EUROPEAN JOURNAL OF PSYCHOTRAUMATOLOGY
2024, VOL. 15, NO. 1, 2430925
https://doi.org/10.1080/20008066.2024.2430925

CLINICAL RESEARCH ARTICLE

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Brain connectivity disruptions in PTSD related to early adversity: a multimodal neuroimaging study

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ABSTRACT

Background: Post-traumatic stress disorder (PTSD) is increasingly prevalent in individuals with adverse childhood experiences (ACE). However, the underlying neurobiology of ACE-related PTSD remains unclear.

Objective: The present study investigated the brain connectivity in ACE-related PTSD using multimodal neuroimaging data.

Methods: Using a total of 119 participants with ACE (70 with ACE-related PTSD and 49 ACE-exposed controls), this study acquired T1-weighted MRI, diffusion-weighted MRI, and resting-state fMRI data to examine structural and functional connectivity between groups. Joint connectivity matrix independent component analysis (Jcm-ICA) was employed to allow shared information from all modalities to be examined and assess structural and functional connectivity differences between groups.

Results: Jcm-ICA revealed distinct connectivity alterations in key brain regions involved in cognitive control, self-referential processing, and social behaviour. Compared to controls, the PTSD group exhibited functional hyperconnectivity of the right medial prefrontal cortex (PFC) of the default mode network and right inferior temporal cortex, and functional hypoconnectivity in the lateral-PFC of the central executive network and structural hypoconnectivity in white matter pathways including the right orbitofrontal region (OFC) linked to social behaviour. Post-hoc analyses using the joint brain-based information revealed that the severity of ACE, the number of traumas, and PTSD symptoms later in life significantly predicted the effects of ACE-related PTSD on the brain. Notably, no direct association between brain connectivity alterations and PTSD symptoms or the number of traumas within the PTSD group was observed.

Conclusion: This study offers novel insights into the neurobiology of ACE-related PTSD using multimodal data fusion. We identified alterations in key brain networks (DMN, CEN) and OFC, suggesting potential deficits in cognitive control and social behaviour alongside heightened emotional processing in individuals with PTSD. Furthermore, our findings highlight the combined influence of ACE exposure, number of traumas experienced, and PTSD severity on brain connectivity disruptions, potentially informing future interventions.

Alteraciones de la conectividad cerebral en el TEPT relacionado con la adversidad temprana: un estudio de neuroimagen multimodal

Antecedentes: El trastorno de estrés postraumático (TEPT) es cada vez más frecuente en personas con experiencias adversas en la infancia (EAI). Sin embargo, la neurobiología subyacente del TEPT relacionado con EAI permanece sin estar clara.

Objetivo: Este estudio investigó la conectividad cerebral en el TEPT relacionado con EAI utilizando neuroimagen multimodal.

Métodos: Se incluyeron 119 participantes con EAI (70 con TEPT y 49 controles expuestos a EAI). Se adquirieron datos de T1-MRI, difusión-MRI y fMRI en reposo para evaluar la conectividad estructural y funcional. Mediante análisis Jcm-ICA, se exploraron diferencias de conectividad cerebral compartida entre grupos.

Resultados: Jcm-ICA identificó alteraciones distintivas en regiones cerebrales clave relacionadas con el control cognitivo, el procesamiento autorreferencial y el comportamiento social. En comparación con los controles, el grupo con TEPT mostró

ARTICLE HISTORY

Received 22 July 2024
Revised 8 November 2024
Accepted 9 November 2024

KEYWORDS

Post-traumatic stress disorder; adverse childhood experiences; joint independent component analysis; multimodal neuroimaging; functional connectivity; structural connectivity

PALABRAS CLAVE

Trastorno de estrés postraumático; experiencias adversas en la infancia; análisis de componentes independientes conjuntos; neuroimagen multimodal; conectividad funcional; conectividad estructural; adversidad temprana

HIGHLIGHTS

- In the present study individuals with a history of childhood adversity and PTSD reported distinct alterations in functional and structural connectivity patterns in key brain networks involved in cognitive control, self-referential processing, and social behaviour.
- Additionally, evidence of brain deficits in the right medial prefrontal cortex, right inferior temporal cortex, lateral PFC and right orbitofrontal cortex in ACE-related PTSD was derived from multimodal brain features.
- Furthermore, the study demonstrated a potential link between the severity

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Supplemental data for this article can be accessed online at https://doi.org/10.1080/20008066.2024.2430925.

hiperconectividad funcional de la corteza prefrontal medial derecha de la red neuronal por defecto (RND) y de la corteza temporal inferior derecha, así como hipoconectividad funcional de la corteza prefrontal lateral de la red ejecutiva central (REC) e hipoconectividad estructural en las vías de sustancia blanca, incluida la región orbitofrontal derecha vinculada al comportamiento social. Los análisis post-hoc revelaron que la gravedad de la EAI, el número de traumas y los síntomas de TEPT predijeron significativamente estas alteraciones cerebrales.

Conclusión: Este estudio aporta nuevas perspectivas sobre la neurobiología del TEPT relacionado con EAI mediante el uso de datos multimodales. Las alteraciones en las redes RND, REC y en la región orbitofrontal sugieren déficits en el control cognitivo y social, junto con un mayor procesamiento emocional en el TEPT. Además, se destaca la influencia combinada de la EAI, los traumas y los síntomas de TEPT sobre la conectividad cerebral, proporcionando información clave para futuras intervenciones.

- of ACE, the number of traumas, and PTSD symptoms with the observed brain connectivity disruptions.
- Notably, no direct association between brain connectivity alterations and PTSD symptoms or the number of traumas within the PTSD group was found, suggesting that trauma severity, rather than number of traumas, may play a crucial role in shaping brain structure and function in individuals with PTSD.

1. Introduction

Post-traumatic stress disorder (PTSD) is a mental health condition triggered by experiencing or witnessing a traumatic event and has significant prevalence rates of 3.9% in the general population (Koenen et al., 2017). Adverse Childhood Experiences (ACE), particularly childhood abuse and neglect, are potentially traumatic events that are strongly associated with an increased risk of developing PTSD later in life (Messman-Moore & Bhuptani, 2017; Nooner et al., 2012). A well-known thought about this relationship is that ACE impairs the ability to form social connections (Barnes, 2016; Herzog & Schmahl, 2018) which serve as an important protective factor in the resilience to stress (Bækkelund et al., 2021; Cisler & Herringa, 2021). Among adolescents, the prevalence of ACE-related PTSD is reported to be 57%, compared to 10% for PTSD from natural disasters (Nooner et al., 2012), with symptoms manifesting at least two months post-ACE (Kilpatrick et al., 2013).

