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Multimodal neuroimaging in adverse childhood experiences and related PTSD

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Abbreviations

ACE	Adverse Childhood Experiences
BOLD	Blood Oxygen Level Dependent
CCA	Canonical Correlation Analysis
CAPS-5	Clinician Administered PTSD Scale For DSM-5
CEN	Central Executive Network
CM	Childhood Maltreatment
CoMNA	Complementary Multimodal Neuroimaging Analysis
cPTSD	Current Posttraumatic Stress Disorders
CTQ	Childhood Trauma Questionnaire
DL	Deep Learning
DMN	Default Mode Network
FDS	Questionnaire For Dissociative Symptoms
FBA	Fixel-Based Analysis
FC	Functional Connectivity
fMRI	Functional Magnetic Resonance Imaging
HRF	Hemodynamic Response Function
ICA	Independent Component Analysis
IFOG	Inferior Fronto-Orbital Gyrus
InfTemp	Inferior Temporal Gyrus
jICA	Joint Connectivity Matrix Independent Component Analysis
JoMNA	Joint Multimodal Neuroimaging Analysis
LEC-5	Life Events Checklist
lPTSD	Lifetime Posttraumatic Stress Disorders
ML	Machine Learning
MN	Multimodal Neuroimaging
MPRAGE	Magnetization-Prepared Rapid-Acquisition Gradient Echo
MTG	Middle Temporal Gyrus
PCA	Principal Component Analyses
PFC	Prefrontal Cortex
ROI	Region Of Interest
OFG	Orbitofrontal Gyrus
SN	Salience Network
SCID	Structured Clinical Interview for DSM-5
SC	Structural Connectivity
SBM	Surface based morphometry
SFG	Superior Frontal Gyrus
SLF	Superior Longitudinal Fasciculus
SPL	Superior Parietal Lobe
SPM	Statistical Parametric Mapping
VBM	Voxel-Based Morphometry

Preface

This work is a publication-based cumulative dissertation, and several parts of the thesis have already been published in the peer-reviewed journals. Therefore, certain sections, tables, or figures of this thesis will be identical to these peer-reviewed publications:

Publication 1: Nkrumah, R. O., von Schröder, C., Demirakca, T., Schmahl, C., & Ende, G. (2024). Cortical volume alteration in the superior parietal region mediates the relationship between childhood abuse and PTSD avoidance symptoms: A complementary multimodal neuroimaging study. Neurobiology of Stress, 28 (October 2023), 100586. https://doi.org/10.1016/j.ynstr.2023.100586. IF: 4.3 ("published" status).

Publication 2: Nkrumah, R. O., Demirakca, T., von Schröder, C., Zehirlioglu, L., Valencia, N., Grauduszus, Y., Vollstaedt-Klein, S., Schmahl, C., & Ende, G. Brain connectivity disruptions in PTSD related to early adversity: a multimodal neuroimaging study. IF: 5.78 ("accepted for publication at European journal of psychotrauma" status).

For Publication 1, the corresponding chapter in the dissertation is Chapter III, and for Publication 2, it is Chapter IV. A detailed description of the personal contribution to each publication is listed in the table below.

Summary of the doctoral student's contribution to the work reported in each manuscript.

Work steps	**Publication 1**	**Publication 2**
Conception (%)	95	95
Literature search (%)	95	95
Ethics proposal (%)	0	0
Animal experimentation proposal (%)	n/a	n/a
Data collection (%)	20	30
Data analysis (%)	100	100
Interpretation of results (%)	90	90
Manuscript writing (%)	90	90
Revision (%)	90	90
Indicate which figures and tables resulted from your dissertation work.	All figures and tables	All figures and tables

CHAPTER I: INTRODUCTION

1.1 Adverse childhood experiences and mental health outcomes

Adverse childhood experiences (ACE), such as sexual, emotional or physical abuse and/or neglect have been linked to various mental health problems. These traumatic experiences, occurring during critical developmental periods, can disrupt healthy brain development, leading to a cascade of negative mental health outcomes (Teicher et al. 2022). Research linking ACE to mental health problems includes psychiatric disorders such as post-traumatic stress disorder (PTSD), depression, anxiety, borderline personality disorder, attention deficit hyperactivity disorder (ADHD) and substance abuse (Herzog and Schmahl 2018; Seitz et al. 2022). The prevalence of ACE is alarmingly high, with global data indicating that millions of children suffer from maltreatment each year (Hillis et al. 2016; Hughes et al. 2017). For example, in a recent study by Struck et al., 15% of adult participants without psychiatric disorders reported having experienced moderate-to-severe ACE (Struck et al. 2020). In another study, almost half of a 2531-German sample reported at least one form of ACE and were prone to psychosocial problems involving life satisfaction, psychopathology, and interpersonal aggression (Witt et al. 2019). Such prevalence represents a major public health problem.

Recent studies categorize ACE into two dimensional subtypes (DS): abuse and neglect (Lippard and Nemeroff 2020; McLaughlin et al. 2019; Sheridan and McLaughlin 2014). Abuse involves the presence of an unexpected experience that poses a significant threat of harm to the child, such as physical, sexual or emotional harm. Neglect, which includes physical and emotional deprivation during childhood, is characterized by a lack of expected environmental inputs, specifically a lack of expected cognitive and social inputs. These DS of maltreatment are associated with notable differences in clinical presentation, including earlier onset and more severe symptoms of psychiatric disorders (Lippard and Nemeroff 2020; Teicher and Samson 2013), a more pernicious physical sequence (McLaughlin and Lambert 2017; Zhang et al. 2021), increased risk of suicide (Jones et al. 2024), diminished quality of life (Bosch et al. 2020; Greger et al. 2016), and more psychiatric comorbidities (Teicher et al. 2022). Early research on the psychiatric consequences of ACE primarily focused on all forms of adversity as cumulative risk score, emphasizing on the number of distinct types of adversity a child has experienced regardless of the frequency or severity of the individual incidents of those

experiences. This approach assumed that different types of ACE are quantitatively similar, implying that each distinct type would have an equal impact. However, more recent studies have shifted away from this concept to focus on the DS of ACE. This shift recognizes that the multiple underlying dimensions of experiences may have distinct associations with cognitive, emotional, and neurodevelopmental processes that reflect the core features of abuse and neglect to varying degrees (Sheridan and McLaughlin 2014). For example, physical and sexual abuse, witnessing domestic violence by either parents or friends, and exposure to violence in the community at childhood all involve, in varying degrees, direct threats of harm to the child and are consistently associated with the risk of PTSD, anxiety disorder, panic disorder and depression at adulthood (Comijs et al. 2013; Cougle et al. 2010). Conversely, neglect, which involves low levels of social and cognitive stimulation such as institutional rearing and other forms of parental absence, is associated with higher levels of adult depression symptoms (Infurna et al. 2016; Spinazzola et al. 2014). A review by Colich et al. (2020), also demonstrated the distinct developmental consequences of abuse and neglect, highlighting that abuse is associated with accelerated neurodevelopmental processes while neglect may not be (Colich et al. 2020). These findings suggest that the DS of ACE are linked to distinct patterns of accelerated biological aging, contributing to a variety of health problems. This highlights the significance of the DS categorization and emphasizes the importance of exploring all DS of ACE in a broad context (Khan et al. 2015; Teicher et al. 2022).

Another perspective highlights the dose-dependent nature of the effects of ACE on child development (McLaughlin et al. 2019; Morris et al. 2021; Wiens et al. 2020), showing that severity and chronicity of ACE are associated to the magnitude of their impact ensuing mental and physical health outcomes (Strathearn et al. 2020). This dose-dependent nature, also referred to as intensity and frequency, is evident across various domains, including social, emotional, cognitive, and neurobiological functioning. On a social level, individuals exposed to more severe and prolonged ACE exhibit more pronounced difficulties in interpersonal relationships, social skills, and peer interactions (Mao et al. 2021; Mc Elroy and Hevey 2014). A higher cumulative ACE score is associated with increased risk for social isolation, aggression, and difficulties in forming intimate relationships (Crawford et al. 2022; Majer et al. 2010) as well as social interactions (Mc Elroy and Hevey 2014). The intensity and duration of ACE are directly linked to the severity of emotional dysregulation (Dvir et al. 2014). Individuals with a higher cumulative ACE score are more likely to experience chronic and severe emotional difficulties, including heightened anxiety, depression, and difficulty managing anger. On a

cognitive level, cognitive functioning is significantly impacted by the dose of ACE (Danese and Widom 2024; Goltermann et al. 2021). Children exposed to more severe and prolonged adversity exhibit greater deficits in attention, memory, and executive functions (Irigaray et al. 2013; Majer et al. 2010). A higher cumulative ACE score is associated with increased risk for learning difficulties, academic challenges, and impaired problem-solving skills. The neurobiological consequences of ACE also demonstrate a dose-dependent pattern (Teicher et al. 2016). Individuals with a higher cumulative ACE score exhibit more pronounced alterations in brain structure and function, including reduced gray matter volume in critical regions and dysregulation of the stress response system (Anda et al. 2006; Ansell et al. 2012). These neurobiological changes underlie the increased vulnerability to mental health disorders and behavioral problems. Such a graded relationship underscores the importance of considering the dose-dependent nature of ACE when assessing individual risk profiles.

The multiplicity of ACE can also significantly exacerbate social, emotional, cognitive, and neurobiological impairments (Wiens et al. 2020). The multiplicity of ACE refers to the exposure of a child to multiple types of ACE. This can include a combination of abuse and neglect, or different forms of the same type of maltreatment. For example, a child might experience both physical abuse and emotional abuse or neglect. Research indicates that individuals exposed to multiple forms of abuse and neglect are more likely to experience severe social difficulties, including challenges in forming and maintaining healthy relationships and increased tendencies toward isolation and aggression (Evans and Kim 2013). Emotionally, the effect of multiple ACE amplifies risks for depression, anxiety, and other mood disorders, often leading to chronic stress and emotional dysregulation (Freier et al. 2022; Gardner et al. 2019). Cognitively, the likelihood of impairments in memory, attention, and executive functioning increases with the number of ACE, contributing to difficulties in academic and professional settings (Hawkins et al. 2021; Iverson et al. 2024). Neurobiologically, multiple ACE can result in profound structural and functional brain changes such as altered connectivity and volume reductions in critical areas like the prefrontal cortex and hippocampus, which are crucial for emotional regulation and cognitive processing (Herzog and Schmahl 2018; Lippard and Nemeroff 2020; Pang et al. 2022; Samson et al. 2024). These compounded effects underscore the critical need for considering the long-term impact of multiple ACE on individuals' development and well-being.

The complex interplay of DS, dose and multiplicity of ACE impacts the child development and later mental health outcomes (Fleming et al. 2024; Teicher et al. 2022). These three

factors are not mutually exclusive and can interact in complex ways. Not only does the severity and duration of adverse experiences matter, but also the number and variety of different types of ACE a child is exposed too. For example, a child who experiences both physical abuse and emotional neglect (multiplicity) may also be exposed to severe and frequent instances of abuse (dose-dependent effects), leading to more severe social, emotional, and cognitive impairments compared to a child who experiences only one type of neglect. Similarly, a child exposed to multiple forms of abuse, such as physical, emotional, and sexual abuse, is at greater risk for long-term mental health problems and developmental challenges.

While the focus thus far has been on the detrimental effects of ACE, it is crucial to acknowledge the presence of protective factors that can mitigate their impact (Crouch et al. 2019; Kentner et al. 2019; Sege and Harper Browne 2017). Resilience, defined as the ability to adapt and overcome adversity, plays a pivotal role in determining outcomes for individuals exposed to ACE (Panagou and MacBeth 2022; Richter et al. 2019). Protective factors can operate at various levels, including individual, familial, and community factors (Bellis et al. 2018; Bellis et al. 2019). Physical activity also emerges as a significant individual-level protective factor, contributing to both physical and mental health (Demirakca et al. 2014; Hadwen et al. 2022; Hird et al. 2024). Supportive and nurturing family environments can buffer the negative effects of ACE, while strong community connections can provide essential resources and support (Hughes et al. 2017; Merrick et al. 2020). It is essential to recognize that the interplay between ACE and protective factors is complex. While some individuals exhibit remarkable resilience in the face of adversity, others are more vulnerable (Pusch and Dobson 2017). Given the primary focus of this study is on utilizing neuroimaging methods to enhance the diagnosis and comprehension of ACE, the discussion will be limited to these methodologies.

1.2 **Neuroimaging studies in ACE**

Neuroimaging studies have been pivotal in elucidating the brain's structural and functional changes associated with ACE. Techniques using magnetic resonance imaging (MRI) such as functional MRI (fMRI), structural MRI (sMRI), and diffusion weighted MRI (dMRI) have revealed alterations in brain regions involved in emotion regulation, stress response, and cognitive processing (Hart and Rubia 2012; Herzog and Schmahl 2018; Samson et al. 2024; Teicher et al. 2020; Teicher and Samson 2016). These different neuroimaging modalities are

used because they capture different aspects of brain biology and also provide different visualization of the brain (Modo and Bulte 2011). The use of only one neuroimaging modality in a study is termed a unimodal study.

