., 2021). This analysis used Spearman correlation and permutation tests for significance (with the default Neuromorphometrics atlas; exact *P*-values, $n = 1000$ permutations; adjusted for spatial autocorrelation). Family-wise error was used for

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Table 1. Demographic and clinical characteristics of participants[a]

Variables	Adult sample			Adolescent sample		
	TENP (n = 86)	PTSD (n = 86)	P	TENP (n = 25)	PTSD (n = 26)	P
Age (years)[b]	43.9 ± 9.9	43.2 ± 10.5	0.67[c]	13.0 ± 1.4	13.3 ± 1.8	0.55[c]
Gender (male/female)	25/61	25/61	1.0[d]	11/14	10/16	0.78[d]
Years of education (years)[b]	6.8 ± 3.4	7.1 ± 3.1	0.64[c]	7.9 ± 2.1	7.9 ± 1.9	0.96[c]
Time since trauma (months)[b]	11.7 ± 2.5	11.0 ± 2.3	0.10[c]	12.3 ± 1.9	11.5 ± 1.8	0.12[c]
PTSD checklist score	28.0 ± 6.7	47.9 ± 12.6	< 0.001[c]	23.4 ± 1.8	54.8 ± 5.2	< 0.001[c]
CAPS score	22.1 ± 11.1	63.6 ± 9.0	< 0.001[c]	NA	66.0 ± 6.7	

Note: CAPS, clinician-administered PTSD scale; PTSD, posttraumatic stress disorder; TENP, trauma-exposed non-PTSD.
[a]Data are presented as mean ± SD unless noted.
[b]Age, years of education, and time since trauma defined relative to time of MRI.
[c]P using two-sided two sample t test.
[d]P using two-sided Chi-squared test.

multiple comparisons correction at q < 0.05 for the 30 measures of neurotransmitter receptor/transporter density maps.

Results

Clinical and demographic characteristics

In total, 86 adult PTSD patients (61 females; age: 43.2 ± 10.5 years) and 86 adult TENP controls (61 females; age: 43.9 ± 9.9 years) were included for analysis. Table 1 shows the clinical and demographic characteristics of the participants. There were no significant differences in age, sex, education years, or time since trauma between PTSD and TENP (all $P > 0.05$). As expected, patients with PTSD exhibited significantly higher PCL and CAPS scores than TENP (both $P < 0.001$).

Macroscale gradient patterns in PTSD and TENP

Gradients from individual cortical functional connectomes were derived using diffusion map embedding; the aligned group-averaged principal gradients were then mapped to the cortex. The principal gradient accounted for the largest proportion of variance in the connectomes (PTSD, 12.1 ± 2.5%; TENP, 11.4 ± 2.4%) (Supplementary Figure S1). Similar to the canonical distribution (Margulies et al., 2016), the principal gradient was anchored at one end by the unimodal system (e.g. visual and sensorimotor regions) and at the other by the transmodal system (e.g. default mode regions) (Figure 1A). The spatial patterns of the group-averaged principal gradient were remarkably similar in both groups. In the global histograms, the extremes of the unimodal-to-transmodal gradient were extended in PTSD compared to TENP (Figure 1B). Nevertheless, in between-group comparisons, the principal gradient in PTSD explained more connectivity variance than that in TENP ($P = 0.0232$, Figure 1C left). Furthermore, PTSD had a wider range of gradient scores ($P = 0.0182$) and more spatial variation ($P = 0.0361$) than TENP (Figure 1C middle and right).

Subnetwork-level principal gradient alterations in PTSD

We used a canonical functional network partition to summarize the principal gradient score differences between groups at the subnetwork level (Figure 2A). In the principal gradient of PTSD *vs* TENP, there was a higher gradient score in the visual (FDR corrected q = 0.000056) and limbic networks (FDR corrected q = 0.0013), and lower score in the ventral attention (FDR corrected q = 0.000284) and frontoparietal networks (FDR corrected q = 0.0260).

Given that all participants had experienced major psychological trauma, and PTSD was defined by persistent and severe psychological symptoms, the two participant groups were combined to analyze the associations between brain findings and PTSD symptom severity. CAPS scores showed a positive correlation with the visual ($r = 0.328$, $P < 0.001$) and limbic networks ($r = 0.232$, $P = 0.004$), and a negative correlation with the ventral attention network ($r = -0.262$, $P = 0.001$) (Figure 2B-2D). Nevertheless, when examined within the PTSD group alone, no significant correlations were found between CAPS scores and gradient abnormalities in any of the subnetworks with between-group differences.

Voxel-level principal gradient alterations in PTSD

Comparing the principal gradient between groups at the voxel level (Figure 3A), the PTSD group exhibited higher gradient scores in the bilateral hippocampus/parahippocampus gyrus (extending to fusiform) and occipital-temporal visual areas, including bilateral calcarine cortex/lingual gyrus and middle/superior occipital gyrus, and lower gradient scores in the right supramarginal gyrus and inferior frontal gyrus, opercular part extending to superior temporal gyrus, and insula (voxel-level $P < 0.001$, GRF-corrected cluster-level $P < 0.05$) (Supplementary Table S1).