MRI studies from different modalities have shown widespread abnormalities in brain structure and function in persons with ACE and PTSD. These include regions known to play significant roles in spatial processing, such as the superior parietal lobe (Nkrumah et al., 2024; Wang et al., 2021), and emotional processing, including the medial prefrontal cortex, amygdala, anterior cingulate cortex, and insula (Hosseini-Kamkar et al., 2023; Pollok et al., 2022; Sherin & Nemeroff, 2011; Wang et al., 2016), as well as key regions like the hippocampus, crucial for memory formation and retrieval (Cisler & Herringa, 2021; Morey et al., 2016; Teicher et al., 2018).

In functional connectivity (FC) based research, the concept of the triple network system highlights how systemic regions of the brain relate to each other, including regions involved in internally directed thoughts (DMN; default mode network), externally focused attention (CEN; central executive network or FPN; fronto-parietal network), and salience processing (SN; salience network) (Menon, 2011). Individuals with ACE and PTSD often show functional hyperconnectivity in the DMN due to rumination on intrusive memories and persistent negative thoughts associated with trauma, compared to those without such experiences (Daniels et al., 2011; Hoffmann et al., 2018; Lebois et al., 2022). Conversely, functional hypoconnectivity in the DMN may impair self-referential processing and contribute to dissociative symptoms commonly observed in PTSD (Lanius et al., 2020). However, Lebois et al. (2022) found hyperconnectivity in females with PTSD dissociative subtype. Notably, the literature on DMN abnormalities in PTSD is heterogeneous, with both hyper- and hypoconnectivity findings reported. This variability may be influenced by factors such as trauma type, severity, chronicity, and study methodology (Lanius et al., 2020; Wang et al., 2016). Similarly in the SN, individuals with ACE and PTSD often demonstrate functional hyperconnectivity as a potential correlate of heightened sensitivity to stressors (Thome et al., 2014), increased emotional reactivity, and difficulties in discerning between relevant and irrelevant stimuli, thereby perpetuating the cycle of trauma-related symptoms (Akiki et al., 2017). In contrast, within the CEN, individuals with ACE and PTSD typically show functional hypoconnectivity potentially resulting from distractibility, and difficulties disengaging from trauma-related cues which often impair daily functioning and exacerbate symptoms of PTSD (Kavanaugh & Holler, 2014; Olson et al., 2019). Structural connectivity (SC) based research, persistently reports reduced SC measures at the whole brain level in ACE and PTSD samples compared to healthy participants (Kavanaugh & Holler, 2014; Lim et al., 2019). These SC results suggest impaired neural communication, potentially reflecting neurodevelopmental disruptions associated with ACE and PTSD (Dennis et al., 2021; McLaughlin et al., 2019). While these studies demonstrate significant findings using diverse samples and unimodal MRI methods, understanding the intricate relationships within brain networks such as the triple network system in ACE related

PTSD sample and fusing both SC and FC could offer a holistic perspective on the neural mechanisms involved in ACE related PTSD.

Despite advancements in neuroimaging research, there remains a need for further exploration of the neural correlates of ACE-related PTSD. Fusing structural (e.g. diffusion-weighted MRI) and functional (e.g. Resting state fMRI) data has gained interest in recent times and holds promises to enhance our understanding of the brain (Calhoun & Sui, 2016; Hirjak et al., 2020; Khalilullah et al., 2023; Ooi et al., 2022). Specifically, data-driven joint connectivity matrix independent component analysis (jcm-ICA) has recently been explored in a healthy subject sample and shows promise for connectivity-based multimodal neuroimaging data fusion at the whole-brain level (Wu & Calhoun, 2023). Jcm-ICA enables the analysis of SC and FC data, allowing for the identification of shared and distinct brain patterns and potentially providing novel insights into brain organisation and function in both healthy and diseased brain.

In this study, we performed jcm-ICA in an ACE-related PTSD sample compared to an ACE-exposed control group while controlling for the influence of other lifetime traumatic experiences associated with PTSD. Our aim was to fuse SC and FC features to investigate both features at the whole brain level as well as the triple network systems that would help categorise ACE-related PTSD vs. ACE-exposed control (noPTSD). We hypothesised that individuals with ACE-related PTSD will exhibit different patterns of connectivity compared to noPTSD, particularly within the DMN, SN, and CEN. Specifically, we anticipated functional hyperconnectivity in the DMN and SN, along with functional hypoconnectivity in the CEN in the PTSD group compared to the noPTSD group. We also hypothesised an overall decreased structural connectivity on whole-brain level in the PTSD group compared to noPTSD group. By examining both SC and FC features, we aimed to enhance our understanding of the neural correlates underlying ACE-related PTSD.

2. Methods

2.1. Participants

This study forms part of an ongoing study investigating the effects of ACE on brain structure and function (https://doi.org/10.17605/OSF.IO/S5YDB). For the current study, a total of 148 participants (85.14% females; $Mean_{age}$ = 31.02, SD_{age} = 10.05) with any form of ACE were recruited through distributed flyers, advertisements, and online platforms. The inclusion criteria for the study were persons exposed to any form of ACE and with or without lifetime PTSD diagnostics. Exclusion criteria included any kind of metal implant, pregnancy, traumatic brain injury, claustrophobia, psychosis, or any form of neuropsychological disorder. 29 participants were excluded from the final analysis: 15 had incomplete data and / or exhibited anomalies in their Magnetic Resonance (MR) images, likely due to movement artefacts during data acquisition and a low Signal-to-Noise Ratio (SNR) in the acquired image. 14 participants were excluded due to comprehension difficulties of several crucial questions during diagnostic interviews and incomplete clinical data. Consequently, the final data set used in our analyses consisted of 119 participants (84.87% females; $Mean_{age}$ = 30.66, SD_{age} = 10.07, $Range_{age}$ = 18–59 years).

2.2. Procedure

Kindly see supplementary material.

2.3. Measures

For the current study, we assessed lifetime PTSD diagnoses, ACE severity (computed using the total Childhood Trauma Questionnaire (CTQ) severity score), trauma load (computed using any other non-CTQ related possible events associated with PTSD in the Life Event Checklist (LEC) for PTSD; see Supplementary), PTSD symptom severity (PTSS; computed from the total PCL-5 score), and ACE-related trauma count (the sum of the number of multiple ACE-related PTSD traumatic experiences). Kindly see supplementary 1.2 for additional information on measures. Table 1 shows demographics, symptoms, diagnostics and comparison between groups. Sex, ACE severity, overall trauma load were statistically significantly different between groups hence controlled for in all subsequent analyses. Age was additionally controlled for based on literature (Giedd & Rapoport, 2010; Herzog et al., 2020; Herzog & Schmahl, 2018; Siehl et al., 2018).