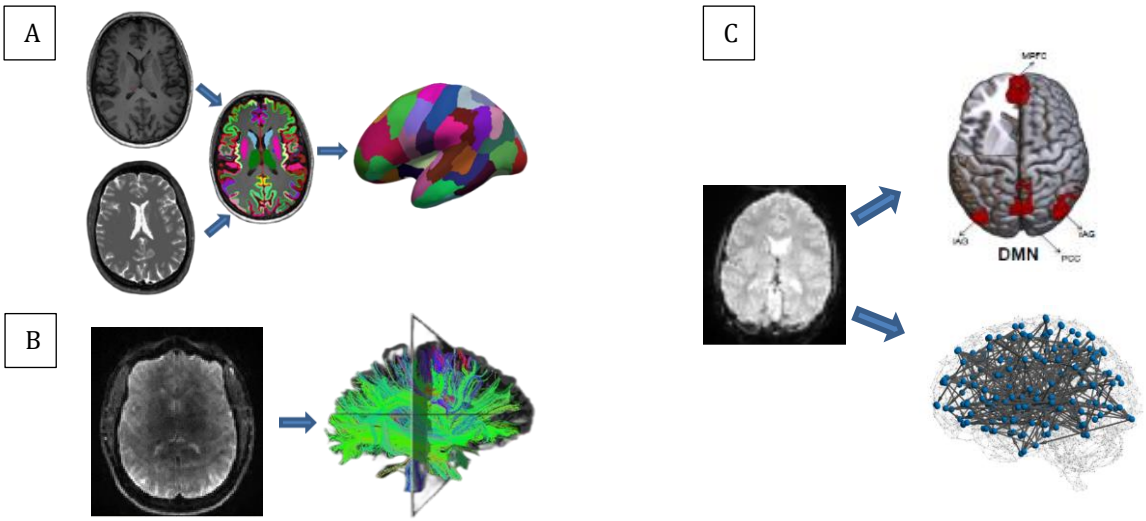

Figure 1. MRI of the brain captured using (A.) sMRI, (B.) dMRI and (C.) fMRI. sMRI utilizes T1 and T2 weighted MRIs, which are segmented and parcellated to obtain structural properties of the brain such as brain volume, cortical area, and cortical thickness. dMRI employs diffusion weighted imaging to construct white matter pathways. Functional MRI utilizes BOLD activity in the brain to inform how brain regions are activated (volumetric activation) or correlate with each other (functional connectivity) during the performance of a task (task-based fMRI) or when at rest (resting-state fMRI).

Unimodal studies in ACE

sMRI has been instrumental in mapping the brain structural abnormalities associated with ACE. Using voxel-based morphometry (VBM), researchers have consistently reported reduced gray matter volumes in individuals exposed to ACE in the inferior frontal gyrus, hippocampus and amygdala (Pollok et al. 2022; Yang et al. 2023), dorsolateral prefrontal cortex and superior parietal cortex (Nkrumah et al. 2024b), as well as the medial prefrontal cortex (Hart and Rubia 2012; Kelly et al. 2013; McLaughlin et al. 2019). Another sMRI method is surface-based morphometry (SBM), which is used to explore cortical alterations such as surface area, cortical gyrification, cortical thickness, and curvature. The advantages of using both voxel- and surface-based morphometry to study gray matter (GM) have been studied elsewhere (Goto et al. 2022). A recent meta-analysis that combined both SBM and VBM studies found ACE to affect cortical thinning in the right medial cingulate and middle frontal gyrus as well as reduced GM volume in the left supplementary motor area (Yang et al. 2023).

- *Abuse and neglect as dimensional subtypes of ACE*: sMRI studies differentiate between the effects of abuse and neglect on brain structure. Abuse is more closely related to reductions in amygdala and PFC volume, regions involved in emotional regulation and threat response (Arnsten et al. 2015; Kelly et al. 2013). Additionally, reduced cortical thickness in prefrontal and temporal regions has been associated to childhood abuse (Gold et al. 2016). Neglect, on the other hand, tends to impact areas involved in social cognition, like the medial PFC and temporal lobes, which are crucial for social interactions and emotional processing (Mackes et al. 2019; Sheridan et al. 2022) .
- *Multiplicity of ACE and its impact*: The number and severity of ACE have been shown to exacerbate these structural changes. Individuals with multiple ACE exhibit more significant reductions in hippocampal volume, a brain region critical for memory and stress regulation (Grauduszus et al. 2024; Herzog et al. 2020; Schalinski et al. 2016). These effects indicate that the brain's structural response to adversity intensifies with the increasing duration and intensity of maltreatment (Anda et al. 2006).

dMRI studies have provided valuable insights into the neurodevelopmental consequences of ACE. Research consistently demonstrates that individuals with a history of ACE exhibit alterations in white matter microstructure, particularly in regions associated with emotion regulation, cognitive control, and stress response (Huang et al. 2012; Lim et al. 2019a; Ohashi et al. 2019). Reduced fractional anisotropy (FA) in key white matter tracts, such as the corpus callosum, uncinate fasciculus, and cingulum bundle, is a common finding (Olson et al. 2020; Puetz et al. 2017) . Voxel-based analysis (VBA) of dMRI, as used in diffusion tensor imaging (DTI), is a method for studying white matter, providing evidence of altered brain connectivity by detecting differences at the voxel level. While DTI studies have underscored the profound impact of early adversity on brain development, they are limited by relatively small sample sizes and the inability to model complex fibre orientations. Consequently, DTI-derived metrics are often challenging to interpret, particularly in regions with crossing fibres. To address these limitations, more advanced dMRI techniques, such as higher-order DWI models like fixel-based analysis (FBA), are emerging (Raffelt et al. 2015; Raffelt et al. 2017). These methods enable the estimation of multiple fibre orientations within voxels, offering greater precision in characterizing white matter microstructure. However, at the time of this thesis, only one study (Kanel et al. 2024), has employed FBA in previously institutionalized adolescents. Their findings indicate fixel-based alterations within the cerebellar peduncles,

inferior longitudinal fasciculi, corticospinal tract, and corpus callosum in institutionalized adolescents compared to non-institutionalized ones. Although these findings replicate and extend DTI findings (Sheridan et al. 2022), the application of FBA, particularly in multiple crossing-fibre regions, demonstrates alterations in micro- and macro-structure in previously institutionalized adolescents, indicating that neural correlates are still apparent in adolescents with such experiences.

- *Abuse and neglect as dimensional subtypes of ACE*: The effects of abuse tend to disrupt WM tracts associated with the limbic system such as the fornix (Eden et al. 2015) and tracts connecting the prefrontal cortex to the mid-temporal like the inferior longitudinal fasciculus (ILF) (Lim et al. 2019a), leading to impaired emotional regulation and heightened stress reactivity (Ohashi et al. 2017; Olson et al. 2020). In contrast, neglect, is linked to reduced WM integrity in tracts associated with social and cognitive processing, such as the inferior and superior longitudinal fasciculus (SLF) (Mackes et al. 2022) and arcuate fasciculus (Hanson et al. 2013).
- *Multiplicity of ACE and its impact*: dMRI studies have shown that the cumulative number of ACE correlates with the severity of white matter disruptions (Lim et al. 2020). For instance, individuals exposed to multiple types of abuse or both abuse and neglect tend to show more extensive white matter damage. This is particularly observed in tracts critical for integrating emotional and cognitive functions like the cingulum, SLF (Huang et al. 2012), corpus callosum, uncinate fasciculus (Buimer et al. 2022; Kanel et al. 2024; Sheridan et al. 2022), and pathways linking fronto-limbic and occipital visual cortices, such as anterior thalamic radiation and bilateral fornix (Lim et al. 2020).

fMRI has been pivotal in uncovering functional brain network disruptions in individuals with ACE. Resting state fMRI (rsfMRI) is used to capture spontaneous brain activity when an individual is at rest, revealing patterns of connectivity between brain regions. rsfMRI studies have found aberrant functional connectivity patterns in individuals with a history of ACE (Gerin et al. 2023a; Rakesh et al. 2023; Schröder et al. 2024; Valencia et al. 2024). For example, hyperconnectivity within the default mode network (DMN) is consistently reported, suggesting increased rumination on intrusive memories and persistent negative thoughts related to past trauma (Daniels et al. 2011; Hoffmann et al. 2018; Valencia et al. 2024). Concurrently, hyperconnectivity within the salience network (SN) is associated with heightened emotional reactivity and difficulties in distinguishing between relevant and

irrelevant stimuli (Thome et al. 2014; Watts et al. 2021). Conversely, hypoconnectivity within the central executive network (CEN) is linked to distractibility and impaired cognitive control, affecting daily functioning. Furthermore, a recent meta-analysis study has demonstrated disrupted communication between brain regions involved in emotion regulation, cognitive processing, and self-referential processing, commonly observed in individuals with ACE (Ireton et al. 2024).

- *Abuse and neglect as dimensional subtypes of ACE*: The two subtypes of maltreatment have been shown to affect distinct networks. Individuals exposed to abuse exhibit distinct impaired functioning in brain regions responsible for emotional processing, learning, and self-referential processing, such as the hippocampus, amygdala, and prefrontal cortex (PFC) of the DMN (Liuzzi et al. 2023). Another study found emotional abuse to be specifically associated with hyperconnectivity in the DMN, potentially leading to excessive self-focus and rumination, as seen in disorders like PTSD and depression (Van Der Werff et al. 2013). In contrast, neglect, has been linked to hypoconnectivity in networks responsible for cognitive and social functions, such as the SN (Silveira et al. 2021). Functional alterations in the hippocampus and amygdala have been observed in individuals who have experienced institutionalization (Rakesh et al. 2021) and poverty-related neglect (Sheridan et al. 2012).
- *Multiplicity of ACE and its impact*: rsfMRI studies also reveal that the severity and frequency of ACE exposure play a significant role in the extent of functional network disruptions (Gerin et al. 2023a; Valencia et al. 2024). Greater exposure to multiple ACE is associated with more pronounced alterations in corticolimbic regions (e.g., the amygdala, medial prefrontal cortex, and hippocampus) (Gerin et al. 2023a) and the frontoparietal network regions (such as the inferior frontal gyrus and superior parietal regions), which reflects impaired executive function and cognitive control (Gard 2021).

Overall, insights from various unimodal studies provide an understanding of how early trauma can alter brain structure and functioning, potentially contributing to the development of psychopathology later in life. However, research examining the impact of maltreatment on brain structure and functioning at adulthood using multimodal methods remains limited.

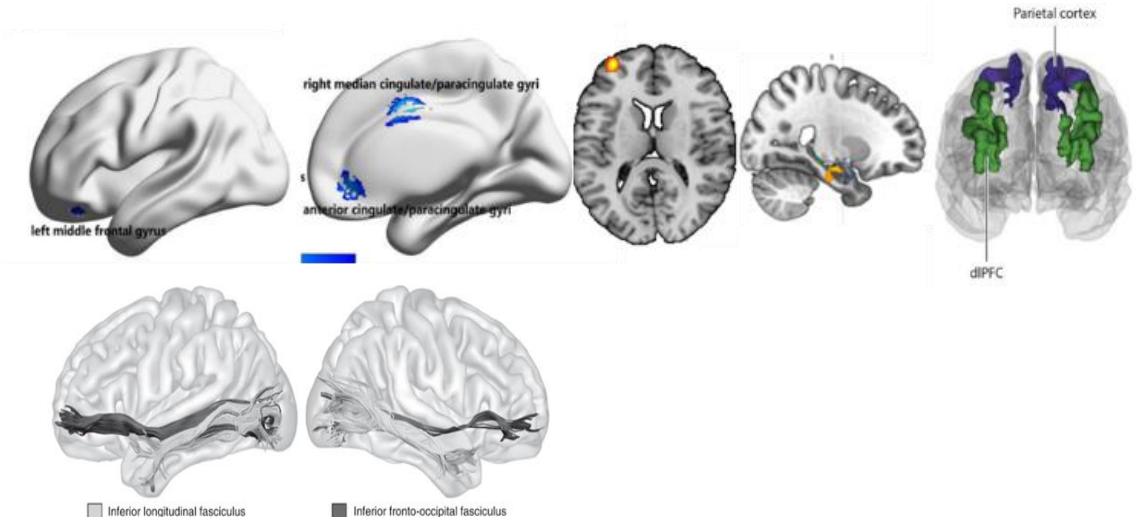

Figure 2. Findings from unimodal sMRI and dMRI meta-analytical studies in ACE. Images were retrieve from (Pollok et al. 2022; Yang et al. 2023)

1.3 **Limitations of current approaches**

Despite significant information provided by current neuroimaging approaches to studying ACE, there are several limitations. Many studies rely on single-modality imaging techniques, which often analyse structural and functional neuroimaging data independently, potentially overlooking crucial interactions and shared information between these modalities (Calhoun and Sui 2016; McLaughlin et al. 2019; Samson et al. 2024), which may lead to missing potential insights and an inability to explore the full complexity of brain alterations associated with ACE. Sample sizes in these studies are also often limited, restricting the generalizability of findings. Moreover, the integration of the various neuroimaging data remains challenging, necessitating the development of sophisticated analytical methods to uncover the intricate relationships between different brain alterations.