The spatial association between the principal gradient alterations and the canonical networks was quantified by computing the proportion of overlapping voxels between the principal gradient alterations and each canonical network; the higher and lower gradient scores principally implicated the visual (overlapping proportion: 64%, Figure 3B) and ventral attention (70%, Figure 3C) networks, respectively.

Interaction between groups and sex/age regarding gradient alterations

No significant diagnosis-by-sex interaction was found in the global, subnetwork, or voxel-level gradient alterations (all $P > 0.05$). Diagnosis-by-age interaction was observed for gradient scores in the subcortical network: lower gradient scores in subcortical network in PTSD *vs* TENP were more marked in adolescents than in adults ($F_{(1, 219)} = 4.38$, $P = 0.037$, partial $\eta^2 = 0.020$, 95% CI [0.00, 0.07]) (Figure 2E). To assess the robustness of this finding, we further examined the simple effects separately by age group.

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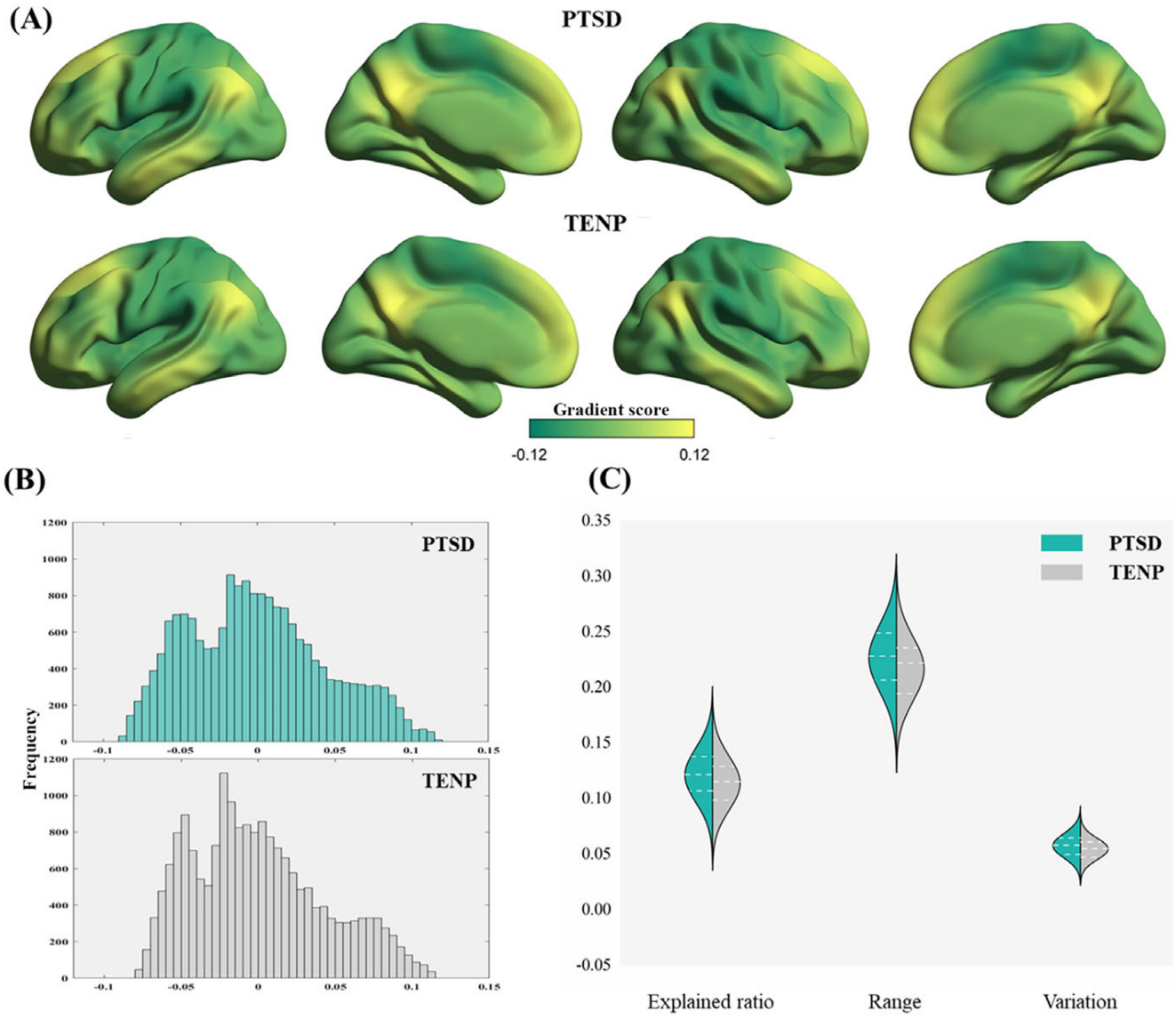


Figure 1. Connectome gradient mapping in PTSD and TENP. (A) The brain images showing that the principal gradient was organized with the unimodal system (visual and sensorimotor) on one end (green) and the transmodal system (default modal) at the other end (yellow). Surface rendering generated using BrainNet Viewer (www.nitrc.org/projects/bnv/). (B) Global histograms showing that the extreme values were extended in PTSD *vs* TENP. (C) Case–control differences in the global metrics of the principal gradient. *Note*: PTSD, posttraumatic stress disorder; TENP, trauma-exposed non-PTSD.