2.4. Imaging data acquisition

All MR data, i.e. T1-weighted (T1w), diffusion and resting state images were acquired using a Siemens Prisma-fit Scanner (Siemens Medical Solutions, Erlangen, Germany) with a 64-channel head coil. The MR protocol for each participant included: A 3-D magnetization-prepared rapid-acquisition gradient echo (MPRAGE; T1-weighted contrast, Echo Time (TE) = 2.01 ms, Repetition Time (TR) = 2000 ms, Inversion time (TI) = 900 ms, Flip angle (FA) = 9o, FOV = 256 × 256 mm, number of slices 192, voxel size 1 × 1 × 1 mm^3), a diffusion image with double spin-echo echo-planar imaging (EPI) sequence for diffusion (82 volumes, 3 at b = 0 and 79 at b = 1000 s/mm^2,

Table 1. Demographics, symptoms and lifetime PTSD diagnostics of noPTSD and PTSD.

	noPTSD	PTSD	Difference	*P* value
N (%)	49 (41.18%)	70 (58.82%)		
Age	29.22 ± 9.48	31.67 ± 10.41	T = −1.309 (df = 117)	.193
Sex	37 F	64 F	X^2 = 5.891 (df = 1)	<.001*
ACE severity (CTQ total)	51.80 ± 11.60	72.59 ± 18.94	T = −6.834 (df = 117)	<.001*
• *Emotional abuse*	14.06 ± 4.99	17.93 ± 5.07	T = −4.121 (df = 117)	<.001*
• *Physical abuse*	8.18 ± 3.53	10.84 ± 5.29	T = −3.070 (df = 117)	.003*
• *Sexual abuse*	6.65 ± 3.21	13.64 ± 6.63	T = −6.833 (df = 117)	<.001*
• *Emotional neglect*	15.12 ± 5.04	18.57 ± 4.99	T = −3.695 (df = 117)	<.001*
• *Physical neglect*	7.78 ± 2.29	11.60 ± 4.39	T = −5.589 (df = 117)	<.001*
PTSD severity (PCL total)	19.06 ± 13.46	35.46 ± 17.09	T = −5.605 (df = 117)	<.001*
• *Reexperiencing*	4.12 ± 3.78	8.13 ± 4.83	T = −4.856 (df = 117)	<.001*
• *Avoidance*	2.69 ± 2.34	4.39 ± 2.49	T = −3.738 (df = 117)	<.001*
• *Negative alterations in cognition and mood*	6.88 ± 5.80	12.84 ± 6.79	T = −5.001 (df = 117)	<.001*
• *Hyper arousal*	5.37 ± 4.76	10.10 ± 5.65	T = −4.792 (df = 117)	<.001*
Overall trauma load	2.04 ± 1.53	2.33 ± 1.80	T = −1.309 (df = 117)	<.001*
Number of ACE-related trauma	0.71 ± 0.71	1.41 ± 0.55	T = −6.061 (df = 117)	<.001*

Note. Data are reported as mean ± standard deviation. Age range for the total sample is 18–59 years. *df* degree of freedom. *: Significant at $P < .05$ level.

TR = 8400 ms, TE = 86 ms, matrix = 128 × 128, number of slices = 64, voxel size = 2 × 2 × 2 mm^3, in-plane acceleration factor of 3) and resting state (400 BOLD fMRI volumes, 36 slices in interleaved ascending order, TR = 1020 ms, TE = 30 ms, FA = 63°, FOV = 192 × 192 mm, matrix size = 64 × 64, voxel size = 3 × 3 × 3.75 mm^3, MB factor of 2, in-plane acceleration factor of 2).

2.5. Data preprocessing

T1-weighted images were preprocessed, parcellated, and segmented into 83 cortical and subcortical nodes of the Lausanne atlas using Connectome Mapper 3 (CMP3; an open-source python neuroimaging processing pipeline software developed by the Connectomics Lab, University Hospital of Lausanne (CHUV)). Diffusion and resting-state fMRI data were also preprocessed using CMP3 (Tourbier et al., 2022). See supplementary material, for in-depth description of data preprocessing. Two structural connectivity measures (i.e. the number of fibres between nodes and normalised density of fibres between nodes) and two functional connectivity measures (i.e. positive and negative functional correlation between nodes) were retrieved from the output of CMP3 and used as features for the jcm-ICA (kindly see Figure 1(A)).

2.6. Quality control and data preprocessing of connectivity matrices

The SC and FC features were visually inspected. Each individual connectivity matrix (with the dimension of 83 × 83) was controlled for age, sex, ACE severity, and trauma load, and subsequently normalised by rescaling the data range to an interval of [0, 1]. This preprocessing step aims to ensure that the features for jcm-ICA are standardised and comparable across subjects, enhancing the robustness and interpretability of the subsequent analysis and ensuring equal contribution from both SC and FC data in the next steps.

2.7. Jcm-ICA for multimodal analyses

Data-driven jcm-ICA was performed using a joint feature matrix obtained by fusing individual subjects' SC and FC data matrices (Figure 1(B), LHS) using the Fusion ICA Toolbox (http://mialab.mrn.org/software/fit).

First, principal component analysis (PCA) was performed as a dimension reduction step on the subject-level matrix to reduce it to a component level. The noPTSD group was used as a reference in the PCA step to decompose the data into 40 ICs (10 for each feature).

Secondly, we performed 10 ICAs on the component level reduced matrix and averaged the results from the 10 runs to ensure component stability. The Infomax algorithm was used to compute ICA, which produced a subject-level shared mixing matrix and connectivity-based whole brain independent sources for both FC and SC features (Figure 1(B), RHS).

Finally, a *t*-test was performed on the shared mixing matrix (also called the joint mixing coefficient matrix) data to identify the corresponding independent components/sources that best categorise neurobiological differences between groups. As previously demonstrated (Hirjak et al., 2020; Liu et al., 2019; Sui et al., 2009; Wu & Calhoun, 2023), exploring the joint mixing coefficients obtained using information from all features in the joint feature matrix offers a comprehensive approach by incorporating information from both FC and SC features.