1.4 **Aims of this work**

To address the limitations of current research, this study aims to investigate the complex interplay between structural and functional brain alterations in individuals with a history of ACE. By employing a multimodal neuroimaging approach, we seek to uncover shared and unique neural correlates associated with ACE-related psychopathology. Specifically, this study aims to:

a. Characterize structural and functional brain abnormalities in individuals with ACE using MRI analyses, such as surface-based morphometry for sMRI data, tract-based spatial statistics for dMRI data, and functional connectivity analysis for rsfMRI data.
b. Examine the relationship between structural GM and WM brain alterations and ACE using sMRI and dMRI.
c. Explore the potential relationship between structural and functional brain alterations and ACE, as well as ACE-related psychopathology, through multimodal analysis.
d. Provide potential insights for future directions of the application of multimodal neuroimaging in ACE research.

By achieving these objectives, this study will contribute to a deeper understanding of the neurobiological underpinnings of ACE and related psychopathology, ultimately improving the diagnosis, prognosis, and treatment of mental health disorders with or without ACE which aligns with the overarching goal of precision neuropsychiatry (Koutsouleris and Fusar-Poli 2024).

1.5 **Introduction to Multimodal Neuroimaging**

Multimodal neuroimaging has emerged as a powerful tool in neuroscience, offering unprecedented insights into the intricate structure and function of the human brain (Calhoun and Sui 2016). This approach involves acquiring various forms of neuroimaging data from the same individual using multiple imaging modalities, such as sMRI, fMRI, dMRI, magnetic resonance spectroscopy (MRS), arterial spin labelling (ASL) MRI, electroencephalography (EEG), magnetoencephalography (MEG), and positron emission tomography (PET) (Tulay et al. 2019). Each modality brings unique strengths and limitations, depending on its ability to provide different aspects of structural and functional properties of the brain.

For instance, sMRI provides detailed images of the brain's anatomy, highlighting GM, white matter (WM), and cerebrospinal fluid (CSF), which can be quantified in terms of volume or surface area. In contrast, fMRI measures changes in blood oxygenation levels, offering insights into brain function by detecting activity in specific regions during tasks or at rest. Similarly, dMRI elucidates white matter architecture, with advanced techniques like NODDI modelling revealing microstructural anomalies (Kamiya et al. 2020). Additionally, MRS provides metabolic information about the brain, allowing for the quantification of

neurotransmitters, metabolites, and other molecules such as Glutamate, Gamma-aminobutyric acid (GABA) and N-acetyl aspartate (NAA) (Soares and Law 2009).

By integrating these complementary neuroimaging modalities, we can explore the complex interplay between brain structure and function, identify neural correlates of specific behaviours or disorders, and develop more accurate biomarkers for diagnosis and prognosis. There are two primary approaches to the analyses of multimodal neuroimaging data—Complementary and joint analysis.

- *Complementary multimodal neuroimaging analysis (CoMNA)* involves using different modalities to provide complementary information about the same brain region. This approach is also thought to be an asymmetric data fusion where one modality is used to constrain the analysis of another. For instance, sMRI can provide structural information about a specific brain region, while fMRI can be used to reveal its regional functional activity in a disease state. CoMNA has been used in previous research to highlight group differences, such as dMRI tractography combined with transcranial magnetic stimulation (TMS) (Mirchandani et al. 2021), quantitative MRI methods (Rokickia et al. 2020), and fMRI with dMRI (Harneit et al. 2019). While this approach has been used to identify modality-specific and complementary modality effects, it has some limitations. CoMNA is known to provide limited information as this analysis does not fully utilize common as well as distinct information from all available complementary modalities.

- *Joint (or fusion) multimodal neuroimaging analyses (JoMNA)* aim to overcome the limitations of CoMNA by combining data from multiple modalities into a unified analysis where all modalities contribute equally. JoMNA provides the ability to take full advantage of the different data types to uncover significant relationships or variability that could explain unusual brain patterns (Adali et al. 2015). JoMNA is considered the gold standard for truly exploiting the combined power of multiple modalities (Calhoun and Sui 2016). By leveraging the unique strengths of each imaging technique, JoMNA can uncover complex relationships and patterns that would be missed using unimodal or complementary approaches (Tulay et al. 2019). An in-depth explanation of JoMNA will be made in chapter 2 of this thesis.

In all, multimodal neuroimaging offers significant potential to improve our understanding of brain disorders, including those associated with ACE. By leveraging the strengths of different imaging techniques, MN allows for unravelling the complex neurobiological mechanisms underlying the long-term consequences of ACE and its related psychopathology. This thesis will primarily focus on the cumulative impact of childhood maltreatment (Bryce 2018; Bryce and Collier 2022), considering the DS (i.e., abuse and neglect) without examining the dose-dependent effects of individual experiences (Teicher et al. 2016; Teicher and Samson 2016). As an initial step in exploring the effects of ACE using multimodal methods, this approach is expected to simplify the focus of the study, providing a foundation for investigating the complex relationship between ACE, brain development, and mental health outcomes.

1.6 **Research Questions**

To effectively employ MN in exploring the neurobiological underpinnings of ACE and their relationship to psychopathology such as PTSD, this study aims to answer the following questions.

I. How can complementary multimodal neuroimaging data analyses be used to investigate ACE?
II. What specific brain alterations are associated with PTSD related to ACE, as identified using JoMNA approach?
III. How can multimodal neuroimaging biomarkers enhance our understanding of the neurobiological underpinnings of ACE and their related mental health outcomes?
IV. What are the potential applications of MN in ACE research for early diagnosis and prognosis of ACE and its related disorders?

In the following chapters, I provide an overview of CoMNA and JoMNA methods and discuss two published studies that employed these methods to address our four major research questions. By addressing these questions, this work aims to advance our understanding of the neural correlates of ACE and PTSD, ultimately contributing to improved diagnostic approaches and proposing a framework for the clinical translation of MN.

CHAPTER II: MULTIMODAL NEUROIMAGING METHODS

2.1 Introduction to CoMNA and JoMNA methods

This section will provide an overview of the primary methodological approaches employed in multimodal neuroimaging (MN) research. We will delve into the details of complementary multimodal neuroimaging analysis (CoMNA) and joint or fusion multimodal neuroimaging analysis (JoMNA). CoMNA involves using different modalities to provide complementary information about the same brain region, while JoMNA integrates data from multiple modalities into a unified analysis. By examining the strengths and limitations of these methods, we aim to elucidate the optimal approaches for investigating the complex interplay between brain structure and function in relation to adverse childhood experiences (ACE).

2.2 CoMNA methods

The first stage of CoMNA involves independently processing and analysing data from various imaging modalities followed by a comparative analysis of the results usually in the same brain regions. This approach aims to identify complementary information provided by each modality, contributing to a deeper understanding of brain structure and function by leveraging the strengths of each imaging modality.

Combining sMRI and dMRI is a common example of CoMNA. sMRI provides detailed anatomical information about GM, including its volume in cortical and subcortical structures and other cortical morphological measures such as thickness, curvature, gyrification and area (Dale et al. 1999; Fischl et al. 1999; Luders et al. 2006; Van Essen et al. 2001). Neuroimaging tools such as FreeSurfer (Fischl 2012), Computational Anatomy Toolbox (Gaser et al. 2024) and Mindboggle (Klein et al. 2017) are commonly used to compute these measures. dMRI offers insights into white matter microstructure, such as fibre tract connectivity and integrity. dMRI provides quantitative measures such as fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD) and axial diffusivity (AD) (Tromp 2016), and other advance measures such as fibre density (FD), fibre cross-section (FC) and fibre density and cross-section (FDC) (Smith et al. 2022; Tournier et al. 2019). By analysing these modalities separately and then comparing the results, we can identify potential associations between GM and WM brain abnormalities associated with a brain state. For instance, sMRI might reveal reduced gray matter volume in a specific brain region, while dMRI could demonstrate corresponding

changes in white matter connectivity in that area. This complementary information can provide valuable insights into the underlying neuropathology of a particular condition.

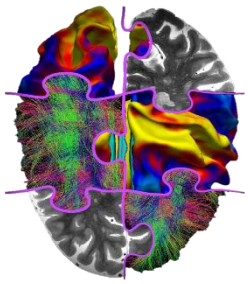

Figure 3. Example of CoMNA using T1-weighted MRI (sMRI) and diffusion weighted MRI (dMRI).sMRI provides information such as gray matter volume, cortical thickness, cortical area and subcortical structures. dMRI provides quantitative measures such as fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD) and axial diffusivity (AD), and other advance measures such as fibre density (FD), fibre cross-section (FC) and fibre density and cross-section (FDC). Image was accessed from (Mangeat 2018)

Other common combinations of CoMNA

- ***sMRI and fMRI***: Combining structural and functional MRI allows for the investigation of how brain anatomy relates to brain activity. For example, researchers can examine whether changes in gray matter volume correlate with altered functional connectivity.
- ***dMRI and fMRI:*** This combination helps to elucidate the relationship between white matter connectivity and functional brain networks. By examining how structural connections influence information flow, researchers can gain insights into the neural basis of cognitive processes.
- ***MRS and DTI:*** Combining MRS with DTI allows for the simultaneous study of brain metabolism and white matter microstructure. This combination can provide a more comprehensive understanding of brain pathology, as both metabolic and structural abnormalities can contribute to disease progression (Lawrence et al. 2019).

These combinations of CoMNA offer unique perspectives on brain structure and function and can be applied to various research questions, including the study of ACE and related mental health disorders.

Although CoMNA is a valuable method compared to individual analyses of neuroimaging data, it has limitations. First, its analysis provides limited information, as it does not fully utilize both the common and distinct information from all available neuroimaging modalities. The abundance of data provided by diverse neuroimaging sources requires aggregation to enable a more comprehensive understanding of the brain (Calhoun and Sui 2016; Tulay et al. 2019). Second, recent advancements in the application of machine learning enable the complete utilization of all neuroimaging data to improve its utility. For example, compared to the

correlation analysis methods employed by CoMNA, machine learning techniques allow for multivoxel pattern analyses, which facilitate the examination of the relationship between disease states and multiple voxels in one or more brain regions simultaneously (Xiao et al. 2021). Additionally, predictive machine learning models could achieve improved generalizability by using information from multiple neuroimaging modalities to enhance broader implications (Dwyer et al. 2018; Radua and Koutsouleris 2023).

2.3 **JoMNA methods**

Most methods applied in JoMNA are both multivariate and data driven machine learning approaches which provide more information and flexible data fusion (Sui et al. 2013). These methods basically either use the full neuroimaging data or extract features from each modality and search for common variations in terms of structural and functional properties in the extracted feature space. A ***feature*** is a distilled dataset representing an interesting part of each distinct modality and is used as the input to the fusion analysis for each modality and each subject (Calhoun and Sui 2016). Common feature extraction methods include extracting components from principal component analyses (PCA) of the full neuroimaging data. By investigating variations between or across disease and control groups at the feature level, rather than the full image level, we can find multimodal associations and alleviate challenges associated with fusion data type of diverse dimensionality, nature and resolutions (Bießsmann et al. 2011; Liu et al. 2015). Recent studies have also demonstrated the use of full neuroimaging data in JoMNA to enhance the precision and depth of neuroimaging analyses (Koutsouleris et al. 2016; Koutsouleris et al. 2023; Koutsouleris and Fusar-Poli 2024). Rather than relying solely on feature extraction, these modern approaches leverage entire datasets, capturing a broader range of variability across structural and functional modalities.

Motivated by blind source separation (BSS), the multivariate data driven analysis of JoMNA has been possible in recent times due to an improved computation and the existence of large multimodal datasets (Rasgado-Toledo et al. 2024; Silva et al. 2016). BSS is used to decompose the JoMNA with few assumptions and without the need of introducing additional constraints (Adali et al. 2015). The computations of JoMNA using BSS can be categorized into Independent Component Analysis (ICA) based techniques (e.g. Joint ICA and Parallel ICA), Canonical Correlation Analysis (CCA) based techniques (e.g. Multimodality CCA), partial least squares (PLS) based techniques, machine learning classification/ regression (MLC/R) based techniques (e.g. by using L1-Multiple Kernel Learning), and deep learning (DL) based

techniques (e.g. by using Deep Belief Networks) (AdalI et al. 2015; Calhoun and Sui 2016; Dwyer et al. 2018; Lottman et al. 2018; Qu et al. 2024; Silva et al. 2016; Wu and Calhoun 2023). Notably, these are multivariate data driven approaches and hence, they do not require a prior hypothesis about all specific group data used. This offers a more effective way to handle the inherent complexity and variability of neuroimaging data, leading to improved accuracy in diagnosis and prediction, which could be particularly valuable in cases of ACE-related mental health outcomes (Koutsouleris and Fusar-Poli 2024).