In the adolescent-only analysis, after adjusting for age, sex, education years, time since trauma, and mean FD, the PTSD *vs* TENP difference in subcortical network gradient was significant (adjusted Cohen's d = −0.664, 95% CI [−1.270, −0.057], P = 0.028). In the adult-only analysis using the same covariates, the difference was not significant (adjusted Cohen's d = 0.014, 95% CI [−0.293, 0.320], P = 0.930). These findings suggest that the observed interaction was primarily driven by a stronger diagnostic group difference in adolescents and should be interpreted cautiously given the smaller adolescent sample.

Meta-analysis of cognitive functions associated with gradient changes in PTSD

Regions with higher principal gradient scores in PTSD *vs* TENP were correlated with meta-analytic cognitive terms primarily involving visual and high-order cognitive functions including memory (Figure 3D). The regions with lower principal gradient scores in PTSD were correlated with sensorial and perceptional process, such as pain, sensory, and audiovisual processes (Figure 3E). Details are given in Supplementary Table S2.

Molecular mechanisms associated with gradient changes in PTSD

The PLS1 explained 31.4% of the variance of the PTSD-related alterations in the principal gradient, which is significantly higher than chance (P_{moran} = 0.0198) (Figure 4A). The gene expression map of PLS1 showed a positive correlation with the case–control Z-map of the unimodal-to-transmodal gradient (Figure 4B, $r_{(224)}$ = 0.5608, P_{moran} = 0.0012). After correcting the normalized weights of PLS1, the PLS+ gene set (936 genes) was overexpressed in regions

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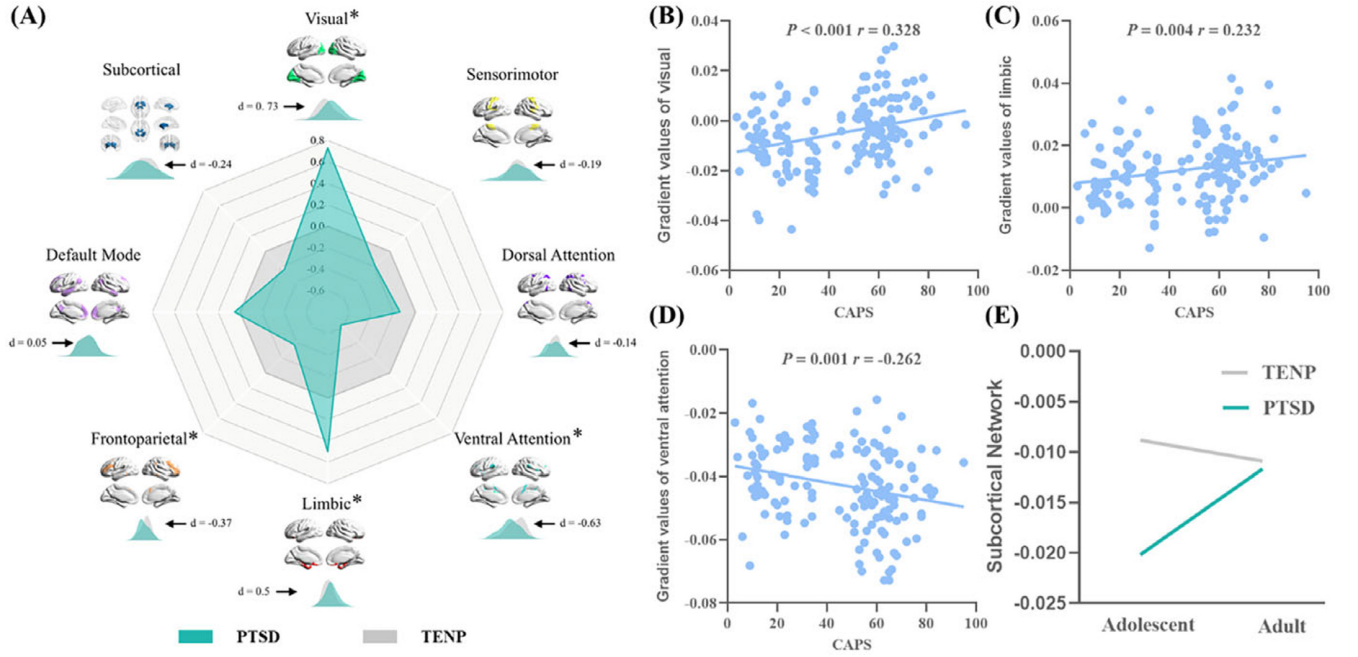