Conversely, whole brain connectivity-based independent components and intra and inter network connectivity of the triple network (i.e. DMN, SN and CEN) of the significant components which showed differences between noPTSD vs. PTSD were then explored.

2.8. Relation between joint mixing coefficient and clinical data

In an exploratory post hoc analysis, we evaluated the joint mixing coefficients for the identified significant

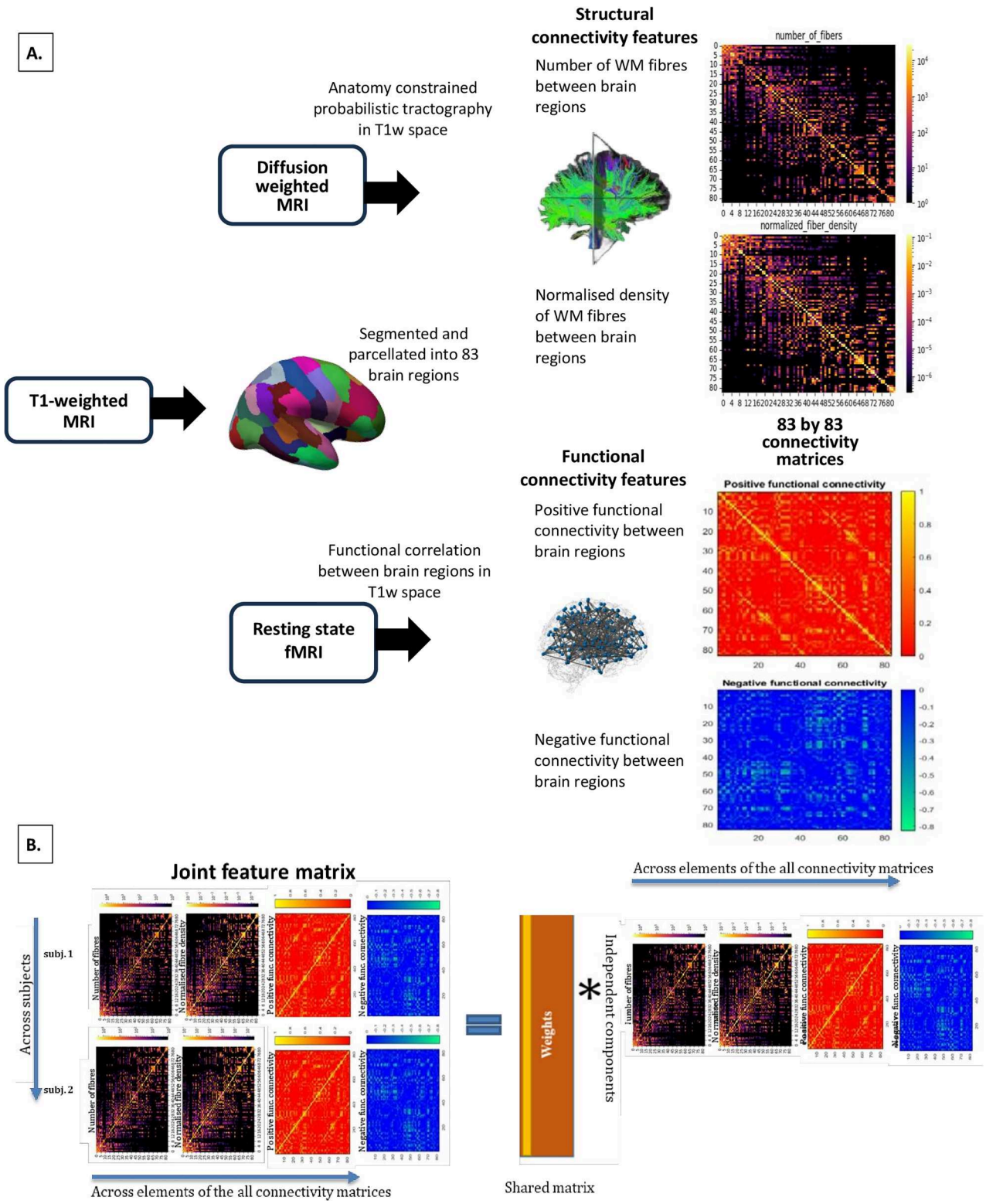

Figure 1. This figure shows our multimodal analysis pipeline. (A) Subject-level processing: T1-weighted (T1w) images were pre-processed, segmented, and parcellated into 83 regions in Lausanne scale 1 space. Diffusion and resting-state images were also preprocessed, and both structural connectivity (SC) features (i.e. number of fibres and normalised fibre density between brain regions) and functional connectivity (FC) features (i.e. positive and negative functional connectivity) were extracted in the T1w parcellation space. (B) This panel shows the jcm-ICA pipeline. All four connectivity matrices were subsequently quality-checked, controlled for covariates, normalised, and used as features to create a joint feature matrix. The joint feature matrix is then modelled as spatially independent components with a shared mixing matrix (also called the joint mixing coefficient matrix)

components to determine if any relationship exists between these coefficients and clinical data. Our aim was to verify if the identified significant component were indeed best predictor of PTSD diagnosis, hence we focused on the PTSD group. We explored whether the number of multiple ACE-related PTSD traumas

(listed in Table 1 as ACE-related trauma count), PTSD symptoms (using PCL total) and ACE severity could relate to PTSD-related brain information. This analysis aimed to examine the potential impact of multiple ACE-related traumatic experiences, PTSD severity, and overall ACE severity on the joint PTSD-related brain information obtained from both structural and functional data.

3. Results

3.1. Group differences (noPTSD > PTSD) on joint mixing coefficient

Figure 2(A) shows the two-sample *t*-test results on the 10 joint mixing coefficients of the 10 estimated components. After correcting for multiple comparisons using the Bonferroni method, the joint mixing coefficient (MC) for component 9 was significantly different between groups ($p = .004$, Figure 2(A)). Figure 2(B) shows the *t*-test results for MC of independent component (IC) 9. Compared to the PTSD group, the higher mixing coefficients in the noPTSD group indicate that IC 9 (which includes both SC and FC features) is expressed more in the noPTSD group.