Several algorithms have been developed to perform JoMNA computation. Overall, all algorithms conform to the following steps: full image and / or feature selection and normalization, data matrix composition, dimensionality estimation and reduction, application & optimization of a computational method, and visualization of results. The following is a brief overview of the processes:

- *Full image and / or feature selection and normalization*: this involves either preprocessing full image and / or selection of significant features from each data type.
- *Data matrix composition*: extracted full data and / or features are concatenated into matrix form for easy computation.
- *Dimensionality estimation and reduction*: composed matrices are reduced to avoid overfitting (e.g. is by performing PCA).
- *Application & optimization of computation method*: algorithm specific computation is implemented, and the performance of the models computed are estimated through various cross validation techniques. Here several computations (e.g. JICA, SVM/LR, Decision Tree, Random Forest and Support Vector Elastic Net) and cross validation (nested cross validation) methods have been proposed.
- *Visualization and interpretation of results*: only results that pass an algorithm specific confidence test are displayed. This typically involves using a statistical method to assess the significance of the findings (Radua and Koutsouleris 2023). Common methods include:
    - False discovery rate (FDR) test: A linear statistical method that controls the proportion of false positives among significant findings (Bennett et al. 2009; Lv et al. 2024).
    - Permutation test: A non-parametric statistical method that assesses the significance of results by randomly permuting the data and comparing the

observed results to the distribution of permuted results (Lv et al. 2024; Winkler et al. 2014).

- ROC curve: A graphical plot that illustrates the trade-off between sensitivity (true positive rate) and specificity (true negative rate) of a classification or prediction model (Zou et al. 2007).
- Area under the curve (AUC): A measure of the performance of a classification model, often used in conjunction with receiver operating characteristic (ROC) curves. The AUC represents the probability that a randomly selected positive instance will be ranked higher than a randomly selected negative instance (Hanley and McNeil 1982; Huang and Ling 2005). A higher AUC indicates better performance.

Despite the potential benefits of JoMNA, CoMNA is still more commonly used even with the growing availability of study specific multimodal datasets, high computing capability and application of machine learning in neuroimaging analysis. This preference can be attributed in part to the challenges associated with heterogeneity in neuroimaging data, which encompasses variability in data types, scales, and formats across modalities. Moreover, the lack of a perfect data integration and interpretation framework within a cohesive analytical context has hindered the widespread adoption of JoMNA (Qu et al. 2024). As individual unimodal analysis and CoMNA have revealed promising structural-functional properties of the brain, fusion of these heterogeneous neuroimaging data should provide relational as well as specific findings from each modality prompting the need for multimodal data fusion. Another reason hindering researchers from using JoMNA is the doubt that CoMNA and what is learnt from unimodal analysis are incomplete. Researchers doubt whether there is any missing link worth finding as we have been enlightened “enough” with results from unimodal and complimentary analysis. As suggested by Luque Laguna et al. (2020) and Bzdok and Meyer-Lindenberg (2018), multimodal and multiparametric analysis of neuroimaging data is essential for improving reproducibility, reliability, variability, and clinical translation of neuroimaging research (Bzdok and Meyer-Lindenberg 2018; Luque Laguna et al. 2020; Radua and Koutsouleris 2023). CoMNA and JoMNA are promising approaches to achieve this goal, particularly in the context of addressing the challenges posed by heterogeneous data and the need for a cohesive analytical framework.

The subsequent sections of this chapter (Sections 2.4 and 2.5) will discuss the specific aims guiding our application of CoMNA and JoMNA in ACE research. Following this, I will present the two studies – **CHAPTER III: CoMNA Study** and **CHAPTER IV: JoMNA Study** – detailing the neuroimaging data acquisition, preprocessing techniques, analyses, and published findings. Finally, in **CHAPTER V: DISCUSSION**, I will conduct a comparative discussion of the findings from both studies, exploring how they collectively address our research questions.

2.4 Application of CoMNA in ACE study

The first study employed a CoMNA approach to focus on the cortical morphology alterations using surface-based morphometry and complementing the findings with those from dMRI measures. This methodology aimed to leverage the unique strengths of sMRI and dMRI, providing a comprehensive assessment of structural changes in both gray matter and white matter associated with ACE. By integrating data from both modalities, the study overcame the limitations of single-modality analyses, offering a more nuanced understanding of how ACE impacts brain structure. The scope of the CoMNA study was to investigate the effect of ACE on gray matter and adjacent white matter regions using a sample of 78 participants (see section 3.3 for more information on the demographics and clinical data). For sMRI data (i.e., T1w), whole-brain surface-based analysis was performed to explore the relationship between cortical morphology and the cumulative impact of ACE. We also explored brain morphometry associated with abuse when controlling for neglect (and vice versa). For diffusion MRI, we examined the white matter integrity in fibre tracts connecting key areas where ACE-related cortical volume alterations were observed. Lastly, we investigated the mediating role of ACE-related cortical volume alterations in the relationship between ACE and PTSD symptoms (PTSS).

2.5 Application of JoMNA in ACE

The second study employed a connectivity-based multimodal neuroimaging approach, a form of JoMNA, to investigate brain connectivity disruptions associated with ACE-related PTSD. This study applied Joint Connectivity Matrix Independent Component Analysis (jICA) to integrate data from sMRI, dMRI, and resting-state fMRI data. jICA involves equally integrating and utilizing full data from all modalities, facilitating a more robust exploration of the relationships between different data types (Wu and Calhoun 2023). The sample used for this

study included a total of 119 participants with ACE (70 with ACE-related PTSD and 49 ACE-exposed controls). T1-weighted MRI, diffusion-weighted MRI, and resting-state fMRI data were acquired to examine structural and functional connectivity between groups. A detailed description of our methodology and the literature driving this study can be found in Figure 4 and CHAPTER IV: JoMNA Study, respectively.

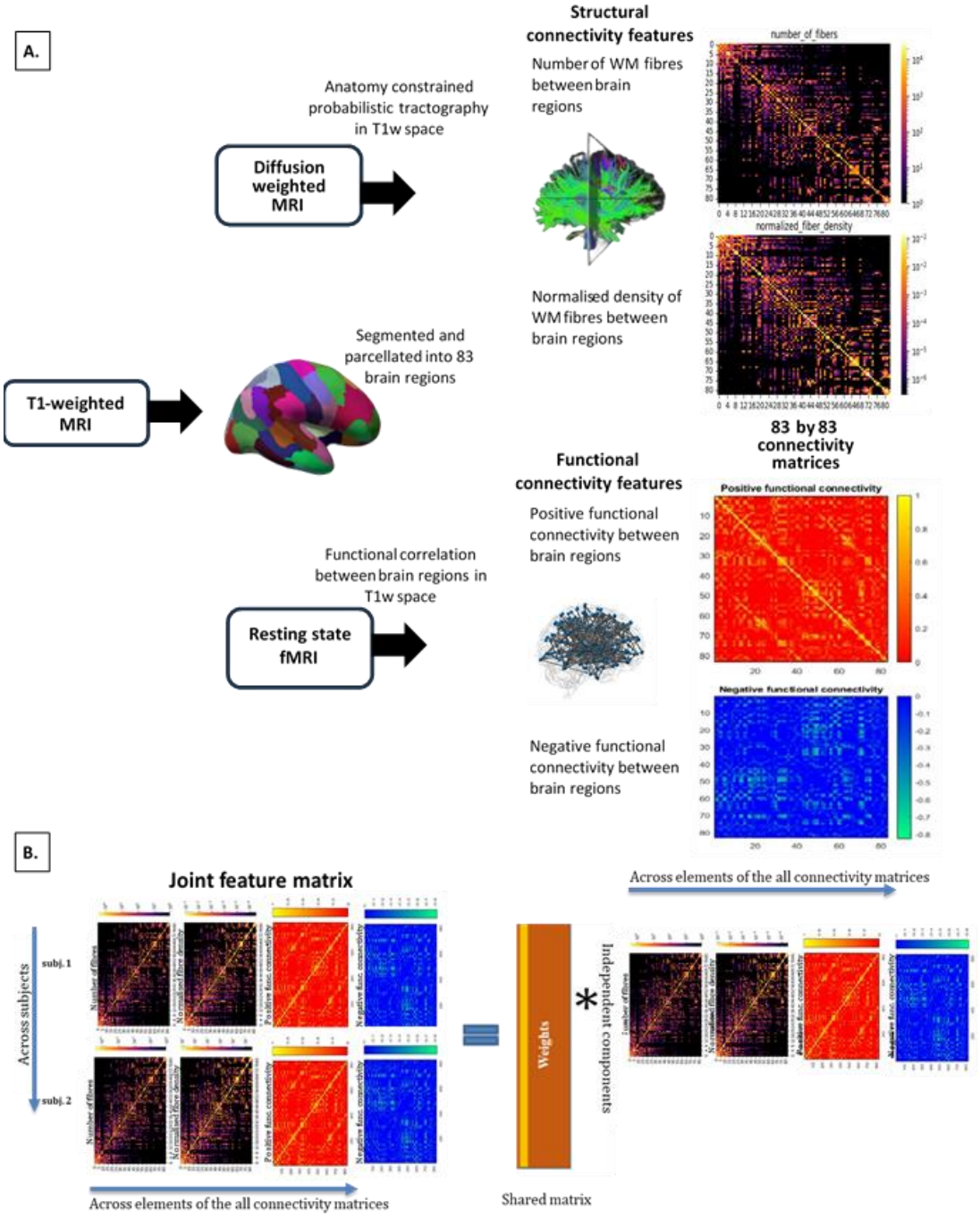

Figure 4. This figure shows our multimodal analysis pipeline. (A) Subject-level processing: T1-weighted (T1w) images were preprocessed, segmented, and parcellated into 83 regions in Lausanne scale 1 space. Diffusion and resting-state images were also preprocessed, and both structural connectivity (SC) 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). Image assessed from (Nkrumah et al. 2024a).

CHAPTER III: COMNA STUDY

Title: Cortical volume alteration in the superior parietal region mediates the relation between the childhood abuse and PTSD avoidance symptoms: a complementary multimodal neuroimaging study.

3.1 Abstract

Background: Adverse childhood experiences (ACE), which can be separated into abuse and neglect, contribute to the development of post-traumatic stress symptoms (PTSS). However, which brain structures are mainly affected by ACE as well as the mediating role these brain structures play in ACE and PTSS relationship are still being investigated. The current study tested the effect of ACE on brain structure and investigated the latter`s mediating role in ACE-PTSS relationship.

Methods: A total of 78 adults with self-reported ACE were included in this study. Participants completed the childhood trauma questionnaire (CTQ) and a Posttraumatic Stress Disorder Checklist for DSM-5 (PCL-5) to ascertain ACE history and PTSS, respectively. T1w images and diffusion MRI scans were then acquired to assess cortical morphometry and white matter (WM) integrity in fibre tracts connecting key areas where ACE-related cortical volume alterations were observed.

Results: The combined effect of ACE was negatively associated with total grey matter volume and local cortical area in the right superior parietal region (rSP). Childhood abuse was negatively related to right superior parietal volume after controlling for neglect and overall psychological burden. The right superior parietal volume significantly mediated the relationship between childhood abuse and avoidance-related PTSS. Post-hoc analyses showed that the indirect relation was subsequently moderated by dissociative symptoms. Lastly, a complementary examination of the WM tracts connected to abuse-associated cortical GM regions shows that abuse was negatively related to the normalised fibre density of WM tracts connected to the right superior parietal region.

Conclusion: We provide multimodal structural evidence that ACE in the first years of life is related to alterations in the right superior brain region, which plays a crucial role in spatial processing and attentional functioning. Additionally, we highlight that the cortical volume alteration in this region may play a role in explaining the relationship between childhood abuse and avoidance symptoms.

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3.2 **Introduction**

Adverse childhood experiences (ACE) are associated with higher rates of psychiatric disorders later in life (Hailes et al. 2019), and include sexual, physical or emotional abuse and/or neglect experiences. Recent conceptualizations of ACE comprise two dimensional subtypes (DS) : abuse and neglect (McLaughlin et al. 2019; Sheridan and McLaughlin 2014). Abuse involves the presence of an unexpected experience that poses a significant threat of harm to the child, such as sexual, physical, or emotional harm. Neglect, which includes physical and emotional deprivation during childhood, is characterised by a lack of expected environmental inputs, specifically a lack of expected cognitive and social inputs. The frequency and consequences of abuse and neglect were investigated in a 2531-person German sample. Almost half of the sample reported at least one form of abuse and/or neglect and were prone to psychosocial problems involving life satisfaction, psychopathology, and interpersonal aggression (Witt et al. 2019). Consequences of ACE include major depressive disorder, post-traumatic stress disorder (PTSD), borderline personality disorder, attention deficit hyperactivity disorder (ADHD), bipolar disorder and elevated symptom levels of depression, anxiety and dissociative symptoms (Herzog and Schmahl 2018; Seitz et al. 2022). The general consensus is that childhood abuse and neglect can result in severe developmental problems that are interpersonal, enduring, co-occurring, and linked to high rates of PTSD symptoms (De Bellis and Zisk 2014).