Figure 2. Network-level principal gradient comparisons and their associations with PTSD symptom severity and age. (A) The radar chart shows the PTSD *vs* TENP gradient Z-score: PTSD showed higher gradient values in the visual and limbic networks, and lower values in the ventral attention and frontoparietal networks ($P < 0.05$, false discovery rate corrected). Around the chart, for each network, is shown the cortical location, the two groups' distributions compared, and Cohen's d. (B-D) shows the association between gradient alterations in three networks (visual, limbic, and ventral attention, respectively) and PTSD symptom severity (measured by CAPS). (E) shows gradient scores in subcortical network of the adolescent and adult samples: the lower gradient scores in the subcortical network in PTSD *vs* TENP were greater in adolescent than adult ($F_{(1, 219)} = 4.38$, $P = 0.037$). *Note*: CAPS, Clinician-Administered PTSD Scale; PTSD, posttraumatic stress disorder; TENP, trauma-exposed non-PTSD.

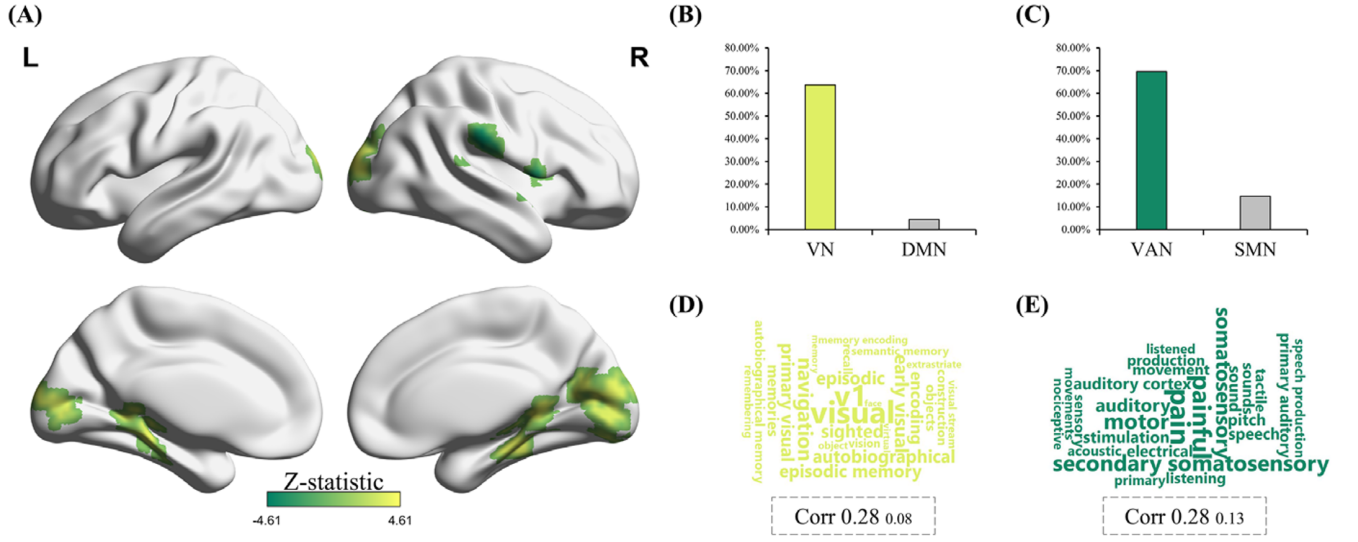


Figure 3. Voxel-wise statistical comparisons of principal gradient between PTSD and TENP and their distribution in different systems and cognitive functions. (A) shows voxel-wise comparisons of principal gradient between PTSD and TENP; higher/lower values in PTSD are presented as warm/cold colors; statistical significance was set as voxel-level $P < 0.001$ and Gaussian random field cluster level-corrected $P < 0.05$. (B) and (C) are bar plots showing the proportion of overlapping voxels between regional gradient PTSD–TENP differences and canonical networks, displaying only networks with >3% overlap. (D) and (E) show the cognitive terms corresponding to the PTSD-TENP principal gradient differences, presented as word clouds of cognitive terms associated with brain regions that exhibited higher (warm) or lower (cold) gradient scores in PTSD; their font size corresponds to the correlation coefficient of the between-group Z-map of the principal gradient and meta-analytic map of that term generated by Neurosynth; the box below the word clouds shows the correlation coefficient in clusters of cognitive terms. Note: DMN, default mode network; L, left; PTSD, posttraumatic stress disorder; R, right; SMN, sensorimotor network; TENP, trauma-exposed non-PTSD; VAN, ventral attention network; VN, visual network.

with a higher principal gradient, while the PLS- gene set (1566 genes) was overexpressed in regions with a lower principal gradient in PTSD *vs* TENP ($P_{fdr} < 0.001$, Figure 4C).