3.2. Cortical representation of the independent component 9 differentiating between PTSD and noPTSD groups

As identified in the analysis of the MC above, IC 9 best categorises neurobiological differences between groups. Hence, we explored the respective features of

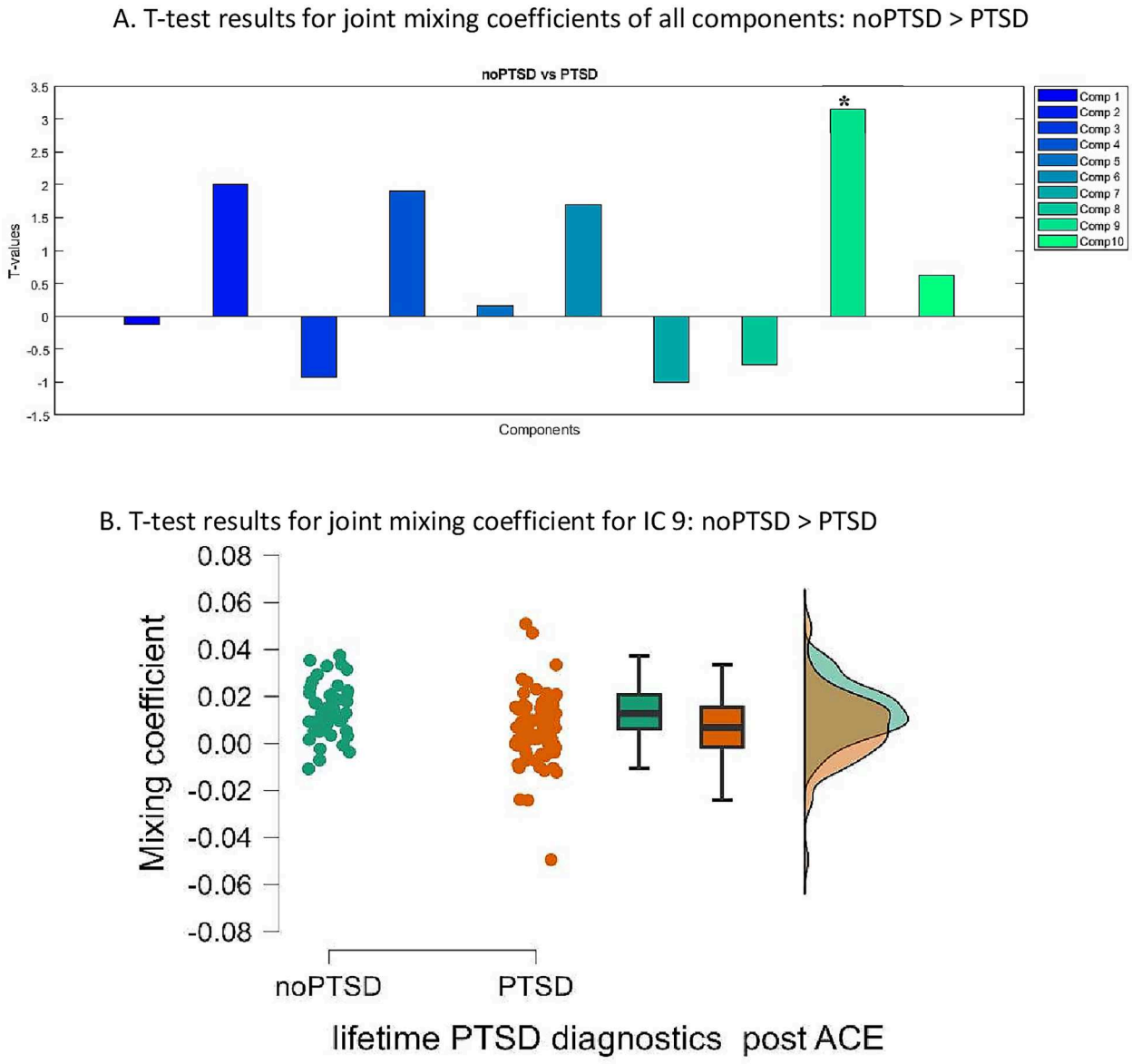

Figure 2. A two-sample *t*-test was computed on the joint mixing coefficients between the noPTSD and PTSD groups. 2A shows a bar graph of the T-values from the *t*-test computed on the mixing coefficients of all 10 components. (*) indicates components with significant *p*-values after Bonferroni correction. 2B shows a plot of the *T*-test results for the joint mixing coefficient of component 9 between the noPTSD and PTSD groups.

this component. For visualisation purposes, all features of IC 9 were plotted on the cortical surface, transformed into Z scores, and thresholded at $z > 2$ (hyperconnectivity in red) and $z < -2$ (hypoconnectivity in blue), indicating increases and decreases in FC and SC measures, respectively. After thresholding, no significant results were found for the number of fibres and negative functional connectivity features. Compared to the noPTSD group, the PTSD group exhibited functional hypoconnectivity (i.e. decrease in the positive FC measure and indicative of colour blue in Figure 3(A)) in the left and right lateral prefrontal cortex (lPFC) and functional hyperconnectivity (i.e. an increase in the positive FC measure and indicative of the colour red in Figure 3(A)) in the right medial prefrontal cortex (rmPFC) and right inferior temporal gyrus. Additionally, individuals with PTSD showed reduced (i.e. hypoconnectivity) of the NFD measure in the right orbitofrontal cortex (rOFC) compared to controls.