Evidence shows that ACE influences neural development, leading to changes in brain structure and consequently its function. Several neuroimaging studies on the effects of ACE show that the orbitofrontal cortex (OFC), amygdala, hippocampus and thalamic regions, which are part of the limbic system and play a role in survival behaviour such as feeding and reproduction, and emotional responses, as well as parietal regions including the superior parietal lobe (SPL), are altered in individuals with ACE (McQuaid et al. 2019b; Pollok et al. 2022). The SPL forms part of the frontal parietal network (FPN) and also receives input from the thalamus through the medial route of the dorsal visual stream. Therefore, the corollary that both limbic and SPL regions are affected by ACE provides useful information that could be further investigated in future research (Gamberini et al. 2021; McLaughlin et al. 2019). Recent meta-analyses also found ACE to affect cortical thinning in the right medial cingulate cortex and gm volume reduction in the left supplementary motor area (Yang et al. 2023). Following the consistent account of the combined effect of ACE on brain structure, the ds of childhood adversity—abuse and neglect—appear to affect brain structure differently. There is strong evidence that

abuse alters the structure of regions that underlie attentional functioning, emotional memories, and inhibitory control, including the hippocampus and regions in the anterior part of the FPN such as the dorsolateral prefrontal cortex(Hart and Rubia 2012). Neglect, on the other hand, has been shown to alter parts of the orbitofrontal, superior temporal and rostalmiddle frontal gyri, which are involved in the anticipation and receiving of rewards, as well as regions in the posterior part of the FPN such as the SPL (Lim et al. 2014; Mackes et al. 2020). For anatomical and functional details of FPN, please see (Budisavljevic et al. 2017; Marek and Dosenbach 2018; Parlatini et al. 2017; Thomas Yeo et al. 2011). Some alterations in the amygdala and hippocampus, for example, have been associated with both abuse and neglect. There are, however, some limitations as to how ACE and its subtypes have previously been investigated. Importantly, comorbid mental disorders have not been adequately controlled, which makes it difficult to disentangle which of the effects are due to abuse and/or neglect, or the associated mental conditions, or a combination or interaction of all.

PTSD is a mental health condition that can develop after a person experiences a traumatic event (or a sequence of reoccurring events) such as ACE. Post-traumatic stress symptoms (PTSS) include persistent re-experiencing of the trauma, avoidance of trauma-related circumstances, hyperarousal, and negative alterations in mood and cognition lasting more than a month after experiencing a traumatic event that threatens one's life or bodily integrity. The persistence of PTSS following ACE and its effects on the brain have been documented elsewhere (Siehl et al. 2022; Wang et al. 2021; Xie et al. 2022). For example, cortical alterations in the SPL have previously been negatively associated with PTSS and childhood neglect (Edmiston 2011; McLaughlin et al. 2014; McLaughlin et al. 2019; Tan et al. 2013). Additionally, correlations between subcortical brain volumes such as the hippocampus and thalamus with ACE and PTSS have previously been reported (Xie et al. 2018; Xie et al. 2022). The findings suggest ACE is negatively associated with thalamic volume post-trauma, which, in turn, is inversely associated with PTSS. Despite this insightful evidence, no study has tested the effects of ACE on cortical morphology while exploring their indirect effect on PTSS, notwithstanding recent ACE-thalamic-PTSS findings and the effect of both ACE and PTSS on some cortical regions such as the SPL.

Extant literature supports the relationship between ACE and white matter alterations measured by diffusion MRI. Over the years, voxel-averaged diffusion quantitative measures like fractional anisotropy (fa), mean diffusivity (md) and axial diffusivity (ad) have been related to ACE using tract-based spatial statistics (TBSS) (Lim et al. 2019a). Despite these findings,

quantitative measures based on averaging voxels are not fibre-specific and may have limited interpretability because most WM voxels contain contributions from multiple fibre populations (commonly referred to as crossing fibres) (Raffelt et al. 2017). Recent advanced 3D DTI fibre tractography provides fibre measures that can be used as the basis for quantitatively assessing the microstructure of specific white matter tracts in mental health studies. For example, the number of fibres indicates the total number of axons in the specific white matter region, while fibre density provides more precise information on the microstructural integrity of a WM tract. These measures are probably more sensitive to certain pathologies, are more directly interpretable, and provide a basis for investigating macroscopic intra-axonal WM volume of biological significance (Riffert et al. 2014). Since certain gm regions are also altered by ACE, it is crucial to consider the structure of the WM regions connected to disease-associated cortical gm regions in order to understand the structural brain alterations associated with mental disorders. This is what we term here "complementary multimodal neuroimaging" i.e., where one neuroimaging modality complements the other, thereby allowing us to shed more light on a wide range of structural brain alterations related to a mental trait.

The scope of the current work was to investigate the effect of ACE on grey matter and adjoining white matter connections. We used a comprehensive approach to first examine the relationship between ACE and total grey matter volume (TGV). Then we tested whether any changes persisted after covarying for potential confounders such as sex, age, estimated total intracranial volume (eTIV), and overall psychological burden. The links between ACE and localised alterations in cortical volume, surface area, and thickness were then explored. We hypothesised that ACE would be negatively related to TGV and that local cortical alterations in several limbic and FPN regions, as mentioned above, would show a negative relationship with ACE after controlling for overall psychological burden. We also aimed to identify brain morphometry associated with abuse when controlling for neglect (and vice versa) and overall psychological burden. Based on previous literature (Morey et al. 2016), we hypothesised that abuse would be negatively associated with cortical alterations in the FPN, including the SPL. Similarly, we hypothesised that neglect would be negatively associated with alterations in the superior temporal and rostral middle frontal gyri. In addition, we investigated the mediating role of ACE-related cortical volume alterations in the relationship between ACE and PTSS. More specifically, given that previous literature supports the mediating role of subcortical regions such as the thalamus volume in the ACE-PTSD relationship, we sought to confirm if

ACE-related cortical volume alterations in our sample mediate the relationship between ACE and PTSS. We hypothesised that ACE-related cortical volume alterations would be an important aspect of any explanation of how ACE lead to adult PTSS. Lastly, an exploratory complementary analysis using the number of fibres, normalised fibre density, average fibre length, and mean fa of WM tracts connected to local cortical ACE-related volumetric alterations would help shed more light on the diverse structural brain alterations related to ACE.

3.3 **Methods**

Participants

Eighty participants with self-reported ACE and living in Germany were recruited for the current study. Inclusion criteria for the study were any type of abuse (physical, emotional, and sexual) and/or neglect (emotional and physical) experienced before the age of eighteen. Exclusion criteria included any kind of metal implant, pregnancy, traumatic brain injury, claustrophobia, psychosis, or any form of neuropsychological disorder. Two female participants were excluded at the analysis stage, one due to abnormal brain structure and the other due to an acquisition error in diffusion MRI data, leaving a total of N=78. A summary of the demographics and psychological measures at the time of assessment is shown in Table 1. The study was approved by the Ethics board of the Medical Faculty Mannheim at Heidelberg University, Germany, and was conducted in accordance with the Helsinki Declaration at the Central Institute of Mental Health in Mannheim. All participants gave written informed consent.

Procedure

See method section of the Supplementary Information for details on the study procedure.

Measures

ACE severity was quantified using the sum of individual sub-types of ACE from the Childhood Trauma Questionnaire (CTQ). A detailed report on the CTQ has been reported in prior literature (Thombs et al. 2007). The CTQ consists of five questions for each type of exposure, and each question prompts participants to rate a particular event on a scale ranging from "Never True" to "Very Often True". Here, we calculated the abuse severity score as the sum of all abuse subtypes of the CTQ (i.e., sexual, physical, and emotional abuse), the neglect severity score consisted of the sum of all neglect subtypes of the CTQ (i.e., emotional &

physical neglect) and the combined ACE (CTQ total) was calculated as the sum of abuse and neglect scores.

Overall psychological burden was accessed using the self-report Brief Symptom Inventory (BSI) to identify relevant psychosocial symptoms in our sample. The BSI includes 53 items that cover nine symptom dimensions: depression, anxiety, phobic anxiety, somatization, paranoid ideation, interpersonal sensitivity, obsession-compulsion, psychoticism, and hostility. Items are scored on a 5-point Likert scale ranging from 0 (not at all) to 4 (extremely). The Global Severity Index was calculated by adding the sums of the nine symptom dimensions plus the four additional items that were not included in any of the dimensional scores and dividing by the total number of items to which the individual responded, this score was used to assess current or past symptomatology (BSI total).

The PTSD symptom severity was assessed using the Posttraumatic Stress Disorder Checklist for DSM-5 (PCL-5), which is a self-report measure that corresponds to each of the 20 core DSM-5 PTSD symptoms and asks respondents to rate how much each symptom has bothered them in the past month, scoring responses on a Likert scale ranging from 0 (not at all) to 4 (extremely) (Blevins et al. 2015). Symptoms are classified into four domains in accordance with the DSM-5 criteria for PTSD: re-experiencing, avoidance, negative changes in cognition and mood, and hyperarousal, with total PTSS severity score ranging from 0 to 80 indicating more severe symptoms. The PCL-5 is regarded as the "benchmark" self-report measure of PTSD symptom severity, with strong test-retest reliability (r=0.84) as well as convergent and discriminant validity (Bovin et al. 2016; Harper et al. 2022; Keane et al. 2014).

The German version of the Dissociative Experience Scale (FDS) was used to assess dissociation symptoms in our study (Spitzer et al. 1998). The FDS is a 44-item self-administered questionnaire which measures the frequency of dissociation symptoms such as absorption, amnesia, and identity disturbances. Items are scored on a scale from 0 (never) to 100 (always). In the FDS, the mean of 44-items is calculated and used as overall dissociative symptoms, and this has been shown to have good reliability and validity based on the DSM definition of dissociation (Spitzer et al. 1998).

Table 1. Descriptive statistics for demographics and psychopathology variables.

Variable	Mean (SD)	Range
AGE	31.628 (10.790)	18 – 59
SEX (female)	65 (83%)	
ACE (CTQ total)	62.538 (19.944)	32.00 – 117.00
Abuse (CTQ abuse)	26.628 (8.590)	10.00 – 46.00
Neglect (CTQ neglect)	35.910 (13.167)	17.00 – 71.00
Psychological burden (BSI total)	0.913 (0.617)	0.06 – 2.55
Dissociation symptoms (German version of the Dissociative Experience Scale (FDS))	14.158 (12.338)	0.23 – 55.91
PCL-5	28.090 (17.390)	0.00 – 69.00
PTSS (PCL- sub scales)		
• Reexperiencing	6.256 (4.453)	0.00 – 19.00
• Avoidance	3.731 (2.597)	0.00 – 8.00
• Negative alterations in cognition and mood	10.77 (7.058)	0.00 – 28.00
• Hyper arousal	8.026 (5.871)	0.00 – 21.00

Note: N= 78; CTQ total = total score of Childhood Trauma Questionnaire; CTQ abuse = sum score of all abuse subtypes of CTQ; CTQ neglect = sum score of all neglect subtypes of CTQ; BSI total = Global Severity Index of Brief Symptom Inventory (BSI); PCL-5 = Posttraumatic Stress Disorder Checklist for DSM-5.

Data acquisition

Both T1-weighted (T1w) and diffusion images were acquired using a Siemens Prisma-fit Scanner (Siemens Medical Solutions, Erlangen, Germany) with a 64-channel head coil. A 3-D magnetisation-prepared rapid-acquisition gradient echo (MPRAGE; T1-weighted contrast, Echo Time (TE): 2.01 ms; Repetition Time (TR): 2000 ms; Inversion time (TI): 900ms; FA = 9°; FOV: 256 x 256 mm; number of slices 192, voxel size 1x1x1 mm^3) and a double spin-echo echo-planar imaging (EPI) sequence (82 volumes, 3 at b=0 and 79 at b=1000 s/mm^2, TR=8400 ms, TE=86 ms, matrix = 128 x 128 ; number of slices 64, and voxel size=2×2×2 mm^3) scans were acquired for each participant.

Data processing

Preprocessing for both T1w and diffusion images was performed using Connectome Mapper 3 (CMP; an open-source Phython3 neuroimaging processing pipeline software developed by the Connectomics Lab, University Hospital of Lausanne (CHUV)). CMP uses a combination of well-known neuroimaging software packages to implement full anatomical and diffusion processing pipelines from raw images (Tourbier et al. 2022). All images were controlled for quality (see supplementary method for details). The preprocessing steps that were used in this study can be seen below.

T1-weighted images were preprocessed, parcellated, and segmented into cortical thickness, surface area, and volume using the FreeSurfer version 6.0.1 recon-all program. An in-depth explanation of the steps used by FreeSurfer's recon-all has previously been

described elsewhere (Dale et al. 1999; Fischl et al. 2004). In brief, the white matter and pial surface were identified after motion correction, non-uniform intensity normalization and normalization, by creating a mesh around the white matter and pial voxels. Surface-based maps of each individual scan were created using spatial intensity gradients across tissue classes (Desikan et al. 2006). Cortical thickness, surface area, and volume maps were extracted and smoothed with a 10-mm kernel at full width at half maximum (FWHM). FreeSurfer morphometric procedures have been demonstrated to show good test-retest reliability across scanner manufacturers and across field strengths (Reuter et al. 2012). Visual inspection was done to inspect the anatomical accuracy of FreeSurfer's automated parcellations and segmentations.