The PLS1+/− gene list showed significant enrichment in multiple clusters ($P_{fdr} < 0.001$). After removal of discrete clusters, the most enriched terms predominantly pertained to mitochondria and

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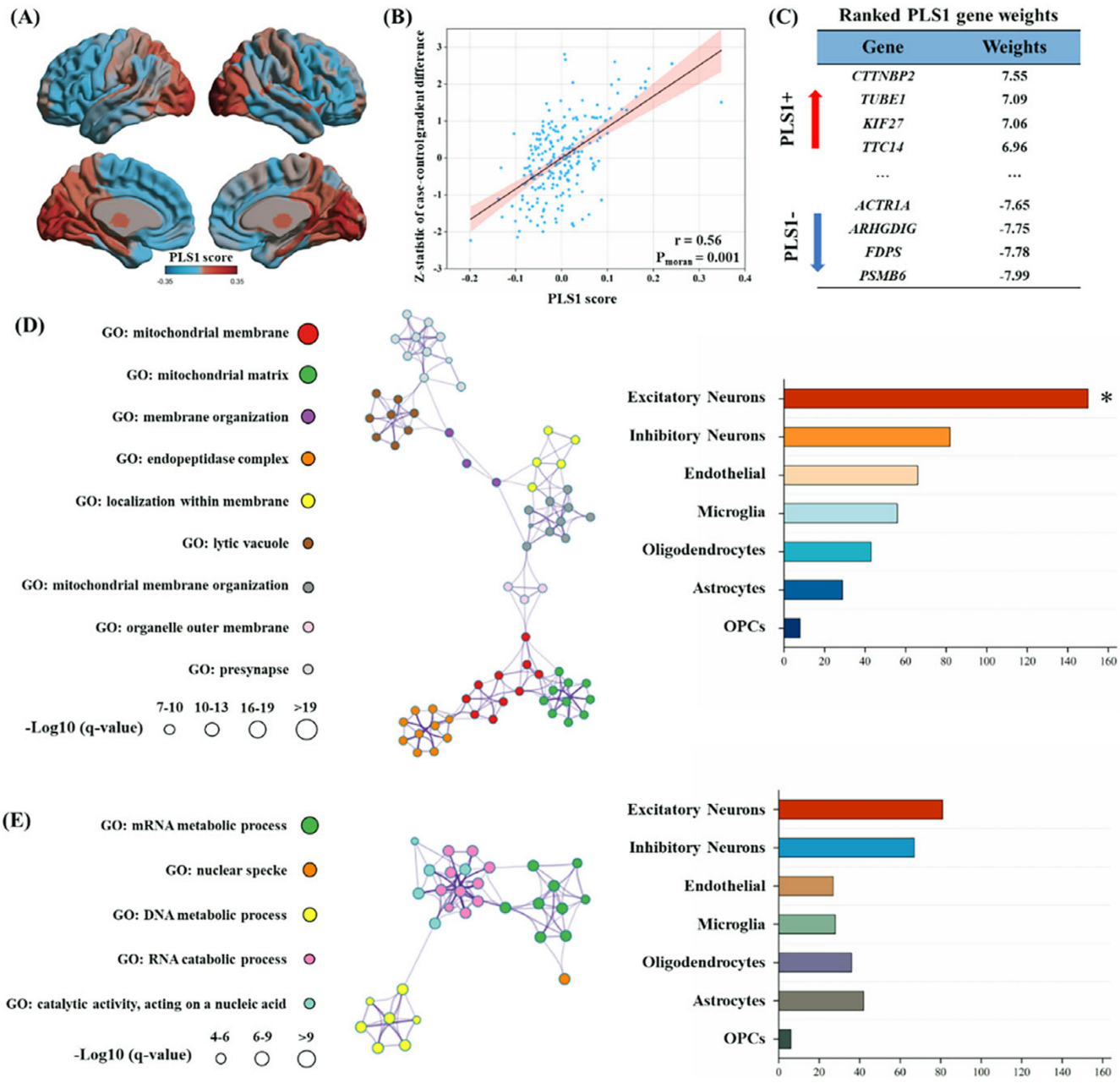


Figure 4. Transcriptional profiles associated with PTSD-related gradient alterations. (A) shows brain maps of the PLS1 scores, color-coded as in key. (B) shows the correlation between PLS1 score and PTSD-TENP gradient alterations; each dot represents a region, and the regression line is shown. (C) lists the PLS1+ and PLS1− genes. In (D), the left panel shows enrichment for the PLS1− genes; the middle panel is the enrichment network, showing the intra- and inter-cluster similarities of enriched annotations (each term is one node, whose size represents the number of input genes included in that term, and color represents its cluster identity, as per key); the right panel shows their overlap with gene sets for each cell type. (E) likewise shows enrichment for the PLS1+ genes and their overlap with gene sets. Asterisk indicates FDR-corrected $P < 0.05$. *Note*: GO, Gene Ontology; OPCs, oligodendrocyte precursors; PLS1, first component of partial least square.

DNA/RNA metabolism (Figure 4D and 4E). Based on the gene distribution of the seven typical cell types, only some PLS1- genes were significantly associated with excitatory neurons (n = 150, P = 0.002) (Figure 4D).