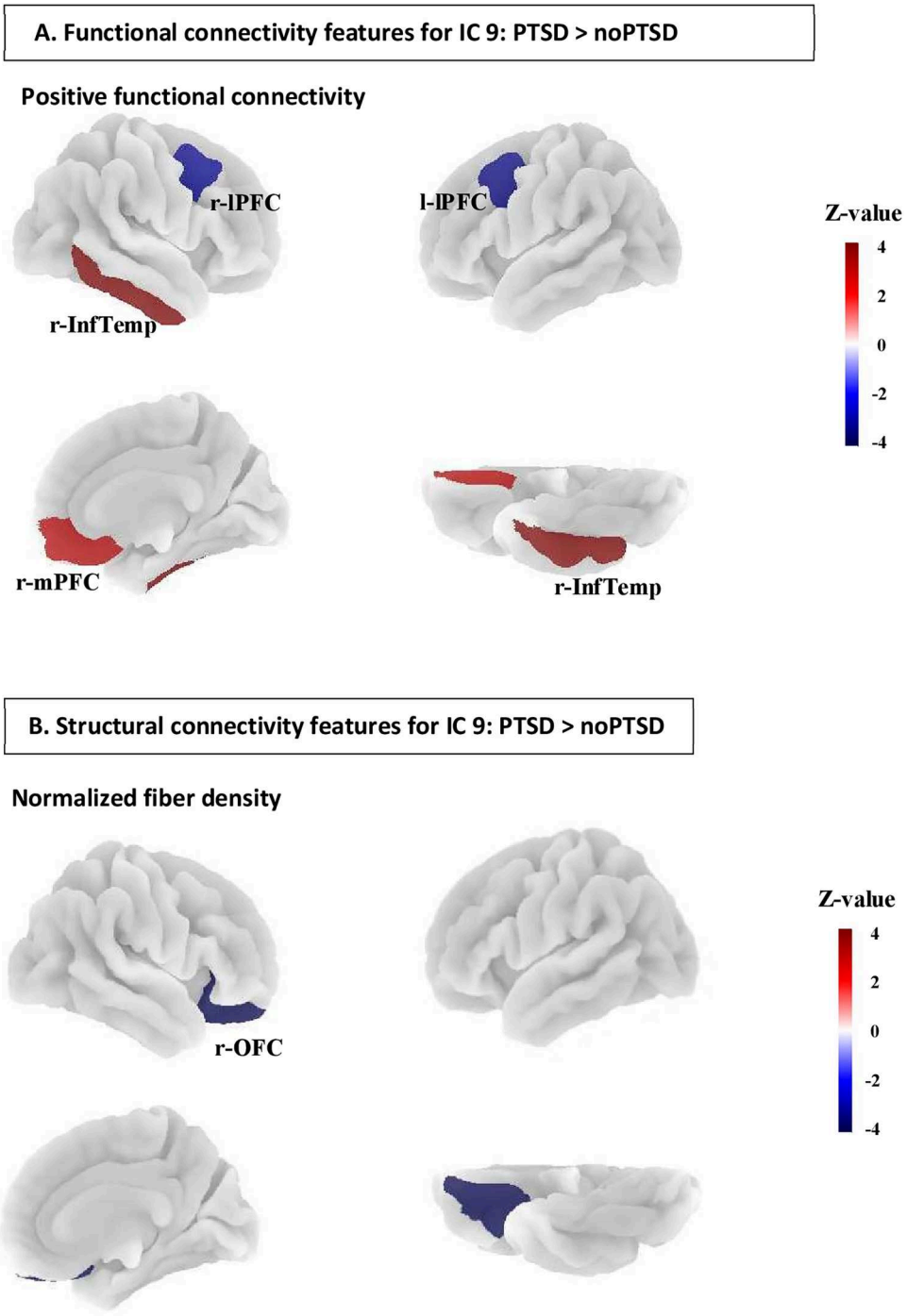

Figure 3. Back-reconstructed cortical functional and structural connectivity features for independent component 9, which differed between the PTSD and noPTSD groups. All features were transformed into Z scores and thresholded at $z > 2$ (hyperconnectivity in red) and $z < -2$ (hypoconnectivity in blue) for visualisation purposes. (A) Positive functional connectivity features for IC 9. (B) Normalised fibre density features for IC 9. InfTemp = inferior temporal gyrus, mPFC = medial prefrontal cortex, lPFC = lateral prefrontal cortex, OFC = orbitofrontal cortex. r- and l- represent the right and left hemispheres, respectively.

3.3. Relation between joint mixing coefficient (MC) and clinical data

Here, our focus was to check whether the MC from both structural and functional features were indeed best predictor of PTSD diagnostics hence, we focused on the PTSD group. First, we conducted correlational analyses between the MC and clinical measures, including PCL-5 and CTQ subscale scores. The results of these analyses are presented in Supplementary Table S2. We found that within the PTSD group, MC of IC9 was negatively correlated to ACE severity (total CTQ score; $r = -.275$, $p = .021$) but not the number of ACE-related traumatic events ($r = .048$, $p = .695$) and PTSD symptomatology (total PCL-5 score; $r = -.174$, $p = .149$). Further moderation analysis revealed that the number of ACE-related traumatic events significantly moderated the relationship between ACE severity and MC of IC9 (interaction term: t-value $= -3.03$, $\beta = -.0004$, SE $= .0001$, $p = .0035$, $R^2 = .1967$). Specifically, at higher levels of ACE-related traumatic events (i.e. 2 and 3), the negative relationship between ACE severity and MC of IC9 was stronger (simple slope analysis in Figure 4(A)). Although PTSD symptoms did not individually moderate the relationship between ACE severity and MC of IC9 (interaction term: t-value $= -1.44$, $\beta = -.00000962$, SE $= .00000667$, $p = .1543$), using Hayes' Model 2, with ACE severity as independent variable, the number of ACE-related traumatic events and PTSD symptoms as moderators and MC of IC9 as dependent variable was significant (both interactions: Figure 4(B): $F(2, 64) = 5.29$, $p = .0075$, $R^2 = 0.2165$). This indicates that the combined presence of multiple ACE-related PTSD traumas and higher levels of PTSD symptoms further strengthens the negative relationship between ACE severity and MC of IC9. To address potential multicollinearity, assess model improvement, and provide a comprehensive understanding of our results in the PTSD group, we report the VIF values, detailed model fit statistics, and correlations between clinical variables in the supplementary material. Briefly, only ACE severity and PTSD symptoms were significantly correlated ($r = .516$, $p < .001$). However, the VIF values for all variables in the model used were below 1.5, indicating no concerns regarding multicollinearity (O'brien, 2007).

4. Discussion

Using a Jcm-ICA, we identified neuronal networks to be different between ACE-exposed individuals with PTSD compared to ACE-exposed controls. These alterations in FC include regions in the DMN and the CEN, as well as the right inferior temporal gyrus responsible for facial processing. SC features also showed differences in rOFC, a region critical for social behaviour.

First in Jcm-ICA, we estimated 10 ICs from both structural and functional brain connectivity features, derived from an average of 10 independent component analysis (ICA) runs. A t-test of the MC for each of the 10 component revealed that IC 9 showed significant differences between the noPTSD and PTSD groups ($p = .004$, Figure 2). As reported in previous studies (Lottman et al., 2018; Sui et al., 2009; Sui et al., 2011), exploring the MC provides a comprehensive comparison between groups, potentially highlighting distinct neural signatures associated with PTSD. The resulting connections of the independent sources reveal whole brain hyperconnectivity (increase of SC or FC measures) or hypoconnectivity (decrease of SC or FC measures) between nodes in the PTSD group compared to the noPTSD group.