Denoising and subsequent correction for bias field, eddy currents, and motion correction were performed on all diffusion data using state-of-the-art methods implemented in the MRtrix3 toolbox (Tournier et al. 2019). Anatomy-constrained probabilistic tractography was performed using the five-tissue-type (5TT) segmented T1w image and a second-order integration over fibre orientation distributions algorithm on the preprocessed diffusion image to produce an initial tractogram with 10 million streamlines (Tournier and , F. Calamante 2010). The tractogram was filtered using SIFT2 approach: an approach to improve the quantitative nature of whole-brain streamlines reconstructions (Smith et al. 2015). Diffusion measures (i.e., number of fibres, average fibre length, normalised fibre density, and mean FA) touching/emerging from the segmented regions were then extracted for subsequent statistical analyses.

Statistical analysis

ACE relation to Total GM volume.

To test the first hypothesis, we extracted the total GM volume from the output of recon-all processing to do a preliminary comprehensive regression analysis and to first examine whether ACE (i.e., CTQ total) is associated to total GM volume as hypothesised. We also tested whether the relation persisted after covarying for potential confounders such as age, sex, estimated Total Intracranial Volume (eTIV), and overall psychological burden (i.e., BSI).

Regional cortical alterations following ACE.

Whole-brain surface-based analyses were performed using FreeSurfer's glmfit. The general linear model was used to locate all regional cortical alterations in thickness, surface area, and volume that were related to CTQ total for the first hypothesis. This resulted in three models,

one for each cortical measure. For the second hypothesis, the effect of subtypes of ACE (i.e., abuse and neglect), regional cortical alterations in relation to ACE subtypes was investigated. First, a simple linear regression was used with either abuse or neglect as variables of interest and age, sex BSI total and neglect or abuse as control variables (6 models in total; 2 variables of interest x 3 cortical measures). Then, a t-test was used to investigate the differences between abuse and neglect in the direction of abuse > neglect, because CTQ total has higher correlation to abuse ($r_{partial}$=0.929, p<0.001), compared to neglect ($r_{partial}$=0.844, p<0.001), and controlling for age, sex, and BSI total (one model). All cortical volume analyses were controlled for eTIV, and all results presented here were corrected for multiple comparisons using Monte Carlo simulation with vertexwise threshold P<0.005 and clusterwise threshold P<0.05 and in both brain hemispheres. Significant clusters were labelled using Desikan-Killiany atlas.

Mediating role of ACE-related cortical volume alteration in ACE– PTSS relationship.

To tackle our third hypothesis, values of significant ACE-related clusters identified in cortical analyses as sensitive to ACE and its sub types were extracted to find out if the significant effects mediate the relationship between ACE and PTSS. The average cortical volume per vertex of each cluster for every participant was multiplied by the number of vertices in the respective clusters to get the total volume per cluster (TVC) for all subjects. This was then used as mediators in the relationship between ACE and PTSS. The bias-corrected CIs and SEs for the mediation effect are reported here using 5000 bootstraps. All mediation analyses were performed using JASP (JASP Team, 2023). As all mediation models were just identified, no model fit indices were computed as previously reported here (Mackes et al. 2020). Lastly, since PCl-5 does not link PTSS to a specific type of trauma, our aim here is to examine the association between ACE and PTSS regardless of whether the cause of the PTSS is due to ACE alone or also due to additional trauma events.

Diffusion measures in WM complements local cortical ACE-related GM volume alterations

To complement the local cortical ACE-related volumetric alterations in GM regions identified in the previous analyses, diffusion measures (i.e., number of fibres, average fibre length, normalised fibre density, and mean FA) in WM pathways that connect to ACE-related GM volume regions were extracted to verify their relation to ACE. Hence, we could further explore the local WM integrity connected to GM regions relation to ACE using regression models. We extracted the diffusion measures touching/emerging from the segmented GM regions in Desikan-Killiany atlas space and correlated diffusion WM measures with TVC from the

abuse/neglect subtype analyses. Each model was corrected for multiple comparisons using the false discovery rate q = 0.05. The effect sizes were bootstrapped using 5000 iterations and bias-corrected CIs and SEs were reported.

3.4 **Results**

Associations between ACE and total GM volume. We observed a negative association between total CTQ score and total GM volume: β=-768.825, t (76) =-2.515 and p= 0.014. This result remained significant after controlling for sex and BSI total (β= -725.517, t (74) =-2.426 and p= 0.018), suggesting that the effects were not simply a reflection of other psychological disorders or sex. Although previous reviews show that BSI captures some form of psychological distress that commonly occurs in the chronic posttraumatic phase (Auxéméry 2018; Recklitis et al. 2017), the check for multicollinearity shows that the presence of the BSI total variable does not affect our regression analysis (i.e., the VIF of 1.112; also see S1). We noticed that including age in the model diminishes the effect, i.e., the relationship between total GM volume and CTQ total becomes statistically non-significant (β= -256.252, t (73) =-0.430 and p= 0.379). Also, CTQ total showed no significant relationship with total GM volume when estimated total intracranial volume (eTIV) was controlled for (Supplementary Table 2). Despite these findings, we did control for age in all cortical analyses and additionally for eTIV in cortical volume analysis based on previous literature (Pollok et al. 2022; Voevodskaya et al. 2014). Lastly, since CTQ total and total GM volume were negatively related, all subsequent cortical regional analyses focused on this negative relationship.

Local Alterations in Cortical Structure following ACE: using the whole brain surface-based analysis approach, we identified a cortical area reduction in the right superior parietal area to be related to CTQ total after controlling for overall psychological burden, age, and sex.

Figure 5. Negative effect of ACE on cortical surface area in right superior parietal region after controlling for overall psychological burden, age, and sex.

Table 2. Cluster showing significant negative relation between CTQ total and cortical surface area.

Cortical Measure	H	Brain region	Size (mm^2)	MNI coordinate [x y z]	Clusterwise P	Effect size
Area	RH	Superior parietal	694.21	18.9 -60.4 54.4	0.0443	-4.0089

Monte Carlo correction for multiple comparisons was applied (clusterwise threshold P < 0.05, vertex-wise threshold P<0.005). Effect sizes (regression coefficients) were taken from whole brain vertexwise effect size brain maps. H, hemisphere; RH, right hemisphere; LH, left hemisphere.

Effect of abuse and neglect on cortical brain measures: we used a simple linear regression with Abuse/Neglect variables of interest and sex, BSI total, age, eTIV and abuse/neglect as control variables. For the differences between abuse and neglect on cortical measures, a t-test was used in the direction of Abuse > Neglect, and controlling for overall psychological burden, age, sex and eTIV (for volume). Abuse was significantly negatively related to cortical volume in the right superior parietal region after controlling for neglect, sex, age, eTIV, and overall psychological burden. No other significant associations were observed between neglect and all cortical measures. Additionally, the t-test of abuse > neglect on all cortical measures also showed no significant association.

Figure 6. Significant effects of abuse on local cortical volume in the right superior parietal region after controlling for the effects of neglect severity, overall psychological burden, age, eTIV and sex

Table 3. Cluster showing a significant negative relation between childhood abuse and cortical volume alteration.

Cortical Measure	H	Brain region	Size (mm^2)	MNI coordinate [x y z]	Clusterwise P	Effect size
Volume	RH	Superior parietal	369.99	21.6 -62.6 37.6	0.0412	-3.5479

Monte Carlo correction for multiple comparisons was applied (clusterwise threshold P < 0.05, vertex-wise threshold P<0.005). Effect sizes (regression coefficients) were taken from whole brain vertexwise effect size brain maps. H, hemisphere; RH, right hemisphere; LH, left hemisphere.

Does abuse-related cortical volume alteration in the right superior parietal lobe (rSPV) mediate the relation between abuse severity and PTSS severity scores? To address this, we used rSPV as a mediator, abuse (assessed with the total CTQ abuse severity score) as a predictor, and all four PTSS severities (assessed with PCL) as outcome variables (giving a total of four mediation models). Each model was deemed significant if the p-value of the total effect was less than the Bonferroni corrected p-value (i.e., $p < 0.05/4 = 0.0125$). All four models were significant after Bonferroni correction (see supplementary table S4). The direct relationship between childhood abuse and each PTSS dimension was significant (see Table 4). rSPV

significantly mediated the relationship between abuse and avoidance PTSS (n = 78, β = 0.021, SE = 0.010, Z=2.130, 95% CI = [0.004, 0.042], R^2 = 0.217, p=0.033). The path plot showing effects is depicted in figure 7 below. No other significant rSPV mediation in the other three models was found, even though the total effects of all models were significant (see supplementary tables S3 and S4). Lastly, the path between abuse and rSPV (β = -4.989, p<0.001), and rSPV and negative changes in cognition and mood PTSS (β = -0.011, p=0.045) were both significant, but their total indirect effect was insignificant in the abuse-rSPV-$PTSS_{\text{negative changes in cognition and mood}}$ model (β = 0.008, p=0.059) (see supplementary table S3).

Table 4. Direct relation of abuse and all PTSD symptoms

							95% Confidence Interval	
			Estimate	Std. Error	z-value	p	Lower	Upper
Abuse	→	INTRU	0.138	0.046	3.000	0.004	0.042	0.224
Abuse	→	AVOID	0.061	0.023	2.636	0.008	0.016	0.109
Abuse	→	COMO	0.236	0.062	3.829	< .001	0.124	0.365
Abuse	→	HYPE	0.198	0.051	3.865	< .001	0.100	0.303

Note. INRU= intrusive PTSS, AVOID= avoidance PTSS, COMO= negative changes in cognition and mood PTSS, HYPE = hyperarousal PTSS. Bias-corrected percentile bootstrap confidence intervals. Estimator= Maximum likelihood, Optimization method=NLMINB.

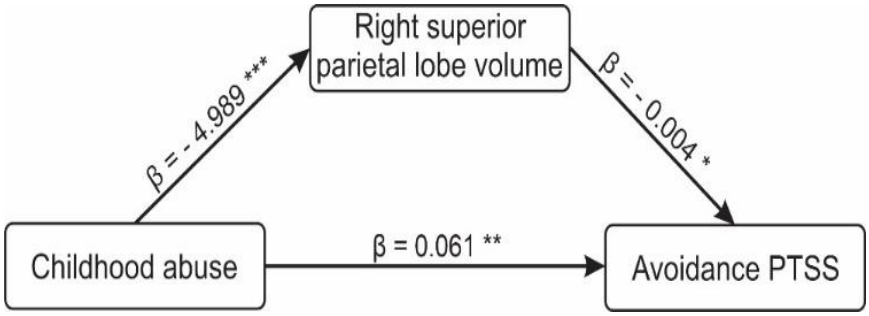

*Figure 7. Significant mediation role of abuse-related volume reduction in the right superior parietal lobe in the relationship between the severity of childhood abuse (assessed with the total CTQ abuse severity score) and PTSD avoidance symptoms (Avoidance PTSS; assessed with the PCL avoidance symptomatology). Asterisks indicate the statistical significance of the bootstrapped standardised regression coefficients (***p < .001; **p < .01; *p < .05).*

Post-hoc Analyses: Does the indirect effect in the abuse-rSPV-avoidancePTSS relationship depend on dissociation symptoms? Several factors, including enhanced memory suppression, developing safety behaviours, and heightened dissociation, contribute to the association between childhood abuse and PTSD symptomatology. Specifically, dissociation is believed to be a coping mechanism for severe trauma experienced during childhood (Kratzer et al., 2018). As post-hoc analyses, we explored whether the significant indirect effect in the abuse -rSPV-avoidance PTSS relationship (mediation analysis in Figure 7) depends on dissociation in our sample. First, we checked whether dissociation mediates the relationship between the

severity of childhood abuse and avoidance PTSS. We found no significant mediation of dissociation in the abuse and avoidance relationship (β =0.014, SE = 0.008, Z=1.848, p=0.065, 95% CI = [0.001 0.030], R^2=0.212) even though the path between abuse and dissociation (β =0.327, p=0.003), and the total effect (β =0.082, SE = 0.020, p<0.001, 95% CI = [0.082 0.418]) were significant. Then we explored whether dissociation symptoms interact with one or both indirect paths in our main mediation model from Figure 7. Prior to the analysis and to improve interpretation, we dichotomised the dissociation symptom measure (i.e., FDS score using cut-off 13;Rodewald, Gast, & Emrich, 2006) in Table 1. The moderated mediation analysis was also performed using lavaan-SEM and is similar to what is implemented in Hayes model 58 (Hayes 2012) (see Figure 8 below). Both indirect paths were significant; hence, we subsequently explored the CIs and SEs using bootstrapping (see also Table 5 below).