After multiple comparison correction, the Z-map of case–control differences in the principal gradient showed significant negative correlations with the spatial distribution of dopamine receptor D2 (D2DR, $r = -0.32$, $P = 0.0007$), kappa opioid receptor (KOR, $r = -0.62$, $P = 0.0005$), noradrenaline transporter (NAT, $r = -0.42$, $P < 0.0001$), and cholinergic vesicular acetylcholine transporter (VAChT, $r = -0.55$, $P < 0.0001$) (Supplementary Figure S2).

Discussion

Using a gradient-based decomposition approach to analyze rs-fMRI data, we identified abnormalities in functional connectome gradients at the global, subnetwork, and regional levels in PTSD patients compared to TENP controls. Globally, both groups showed principal

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gradient organization from unimodal to transmodal located at either end (Figure 1A). Compared to TENP, the principal gradient organization in PTSD was relatively extended (Figure 1B) and disturbed (Figure 1C). PTSD patients also showed subnetwork and region-specific gradient differences: compared to TENP, PTSD patients had higher principal gradient values in visual and limbic systems but lower gradient values in ventral attention and frontoparietal systems (Figure 2A), which were related to symptom severity (Figure 2B-D) and meta-analytic cognitive domains (Figure 3D-E). Further, the diagnosis–age interaction analysis revealed that lower gradient scores in subcortical network were more pronounced in adolescent than adult PTSD patients (Figure 2E). Finally, PTSD-related gradient changes were associated with gene expression patterns enriched for mitochondria and DNA/RNA metabolism (Figure 4D-E), as well as the spatial distribution of dopamine, opioid, noradrenaline, and cholinergic neurotransmitter systems (Supplementary Figure S2). These findings illuminate the neurobiology of PTSD, bridging the gap between brain connectome, microscale transcriptome, and neurotransmitters. We briefly discuss some possible implications of these results.

An intact connectome gradient from unimodal to transmodal networks provides a framework for integrating information across multiple large-scale networks (Margulies et al., 2016). In PTSD, the extremes of the unimodal-to-transmodal gradient were extended compared to TENP (Figure 1B), which aligns with the findings of previous morphology and FC studies that PTSD patients exhibit higher cortical thickness (Li et al., 2022), network modularity (Suo et al., 2019), and network efficiency (Zhu et al., 2019) than TENP. Specifically, in our previous study of FC in a highly overlapping adult PTSD sample, using a different graph theory-based analytical methodology, PTSD patients showed excessive global segregation reflected by higher clustering coefficient and local efficiency (Lei et al., 2015). This expansion pattern was similar to previous reports in bipolar disorder (Lei et al., 2023), schizophrenia (Yang et al., 2023), and epilepsy (Meng et al., 2021). Hierarchical disorganization of unimodal-to-transmodal systems may indicate the disruption in segregated neuronal operations and/or the global integration of segregated functions (Kiebel, Daunizeau, & Friston, 2008), leading to impaired stimulation processing and information integration (Mesulam, 1998). In PTSD, the increased distance from the unimodal to transmodal system in the principal gradient may result from excessive segregation between these systems, disrupting the inherent separation between primary sensorimotor and transmodal cognitive functions. In contrast, the compression of the unimodal-to-transmodal gradient suggests network dedifferentiation, supported by findings of increased global integration and decreased segregation from graph-theoretical analysis (Xia et al., 2022; Xiao, Zhao, Zang, & Xue, 2023b). The findings of these two methodological approaches must of course be related, although the link is not unambiguous. Additionally, the PTSD patients showed wider range and higher explanation ratio and variation in the principal gradient (Figure 1C). A higher explanation ratio in PTSD (Figure 1C) indicates that the gradient embedding axis represents a larger principal component, accounting for more variance in the functional connectome (Margulies et al., 2016). The larger range and variation indicate higher connectome dissimilarity across regions (Hong et al., 2019). At a global level, the wider gradient range found in PTSD patients is indicative of a more differentiated pattern and may be interpreted as a disruption of functional segregation.