After plotting our findings from IC 9 on the cortex, distinct patterns of connectivity in several key brain regions involved in self-referential processing (Lanius et al., 2020), cognitive control (Fenster et al., 2018), and social behaviour (Hinojosa et al., 2024) were revealed, shedding light on the neurobiological mechanisms underlying ACE-related PTSD. For functional connectivity features, notable alterations were observed in the positive functional connectivity feature, which indicates a positive functional correlation between nodes. Specifically, the PTSD group exhibited hypoconnectivity (i.e. decrease in positive FC measure and indicative of colour blue in Figure 3(A)) in the left and right lPFC, a component of the central executive network, responsible for cognitive control and executive functioning (Marek & Dosenbach, 2018; Olson et al., 2019). As hypothesised and supported by existing literature (Akiki et al., 2017; Johnson et al., 2021; McLaughlin et al., 2017), hypoconnectivity in the lPFC suggests potential deficits in cognitive flexibility and decision-making, which is compatible with the symptomatology of individuals with ACE and PTSD. These alterations further underscore the impact of ACE on the neural substrates supporting higher-order cognitive processes, offering insights into the cognitive dysregulation commonly observed in individuals with PTSD (Pankey et al., 2022).

Conversely, functional hyperconnectivity in the rmPFC and right inferior temporal gyrus was found in the PTSD group compared to noPTSD group. This finding aligns with our initial assumptions, as rmPFC forms part of the DMN and is involved in self-referential processing, and memory consolidation (Lanius et al., 2020; Sokołowski et al., 2022), which occur more frequently in individuals with PTSD, especially those with a history of ACE due to persistent re-experiencing of traumatic memories characteristic of PTSD (Pankey et al., 2022; Thomaes et al., 2012). Increased FC in the rmPFC could reflect an enhanced focus on internal experiences, such as rumination and

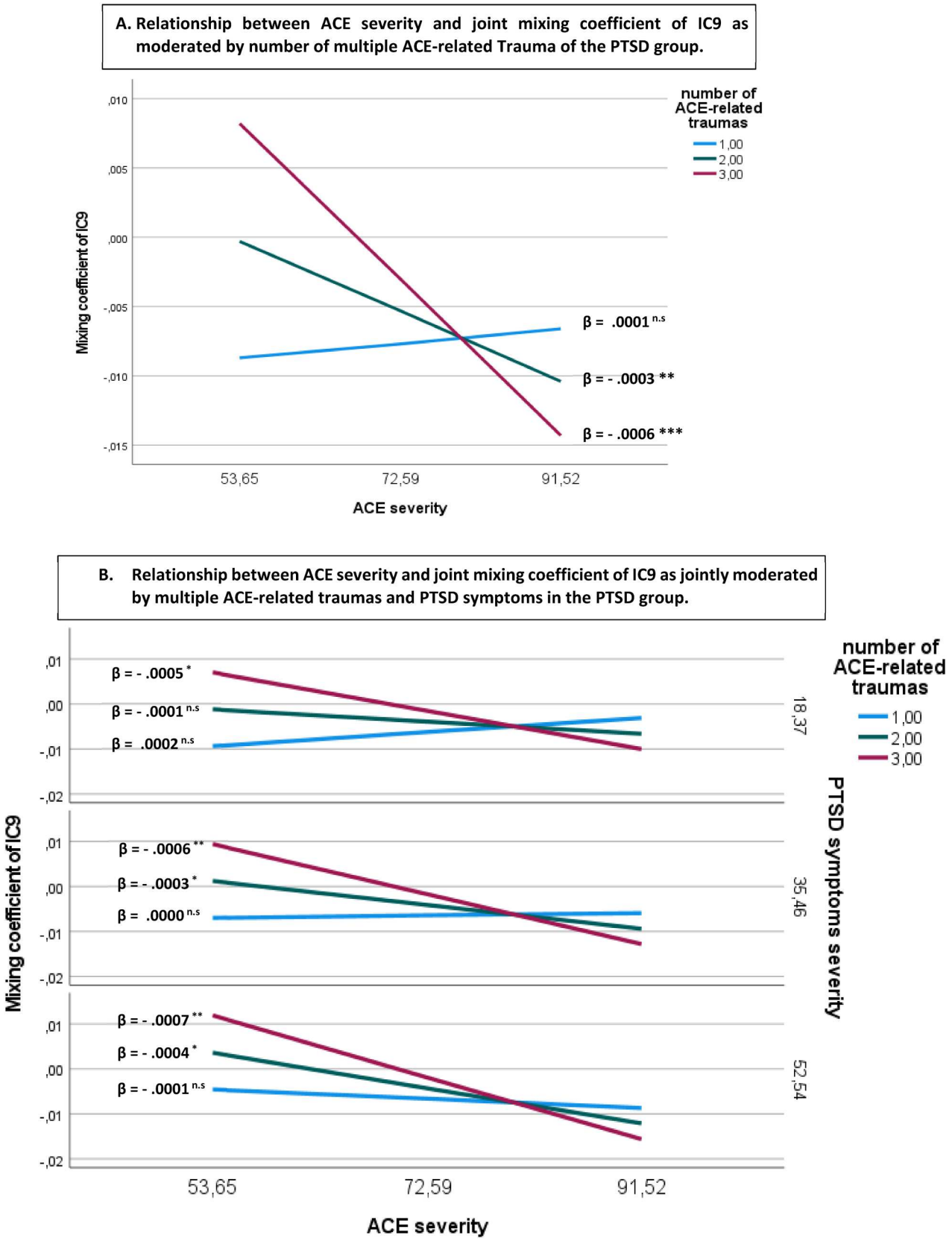

Figure 4. Shows the relation between ACE severity and joint mixing coefficient of IC9 as moderated by (A) number of ACE-related trauma events and (B) number of ACE-related traumas events and PTSD symptoms severity. PTSD symptom severity grouping is shown as ±1 standard deviation around the mean PCL symptoms severity score in the PTSD group (representing low = 18.37, moderate = 35.46, and severe = 52.54 severity, respectively). Asterisks indicate the statistical significance of the boot-strapped unstandardised regression coefficients (***$p < .001$; **$p < .01$; *$p < .05$; n.s – not significant).

intrusive thoughts related to past trauma, potentially exacerbating symptoms (Fitzgerald et al., 2018). Additionally, alterations in the rmPFC could influence social cognition and interpersonal functioning (Fitzgerald et al., 2018), contributing to difficulties in social interactions and forming secure attachments, which are often affected in persons with PTSD. Furthermore, a longitudinal study by Du and colleagues supports the DMN findings; alterations in the DMN persisted at the two-year follow-up post traumatic experience in PTSD groups (Du et al., 2014). This persistence highlights the DMN's central role in PTSD's long-term neurological effects (Hinojosa et al., 2024; Ireton et al., 2024). In addition to the rmPFC findings, functional hyperconnectivity in the right inferior temporal gyrus, known for its involvement in face perception (Shahbazi et al., 2024) and recognition (Faghel-Soubeyrand et al., 2024), was observed in individuals with ACE-related PTSD compared to controls (Holz et al., 2023). This suggests heightened neural responsiveness to visual stimuli, particularly emotional faces, in the context of trauma exposure (Harnett et al., 2021; Hinojosa et al., 2024). Such heightened reactivity to emotional cues may contribute to the re-experiencing of traumatic memories and difficulties in emotional regulation commonly observed in PTSD (Harnett et al., 2021; Kavanaugh & Holler, 2014).