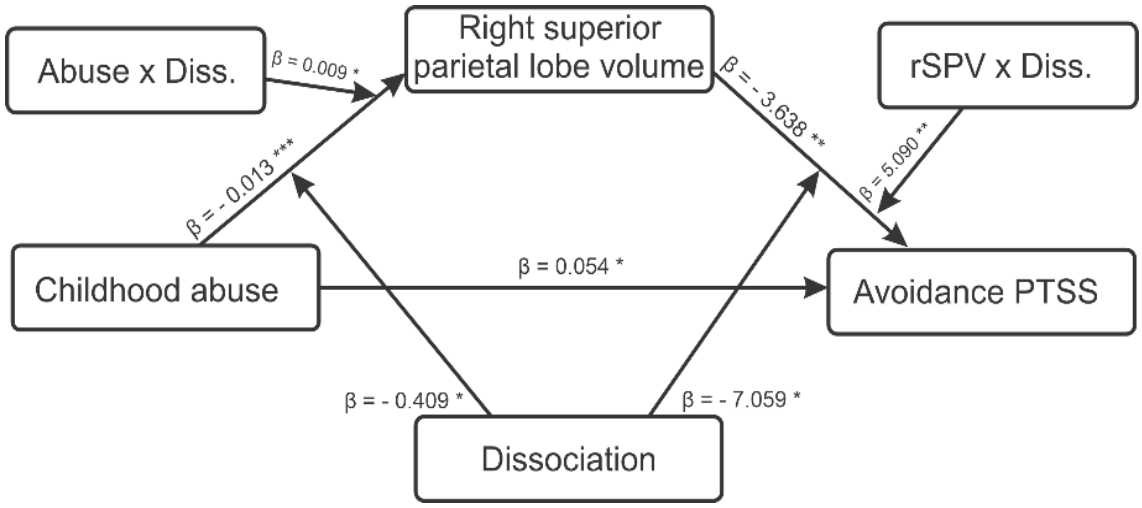

*Figure 8. Model diagram showing moderation role of dissociation in the indirect effect of abuse-rSPV-avoidance PTSS relationship. Asterisks indicate statistical significance of the bootstrapped standardized regression coefficients (***p < .001; **p < .01; *p < .05)*

Table 5.Table showing whether dissociative symptoms interact with one or both paths in the mediation model in Figure 7.

Path	Estimate	Std.Err	95% CI		R^2	p
			L	H		
SPL volume					0.280	
✓ ***a1- Abuse***	**-0.013**	0.003	-0.020	-0.007		< 0.001 *
✓ ***a2-Dissociation***	**-0.409**	0.175	-0.744	-0.065		0.020 *
✓ ***a3- Abuse * Dissociation***	**0.009**	0.004	0.001	0.018		0.036 *
PTSD AVOID					0.346	
✓ ***b1- rSPV***	**-3.638**	1.084	-5.735	-1.401		0.001 *
✓ ***b2-Dissociation***	**-7.059**	2.786	-12.988	-2.050		0.011 *
✓ ***b3- rSPV * Dissociation***	**5.090**	1.737	1.894	8.813		0.003 *

Abuse=childhood abuse, rSPV = right superior lobe volume. Bootstrapping is based on 5000 replicates and the coefficient estimate is based on the percentile of the bootstrap distribution, Std.Err is the standard error, CI is the confidence interval, and p is the p-value. Significant paths are highlighted with * in the p-value column.

Diffusion measures in WM tracts touching the right superior parietal lobe complement the abuse-related effects in the brain: Following CTQ abuse-related changes in the right superior parietal volume, the diffusion measures (number of fibres, average fibre length, normalised fibre density and mean FA) within WM tracts touching the right superior parietal region were extracted for all subjects and put into regression models to explore their relationship with abuse severity using Pearson's correlation. The average vertexwise volume in the abuse related rSPL cortical volume alteration was significantly correlated to almost all our diffusion measures (see Table 6).

Table 6. Complementary correlation analysis of the diffusion measures in WM tracts touching the right superior parietal lobe with abuse-related cortical volume alterations.

Diffusion Measures	Person's r	95% CI		p
		Lower	Upper	
Number of fibres	0.330	0.146	0.499	0.003**
Average length of fibres	0.298	0.105	0.481	0.008**
Normalised fibre density	-0.241	-0.473	-0.010	0.033*
Mean FA	0.266	0.083	0.464	0.019*

Pearson's correlations (r) and CI is the confidence interval based on 5000 replicates and p is the p-value. Since the average vertexwise volume was used (i.e., residuals from cortical analyses) we did not include any control variable at this level. Significant relation was heighted as ***p < .001; **p < .01; *p < .05.

3.5 **Discussion**

This study provides evidence for the combined ACE severity and abuse subtype effects on brain structure. In a multiple regression analysis, ACE was negatively associated with the total GM volume after controlling for the overall psychological burden and sex. Whole brain analyses showed local cortical area reduction in the right superior parietal region to be associated with ACE. No further significant relationships between the combined ACE severity score and whole brain cortical measures were evident in our sample. As opposed to the cumulative account of childhood adversity, the two dimensional subtypes of adversity (i.e., abuse and neglect) may reflect different underlying dimensions of environmental experience that may have distinct associations with neurodevelopmental processes and also influence emotional, cognitive and neural development (McLaughlin et al. 2019). We found cortical volume alterations in the right superior parietal lobe (rSPL) to be associated with abuse while controlling for neglect, age, sex and eTIV. No further significant relationships were present in the ACE subtype analyses after controlling for overall psychological burden, which is crucial to

elucidate the effects of abuse/neglect independently from those associated with mental comorbidities (Pollok et al. 2022). The rSPL forms part of the posterior-FPN and has previously been reported to play a key role in the “top-down” or goal-driven allocation of attention. Cytoarchitectonic research shows that the SPL has a complex, heterogeneous architecture with more than seven sub-regions. The receptor distribution patterns and regional cytoarchitectonic features found three sub-regions in Brodmann (BA) 5 and four in BA 7 (Scheperjans et al. 2005; Scheperjans et al. 2008). Functions of these regions were explored in a resting-state functional MRI study in healthy participants, and the results showed that each of the seven sub-regions was connected to several resting-state networks, with the most consistent connectivity observed with the visual and attention networks (Alahmadi 2021). Although abnormalities in rSPL has been associated with PTSD, PTSS and maternal stress (McQuaid et al. 2019a; Wang et al. 2021), no study that examined the superior parietal cortex structure found childhood trauma-related differences (McLaughlin et al. 2019). Based on these results, it seems likely that our sample gives new insights into the possibility that ACE may, at least in part, be related to cortical alterations in rSPL, whose function is related to visual and attention tasks.

The test of our third hypothesis revealed a significant indirect path in the abuse-rSPL-avoidance PTSS relationship. In our four mediation models and as expected, the direct paths between childhood abuse and all the different PTSS measured by PCL were significantly positive-related. This is an indication that persons with ACE may indeed be more prone to developing PTSS (Kratzer et al. 2018). The only indirect path that remained significant was the abuse-rSPL-avoidance PTSS relationship (see Figure 8 and also S2). Therefore, the right superior parietal volume significantly mediated the relationship between childhood abuse and avoidance PTSS. Comparing the standardised beta estimates of the indirect path ($\beta ab = 0.021$) to the direct path ($\beta c' = 0.061$) describes the reduced effect, implying that rSPL volume may explain part of the impact of childhood abuse in producing avoidance PTSS. Since a previous mega-analysis in a large sample found smaller volumes in the rSPL to be related to PTSD, we are adding to this finding that the rSPL may play a role in the development of avoidance symptoms in individuals with a history of severe childhood abuse.

A moderated mediation analysis is used to measure how much a mediated effect changes with different degrees of a moderator. As opposed to a mediation analysis, the evidence for a moderated mediation can be used to support the evidence for a mediation under less

stringent confounding condition analyses (Loeys et al. 2016). Our post-hoc analyses gave insights into possible conditional indirect findings in the mediation. Dissociative symptoms, including amnesia, depersonalization, and identity fragmentation, often serve as coping mechanisms for severe trauma experienced during childhood (Brand and Frewen 2017). Since there is a close relation to attention, the involvement of the rSPL here is of interest. Many authors have emphasised the importance of dissociation in PTSD. Some authors agree that dissociation serves as a dysfunctional coping mechanism that serves to prevent biographical memories from integrating traumatic memories and hence perpetuates avoidance PTSD symptoms (Dalenberg and Carlson 2012; Kratzer et al. 2018). Starting from the left side of the path plot in figure 9, both abuse severity and dissociation were negatively associated to rSPV. Their interaction, however, was positively related to rSPV, which in turn was positively related (i.e., through rSPV and Dissociation interaction; right hand side of figure 9) to avoidance PTSS. This is interesting because this relationship could help to explain why persons with both childhood abuse and dissociative symptoms (and high abuse related-rSPL volume alterations) exhibit higher avoidance PTSS as a result of dissociation (Kratzer et al. 2018). Since dissociation can serve as a way to cope with the distressing memories and emotions associated with the childhood abuse, leading to higher levels of avoidance behaviours as a means of managing the traumatic experiences indirectly, our findings support this view via the increase in abuse-related cortical volume in the right superior parietal lobe. This view is additionally supported by closely comparing the beta estimates of the interaction in both indirect paths of the moderated mediation model (i.e., abuse-diss. = 0.009 and rSPV-diss. = 5.090), which show the increase in the conditional effect is mostly explained by alterations in the rSPL in the presence of dissociation.

In our exploratory complementary analysis of WM tracts connected to the GM volume regions, we focused on abuse-related cortical alterations in rSPL volume. We made this choice due to the dimension of the cortical volume measure which makes it biologically comparable to 3D DTI fibre tractography measures. The total volume per cluster from the abuse subtype analyses was correlated to almost all the WM measures (i.e., number of fibres, normalised fibre density, average-fibre length, and mean FA) connecting to abuse-related volume alterations. An increase in abuse-related effect on rSPL volume also increases the number of fibres, average fibre length, and mean FA of the WM tracts connected to rSPL, whereas an increase in abuse-related effect on rSPL volume led to a reduced normalised fibre density of WM tracts connected to rSPL. The former relationship was unexpected because the more the

abuse-related effect in rSPL volume increased, we expected all the WM measures to be reduced, to show that childhood abuse to some extent also negatively affects WM tracts connected to rSPL. This might be explained by the fact that these quantitative measures do not account for individual brain size, in contrast to normalised fibre density, which accounts for brain sizes. The normalised fibre density measure is an upgrade of the fibre density measure proposed by Hagmann et al., (2008) to account for individual brain sizes by normalizing the number of fibres connecting two regions by the total number of fibres in the tractogram and additionally, normalizing the surface per volume of the two regions by the total surface per volume of all regions (Daducci et al. 2012; Hagmann et al. 2008; Tourbier et al. 2022). Our findings provide further insight into the structural integrity of the WM tracts connected to the rSPL and affected by childhood abuse. It is noteworthy that not only was the cortical volume negatively associated with abuse, but the abuse-related volume in rSPL was negatively related to the normalised fibre density measure, which accounts for individual brain sizes.

There are some limitations to our study. First, we collected data about ACE using self-reported questionnaires. Thus, there might be a recall bias, as a meta-analysis reported low agreement between prospective and retrospective measures of ACE (Baldwin et al. 2019). However, self-report measures are mostly used in ACE research because they provide a unique window into the subjective experiences of individuals with ACE and allow them to express their feelings, thoughts, and perceptions of the experience. Interestingly, subjective experience of ACE were stronger associated with emotional disorders in adulthood than objective prospective measures (Danese and Widom 2023), and therefore potentially also to brain alterations. Hence, using self-reported measures in our study is justified as it provides first-hand information about the experience and a contextual understanding of its effects. Second, it is still unclear to what extent pubertal development, malnutrition, prenatal drug exposure, and resilience to co-factors from childhood to adulthood may have influenced our findings since we didn’t collect data on this. Hence, not controlling for these factors could be a limitation. Third, despite the positive insights provided by this study's design, mediation and moderated mediation analyses do not infer causality in cross-sectional studies like ours and hence should be cautiously interpreted. Thus, we reiterate that these analyses are exploratory. Despite this limitation, we have tried to ensure the statistical robustness of our findings by implementing bootstrapped confidence intervals as recommended by Edwards & Konold (2020). Fourth, we acknowledge that in a subset of individuals, the PTSS could be due to other traumatic

experiences unrelated to ACE such as adult trauma exposure. Because higher ACE was associated with higher PTSS (which takes into account the experience of traumatic events throughout life, i.e., in both childhood and adulthood), our model examines the association between abuse and PTSS regardless of whether the cause of the PTSS is due to ACE alone or also due to additional trauma events. Finally, since the majority of the participants were female (83%), the findings may not generalize well to men. We recommend that future studies should use longitudinal designs to assess changes in adversity over time (i.e., to include adult trauma exposure) and also balance male and female participants in a large sample size to help generalise the results to different samples.

3.6 **Conclusion**

Our study provides novel perspectives about the association between ACE and brain structure and the mediating role of the right superior parietal volume in the relationship of childhood abuse and PTSD avoidance symptoms. These findings contribute to our understanding of the neural mechanisms underlying the development and maintenance of PTSD symptoms, specifically avoidance symptoms, in individuals with a history of childhood abuse. By examining the role of the superior parietal region, our study provides valuable insights that may inform future research and interventions aimed at treating and preventing PTSD in an ACE population. Furthermore, our findings elucidate the complex interplay between this relationship and dissociative experiences as the later moderated the indirect effect in the abuse-rSPV-avoidance PTSS relationship. These findings underscore the potential long-term impact of childhood trauma on the brain, the role of dissociative symptoms, and the development of avoidance PTSD symptoms. Lastly, the normalised density of the WM tracts connected to the right superior parietal region provides improved information on structural brain alterations in persons with ACE.