At the subnetwork and regional levels, PTSD *vs* TENP exhibited elevated gradient scores in the visual and limbic networks and reduced gradient scores in the ventral attention and frontoparietal networks. We briefly discuss these networks in turn. The visual network is fundamentally involved in visual processing. There are reports of hyperactivity of the visual cortex in PTSD, which may be related to disrupted visual imagery (Zhu et al., 2020). In addition to this traditional role, it is linked to sensory-based involuntary trauma memories, such as flashbacks, a hallmark symptom of PTSD (Bourne, Mackay, & Holmes, 2013). The limbic network, particularly the hippocampus and parahippocampus, is crucial in PTSD, in which higher medial temporal activation is reported (Patel, Spreng, Shin, & Girard, 2012). Gradient changes of these regions in PTSD may facilitate fear conditioning in non-threatening contexts and disrupt normal extinction processes (Patel, Spreng, Shin, & Girard, 2012; Rauch, Shin, & Phelps, 2006). The ventral attention network including the temporoparietal junction and inferior frontal cortex, is involved in bottom-up attention (Corbetta, Patel, & Shulman, 2008), which integrates motivational, affective, and cognitive factors to respond to salient endogenous and exogenous information (Esterman et al., 2020). Weaker FC in the ventral attention system has been associated with verbal memory and attention impairments in individuals with PTSD who respond poorly to psychotherapy (Esterman et al., 2020; Etkin et al., 2019). The frontoparietal network, anchored in lateral prefrontal and parietal cortices, is involved in problem solving, working memory-related tasks, and decision making (Menon, 2011), which are impaired in PTSD. Frontoparietal functional disruption may underlie insufficiencies in top-down control in PTSD (Barredo et al., 2018). FC abnormalities in this network were associated with the treatment outcome of psychotherapy for PTSD (Zhang et al., 2021). Notably, correlations of gradient scores with symptom severity (CAPS scores) across the whole group (positive for visual and limbic networks, negative for ventral attention network) suggest clinical relevance, but the absence of significant CAPS correlations within the PTSD group alone indicates that the combined-sample associations were primarily driven by between-group differences. This pattern suggests that the observed gradient abnormalities may function more as categorical markers of PTSD diagnosis (that is distinguishing affected from nonaffected individuals) rather than as dimensional markers that track symptom severity within the clinical range; this is similar to observations in other psychiatric disorders (Bruhl et al., 2014; Zhang et al., 2022). Nevertheless, this interpretation remains speculative, and future studies with larger samples and broader ranges of symptom severity are warranted to further examine the exact relationship between connectome gradient and symptom dimensions in PTSD.

For gradient scores we found no diagnosis–sex interaction, but a significant diagnosis–age interaction: we found lower gradient scores in the subcortical network in adolescent PTSD relative to adult PTSD, while the trend in TENP controls was in the opposite direction. Gradient alterations in adolescent PTSD may reflect disruptions in brain maturation trajectory, affecting the functional organization and differentiation of complex brain systems and the higher-order psychological processes they support (Dong et al., 2021). The subcortical functional architecture underpins information communications related to emotional and cognitive functioning (Tianet al., 2020). A study on the development of functional gradients in normal children (6–12 y) and adolescents (12–18 y) revealed that in adolescence, the principal connectivity gradient transitions into an adult-like spatial framework (Dong et al., 2021). Our findings suggest that in adolescent PTSD, there may be a delayed maturation of gradients in the subcortical network. More broadly, these findings are consistent with the emerging framework of environmental neuroscience, which emphasizes that lifetime

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environmental exposures may exert cumulative effects on brain structure and function, with particular vulnerability during sensitive developmental windows (Liu et al., 2023). Future studies that systematically characterize the full spectrum of environmental exposures in trauma-affected populations will be needed to disentangle the specific contributions of trauma type, timing, and cumulative burden to connectome gradient dysfunction in PTSD.

Our connectome-transcriptome association analysis identified a link between PTSD-related alterations in functional gradients and gene expression related to mitochondria and DNA/RNA metabolism. There is growing evidence that mitochondria are important in neuropsychiatric disorders, including PTSD (Papageorgiou & Filiou, 2024). Mitochondria play a crucial role in intracellular processes such as signal transduction, neuron survival, and plasticity (Flaquer et al., 2015), and their biology is influenced by chronic and acute stressors (Picard & McEwen, 2018). Postmortem studies in PTSD have revealed changes in gene expression associated with mitochondrial dysfunction (Su et al., 2008). In rat studies, nutritional supplementation of taurine, which improves mitochondrial function, attenuates PTSD-like symptoms (Bhattacharjee, Prajapati, & Krishnamurthy, 2021). There are also broader connections: epigenetic changes in response to trauma have been associated with PTSD (Beucke et al., 2024; Cao-Lei, Saumier, Fortin, & Brunet, 2022); stress-induced mitochondrial dysfunction causes chromatin remodeling (Tian et al., 2016). Assigning PTSD-related genes to specific cell types revealed significant involvement of excitatory neurons, consistent with previous PTSD genome transcription studies (Wingo et al., 2022; Xiao et al., 2023a). This helps explain the link between microscale biology and macroscopic network alterations in PTSD. Nevertheless, these categories of mitochondria and DNA/RNA metabolism are broad, and the present findings should not be taken as evidence of PTSD-specific signatures. Although individuals with comorbid psychiatric disorders were excluded from both groups, this connectome–transcriptome association analysis cannot determine whether these molecular processes are uniquely associated with PTSD or shared across stress-related and other psychiatric conditions, particularly in the absence of psychiatric comparison cohorts and mechanistic validation.