In examining the structural connectivity features, encompassing both the number of fibres (NOF) and normalised fibre density (NFD) of white matter pathways between cortical nodes, our analysis revealed a significant difference between groups solely in the NFD feature. Unlike the NOF measure, the NFD accounts for differences in brain size by incorporating the cortical volume of individual regions in its computation (Nkrumah et al., 2024). Specifically, individuals with PTSD exhibited hypoconnectivity (i.e. decrease) of the NFD measure in the rOFC compared to controls. The rOFC is known to play a role in social behaviour and closely connected to the ventrolateral prefrontal cortex, which is involved in the integration of emotional processes and decision making (Kida & Hoshi, 2016). The observed alteration in the rOFC aligns with previous research highlighting the role of this brain region in modulating emotional responses (Eden et al., 2015) and integrating sensory information to guide adaptive behaviour (Rolls & Grabenhorst, 2008).

Our post hoc analysis which aimed to determine whether the MC derived from both structural and functional data could serve as a reliable predictor of PTSD diagnosis, revealed significant relations between the MC of IC9 and clinical data. We found a significant negative correlation between the MC of IC9 and the severity of ACE within the PTSD group. This relationship appears to be driven by childhood abuse, more specifically physical abuse (see supplementary Table S2). This aligns with previous research demonstrating the detrimental impact of childhood trauma on brain structure and function in individuals with PTSD (McLaughlin et al., 2017; Teicher & Samson, 2016). We did not observe a significant correlation between the MC of IC9 and the number of ACE-related traumatic events or PTSD symptomatology. However, our complementary checks for the post-hoc analyses revealed a significant correlation between ACE severity and PTSD symptom severity but not with the number of traumatic events within the PTSD group (see supplementary Table S3). This suggests a complex relationship between ACE severity, PTSD symptoms, and the number of traumas. Hence, our findings may indicate that the severity of traumatic experiences has a greater influence on the brain connectivity patterns observed in individuals with PTSD than the quantity of traumatic experiences (Bellis et al., 2019). Further analysis in our sample revealed a significant moderation effect of the number of multiple ACE-related traumatic events on the relationship between ACE severity and the MC of IC9. Specifically, higher levels of multiple ACE-related traumas strengthened the negative association between ACE severity and MC of IC9. This interaction underscores the cumulative impact of trauma exposure on brain connectivity alterations, potentially reflecting a heightened vulnerability to maladaptive neurobiological changes in individuals with a history of repeated traumatic experiences (Gerin et al., 2023; Herringa et al., 2013; Teicher et al., 2022). Moreover, while PTSD symptoms alone did not moderate the relationship between ACE severity and the MC of IC9, considering the effects of multiple ACE-related traumas and PTSD symptoms as moderators in the relationship between MC of IC9 and ACE severity was significant. This suggests that the presence of both higher levels of traumatic exposures and severe PTSD symptoms amplifies the association between ACE severity and MC of IC9 (Figure 4(B)), indicating a synergistic effect of cumulative trauma burden and symptom severity on brain connectivity disruptions.

The use of jcm-ICA in this study represents a novel approach to investigating brain connectivity in ACE-related PTSD. This method allowed us to assess shared information from structural and functional connectivity, providing novel insights into the neural mechanisms underlying PTSD related to childhood trauma. Collectively, our findings underscore the multifaceted nature of neural adaptations following exposure to ACE, offering valuable insights into the neurobiological mechanisms underlying PTSD pathology and highlighting potential neural targets for therapeutic interventions for ACE-related PTSD (Karatzias et al., 2020; McLaughlin et al., 2019). The observed disruptions in connectivity measures within the DMN, CEN and inferior temporal brain regions

suggest potential biomarkers or neural signatures associated with the disorder, offering avenues for the development of targeted interventions and treatment strategies (Akiki et al., 2017; Steil et al., 2023). Moreover, structural connectivity findings in the right OFC shed more light on the effects of ACE-related PTSD on the brain. Lastly, our post-hoc analyses reveal the synergistic effects of ACE, cumulative trauma burden, and PTSD symptom severity on brain connectivity disruptions in individuals with ACE-related PTSD.

One potential limitation of the study is the risk of contribution bias in the data reduction step, particularly when using the control group as a reference for principal component analysis outputs from the joint feature matrix. This approach may introduce biases in the derived components, as they could be influenced by the characteristics of the control group rather than solely reflecting intrinsic features of individuals with ACE-related PTSD. Additionally, the gender distribution within our sample was not balanced, potentially affecting the robustness of our results. Furthermore, the use of cross-sectional data limits our ability to establish causal relationships, as the moderation effects observed in this study may be influenced by unmeasured time-varying confounders (Fairchild & MacKinnon, 2009). Future research with larger and more diverse samples, employing longitudinal designs, is warranted to validate and extend our findings.

5. Conclusion

The current study utilised the fusion of multimodal neuroimaging data to identified networks reported in literature to be different between ACE-exposed PTSD compared to ACE-exposed controls. Our functional connectivity findings in the DMN, CEN and inferior temporal region and structural connectivity findings in the right OFC extend the literature on the effect of PTSD on the brain, especially in regions involved in self-referential processing, social behaviour and cognitive control. Finally, our findings suggest that specific brain networks implicated in ACE-related PTSD may be predicted by the combined presence of higher ACE severity, multiple number of ACE-related PTSD traumas, and PTSD symptoms severity later in life.

Acknowledgements

We would like to express our gratitude to all participants who generously contributed their time and effort to this study. We also acknowledge the support of the Deutsche Forschungsgemeinschaft (GRK 2350) for funding this work. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This work was supported by the Deutsche Forschungsgemeinschaft, grant number GRK2350/1.

Data availability statement

The datasets generated and/or analyzed during the current study are not publicly available due to ethical approval and confidentiality agreements made with participants, but are available from the corresponding author on reasonable request.

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