Our neurotransmitter analysis revealed significant correlations between PTSD-related connectome gradient alterations and the dopamine, opioid, noradrenaline, and cholinergic neurotransmitter systems. DRD2 is involved in the fear response (Abraham, Neve, & Lattal, 2014) and may influence genetic susceptibility to PTSD (Zhang et al., 2023) by modulating stress sensitivity and emotional disturbance expression (Xiao et al., 2019). It also moderates the association between PTSD symptomatology and hippocampal atrophy (Yuan et al., 2022). KOR, part of the opioid neuromodulatory system, regulates stress response, reward, and mood (Van't Veer & Carlezon, 2013), and is suggested as a biological marker for dissociative symptoms and negative affective states in PTSD (Rabellino et al., 2018). NAT, a key neuromodulator interacting with dopamine, affects intrusive and hyperarousal symptoms in PTSD via mitochondrial function (Strawn & Geracioti, 2008). Chronic norepinephrine system blockage reverses stress-induced cognitive deterioration (Jett & Morilak, 2013). Animal and human studies indicate that cholinergic system dysregulation in various brain regions contributes to PTSD pathogenesis by affecting fear acquisition and fear extinction processes (Maren, Phan, & Liberzon, 2013). Taken together, these findings, along with previous studies, highlight the significance of brain structure–function alterations involving disorganized neurotransmitters (dopamine, opioid, noradrenaline, and cholinergic) in the pathophysiology of PTSD. Further investigation into these interactions will be helpful for advancing the development of new drugs and other therapies (such as MDMA, which primarily affects dopamine and norepinephrine systems, and has recently been approved by FDA for Phase 3 clinical trial for PTSD (Baldo, 2024).

This study has some limitations. First, the cross-sectional design lacks information on the temporal evolution of the brain gradients in PTSD and precludes investigation of whether the observed gradient abnormalities represent pre-existing vulnerability markers, state-dependent changes tied to symptom fluctuations, or progressive reorganization related to illness chronicity. Longitudinal follow-up studies will be needed to clarify the temporal dynamics of connectome gradient dysfunction in PTSD. Second, cognitive performance was not directly measured; our analysis linking gradient alteration maps to meta-analytic cognitive terms from the Neurosynth database (Yarkoni et al., 2011) serves as indirect evidence of brain-cognition association. Third, we only used rs-fMRI to explore brain functional connectome gradients. Recently, studies on macroscopic/microstructural gradients based on cortical morphometric similarity/diffusion MRI have revealed gradual transitions of multiple structural features along the cortex (Hettwer et al., 2022; Li et al., 2024b; Xue et al., 2023; Yang et al., 2021), yielding valuable insights into the hierarchical disorganization in neuropsychiatric disorders. Given that PTSD is associated with both brain functional and structural abnormalities, it remains unclear whether the observed gradient alterations in PTSD are specific to functional architecture or rather reflect underlying structural/morphological network differences. Future studies combining structural and functional MRI within the same PTSD cohort are needed to examine the relationships between functional and structural gradient alterations and to provide a more complete picture of the multiscale hierarchy disruptions in PTSD. Fourth, while focusing on participants exposed to the earthquake without psychiatric comorbidities enhanced sample homogeneity, it remains uncertain if our findings apply to PTSD resulting from other types of traumas and with psychiatric comorbidities. Fifth, we analyzed gradient alterations, distinguishing the stressed individuals with PTSD from those without. To assess the impact of major life stress itself on connectome gradient, a comparison with nontraumatized healthy controls would be needed. Finally, we examined the associations between PTSD-related functional gradient alterations and gene expression profiles from six healthy donors, acknowledging that variations in gene expression between PTSD and healthy individuals may limit the interpretation.

Conclusion

Our multiscale analysis of principal gradient identified a clinically relevant pattern of brain functional hierarchical disorganization in PTSD. Specifically, PTSD patients showed elevated principal gradient values in the visual and limbic systems and reduced values in ventral attention and frontoparietal systems, which were associated with PTSD symptom severity and meta-analytic cognitive domains. The diagnosis-age interaction analysis revealed that lower gradient scores in the subcortical network were greater in adolescent than adult PTSD patients. Finally, we identified PTSD-related genes enriched for mitochondria and the potential involvement of dopamine, opioid, noradrenaline, and cholinergic systems through gradients-transcriptome/neurotransmitter analysis. These findings enhance our understanding of PTSD-related hierarchical disturbances in brain function and provide insights into the underlying neural mechanisms in individuals with PTSD.

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Supplementary material. The supplementary material for this article can be found at http://doi.org/10.1017/S0033291726105388.

Data availability statement. The neuroimaging data in the present study are in active use by the reporting laboratory and are available from the corresponding author upon reasonable request. Human gene expression data that support the findings of this study are available in the Allen Human Brain Atlas (https://human.brain-map.org/static/download). Transcriptomic data was preprocessed by the abagen toolbox (https://github.com/rmarkello/abagen). The gene enrichment analysis was conducted by Metascape (https://metascape.org/). PET/SPECT neurotransmitter maps are available in the JuSpace toolbox (https://github.com/juryxy/JuSpace).

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Author contribution. X.S. and Q.G. designed the study. L.L. carried out the data collection. X.S., X.Z., W.L., and C.Z. carried out the statistical analysis and produced figures. X.S. wrote the first draft of the manuscript, and all authors contributed to editing and commenting on the final version.

Competing interests. The authors declare that they have no competing interests.

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