3.7 Supplementary Information

Method

Procedure

This study is part of a larger, ongoing study that is investigating the effects of ACE on brain structure and function (https://grk2350.de/research-projects/ace-characteristics/). Participants were recruited through distributed flyers, advertisements, and online platforms. It is important to note that psychiatric conditions did not factor into our recruitment criteria. Instead, our study was designed to investigate brain alterations following ACE, not specific to any psychiatric condition. The study protocol consisted of online questionnaires, a diagnostic interview, and MRI scanning sessions. The online questionnaires included the Childhood Trauma Questionnaire (CTQ; Thombs et al. 2007), the Brief Symptom Inventory (BSI; Derogatis 1975), dissociative symptoms (i.e., German version of the Dissociative Experience Scale, Spitzer et al. 1998) and the diagnostic session included the Clinical version of the Structured Clinical Interview for DSM-5 (SCID-II; First et al. 2016). The diagnostic interview sessions were conducted by doctoral students who have received SCID-II training. The diagnoses that were assessed included affective disorders, anxiety disorders, obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD), attention deficit hyperactivity disorder (ADHD), and substance use disorder (SUD). Past and current disorders were diagnosed based on the presence of DSM-5 criteria for each disorder. Psychotic disorders were an exclusion criterion. Table S1 summarises the diagnostics.

Table S1. Number of participants with SCID diagnostics.

Variable	current	past
PTSD	22	39
Affective Disorders	22	51
Anxiety and Obsessive Compulsive Disorders	27	36
Somatic symptom and related disorders	5	7
Eating Disorders	2	17
Substance Use Disorders	3	14
ADHD	2	3

PTSD = posttraumatic stress disorder; ADHD = attention deficit hyperactivity disorder. Current = current diagnostics based on DSM-5 criteria; past = past diagnostics based on DSM-5 criteria. Participants with missing SCID data = 2.

For the current study, only the lifetime PTSD diagnostics (i.e., current and/or past = 39) were used to correlate with the total PCL score (i.e., PCL-5 from Table 1 in the main text). From the point-biserial correlation, lifetime PTSD and total PCL score were found to be moderately positively correlated, $r_{pb}(74) = .47$, $p < .001$.

Results:

Comprehensive regression analysis between total GM volume and total CTQ score

We examined the potential role of confounders by testing whether they account for the relationship between ACE and GM volume. Statistically taking account of these confounding factors is especially important in order to control for their potential effect in our sample. These variables include age, sex, eTIV, and BSI total, which is the Global Severity Index of the Brief Symptom Inventory (BSI).

Table S2. Comprehensive regression analysis between total GM volume and total CTQ score.

	Models		
	(1)	**(2)**	**(3)**
	total GM volume (mm^3)	total GM volume (mm^3)	total GM volume (mm^3)
Age	-	-	-1990.694*** (276.577)
Sex	-	59407.766 *** (15,829.877)	7988.567^{ns} (8829.914)
eTIV	-	-	0.325*** (0.024)
Psychological burden (BSI total)	-	6058.081 ^{ns} (10113.341)	1071.723 ^{ns} (4934.821)
ACE (CTQ total)	-768.825* (305.702)	-725.517 * (299.019)	57.771^{ns} (158.689)
Intercept	720,615.568 (20054.910)	702,473.549 (19537)	249662.170 (38758.965)
R^2	0.077	0.227	0.822
RMSE	55318	49618.814	24145.284
p-value	0.014	< 0.001	< 0.001
Collinearity Statistics (Tolerance / VIF)		BSI total = 0.899 / 1.112	Age = 0.859 / 1.164 BSI total = 0.881 / 1.135 eTIV = 0.949 / 1.054

Note: N= 78; CTQ total = total score of Childhood Trauma Questionnaire; eTIV = estimated Total Intracranial Volume; BSI total = overall Psychological burden; RMSE= Root Mean Square Error; VIF= Variance inflation factor. The values in the column of each model represent the unstandardized beta coefficients with their standard error in brackets. Asterisks indicate the statistical significance of the bootstrapped unstandardized regression coefficients (***p < .001; **p < .01; *p < .05; ns=not significant).

Supplementary results for the mediation models

Supplementary results for the mediating role of abuse-related cortical volume alteration in the abuse-PTSS relationship. Abuse-related cortical volume alteration in the right superior parietal lobe (rSPV)

significantly mediated the relationship between abuse and avoidance PTSS. Tables S3 and S4 show the indirect and direct paths of all four mediation models respectively.

Table S3. Indirect relation in abuse, rSPV and all PTSD symptoms.

									95% Confidence Interval	
					Estimate	Std. Error	z-value	p	Lower	Upper
Abuse	→	rSPV	→	AVOID	0.008	0.004	2.291	0.022	0.0010	0.0150
Abuse	→	rSPV	→	INTRU	0.006	0.004	1.357	0.175	-0.0030	0.0140
Abuse	→	rSPV	→	COMO	0.008	0.004	1.892	0.059	-0.0003	0.0160
Abuse	→	rSPV	→	HYPE	0.006	0.004	1.537	0.124	-0.0020	0.0140

Note. INRU= intrusive PTSS, AVOID= avoidance PTSS, COMO= negative changes in cognition and mood PTSS, HYPE = hyperarousal PTSS. Bias-corrected percentile bootstrap confidence intervals. Estimator= Maximum likelihood, Optimization method=NLMINB

Table S4. Total effects of all 4 mediation models.

							95% Confidence Interval	
			Estimate	Std. Error	z-value	p	Lower	Upper
Abuse	→	AVOID	0.032	0.007	4.255	< .001	0.017	0.046
Abuse	→	INTRU	0.037	0.008	4.425	< .001	0.021	0.053
Abuse	→	COMO	0.041	0.008	5.388	< .001	0.026	0.056
Abuse	→	HYPE	0.040	0.008	5.134	< .001	0.025	0.055

Note. INRU= intrusive PTSS, AVOID= avoidance PTSS, COMO= negative changes in cognition and mood PTSS, HYPE = hyperarousal PTSS. Bias-corrected percentile bootstrap confidence intervals. Estimator= Maximum likelihood, Optimization method=NLMINB

CHAPTER IV: JOMNA STUDY

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

4.1 **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.

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4.2 **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 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.

4.3 **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 and 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 and Schmahl 2018) which serve as an important protective factor in the resilience to stress (Bækkelund et al. 2021; Cisler and 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. 2024b; 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 and Nemeroff 2011; Wang et al. 2016), as well as key regions like the hippocampus, crucial for memory formation and retrieval (Cisler and 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 and 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 and Holler 2014; Lim et al. 2019b). 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 and 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 and 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 organization 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 categorize ACE-related PTSD vs. ACE-exposed control (noPTSD). We hypothesized 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 hypothesized 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.

4.4 Methods

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).

Procedure

Kindly see supplementary material below.

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 7 below 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 and Rapoport 2010; Herzog et al. 2020; Herzog and Schmahl 2018; Siehl et al. 2018).

Table 7. 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)	0.193
Sex	37 F	64 F	X^2= 5.891 (df = 1)	< 0.001 *
ACE severity (CTQ total)	51.80 ± 11.60	72.59 ± 18.94	T= - 6.834 (df= 117)	< 0.001 *
• *Emotional abuse*	14.06 ± 4.99	17.93 ± 5.07	T= -4.121 (df= 117)	< 0.001 *
• *Physical abuse*	8.18 ± 3.53	10.84 ± 5.29	T= -3.070 (df= 117)	0.003 *
• *Sexual abuse*	6.65 ± 3.21	13.64 ± 6.63	T= -6.833 (df= 117)	< 0.001 *
• *Emotional neglect*	15.12 ± 5.04	18.57 ± 4.99	T= -3.695 (df= 117)	< 0.001 *
• *Physical neglect*	7.78 ± 2.29	11.60 ± 4.39	T= -5.589 (df= 117)	< 0.001 *
PTSD severity (PCL total)	19.06 ± 13.46	35.46 ± 17.09	T= -5.605 (df= 117)	< 0.001 *
• *Reexperiencing*	4.12 ± 3.78	8.13 ± 4.83	T= -4.856 (df= 117)	< 0.001 *
• *Avoidance*	2.69 ± 2.34	4.39 ± 2.49	T= -3.738 (df= 117)	< 0.001 *
• *Negative alterations in cognition and mood*	6.88 ± 5.80	12.84 ± 6.79	T= -5.001 (df= 117)	< 0.001 *
• *Hyper arousal*	5.37 ± 4.76	10.10 ± 5.65	T= -4.792 (df= 117)	< 0.001 *
Overall trauma load	2.04 ± 1.53	2.33 ± 1.80	T= -1.309 (df= 117)	< 0.001 *
Number of ACE-related trauma	0.71 ± 0.71	1.41 ± 0.55	T= -6.061 (df= 117)	< 0.001 *

Data are reported as mean ± standard deviation. Age range for the total sample is 18-59 years. df degree of freedom. *: Significant at P < 0.05 level.

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) = 900ms, Flip angle (FA) = 9◦, 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, 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 = 192x192 mm, matrix size = 64x64, voxel size = 3x3x3.75 mm^3, MB factor of 2, in-plane acceleration factor of 2).

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 normalized 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 4A).

Quality control and data preprocessing of connectivity matrices

The SC and FC features were visually inspected. Each individual connectivity matrix (with the dimension of 83x83) was controlled for age, sex, ACE severity, and trauma load, and subsequently normalized by rescaling the data range to an interval of [0, 1]. This preprocessing step aims to ensure that the features for jcm-ICA are standardized 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.

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 4B, 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 4B, 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 categorize neurobiological differences between groups. As previously demonstrated (Hirjak et al. 2020; Liu et al. 2019; Sui et al. 2009; Wu and 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.

Figure 1 of this paper has been pasted as Figure 4 of the thesis.

Relation between joint mixing coefficient and clinical data

In an exploratory post hoc analysis, we evaluated the joint mixing coefficients for the identified significant 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 7 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.

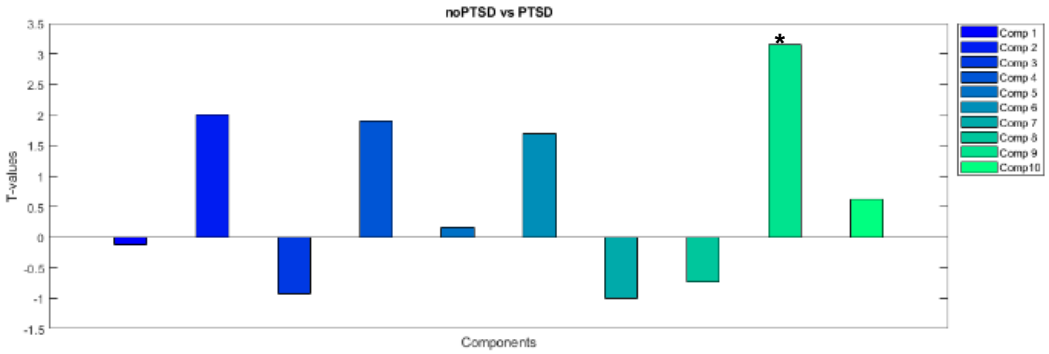
4.5 **Results**

Group Differences (noPTSD > PTSD) on joint mixing coefficient.

Figure 9A 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 ($p = 0.004$, Figure 9A). Figure 9B 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.

9A. T-test results for joint mixing coefficients of all components: noPTSD > PTSD



9B. T-test results for joint mixing coefficient for IC 9: noPTSD > PTSD

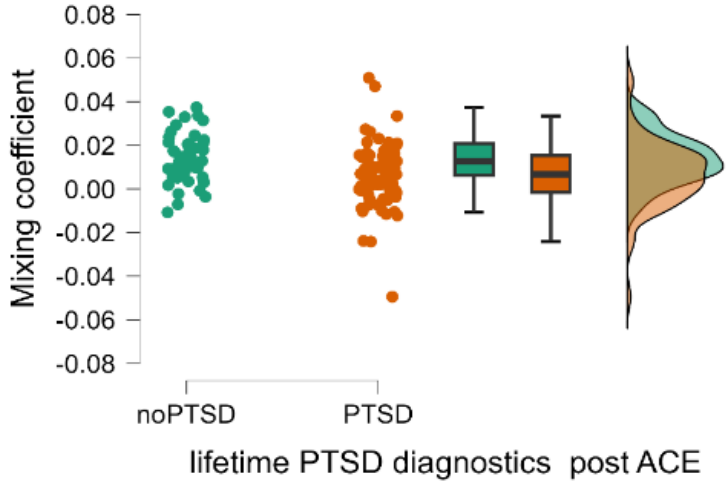


*Figure 9. A two-sample t-test was computed on the joint mixing coefficients between the noPTSD and PTSD groups. **9A** shows a bar graph of the T-values from the t-test computed on the mixing coefficients of all 10 components. (*) indicates components with significant p-values after Bonferroni correction.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

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 categorizes neurobiological differences between groups. Hence, we explored the respective features of this component. For visualization 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 10A) 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 10A) 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.

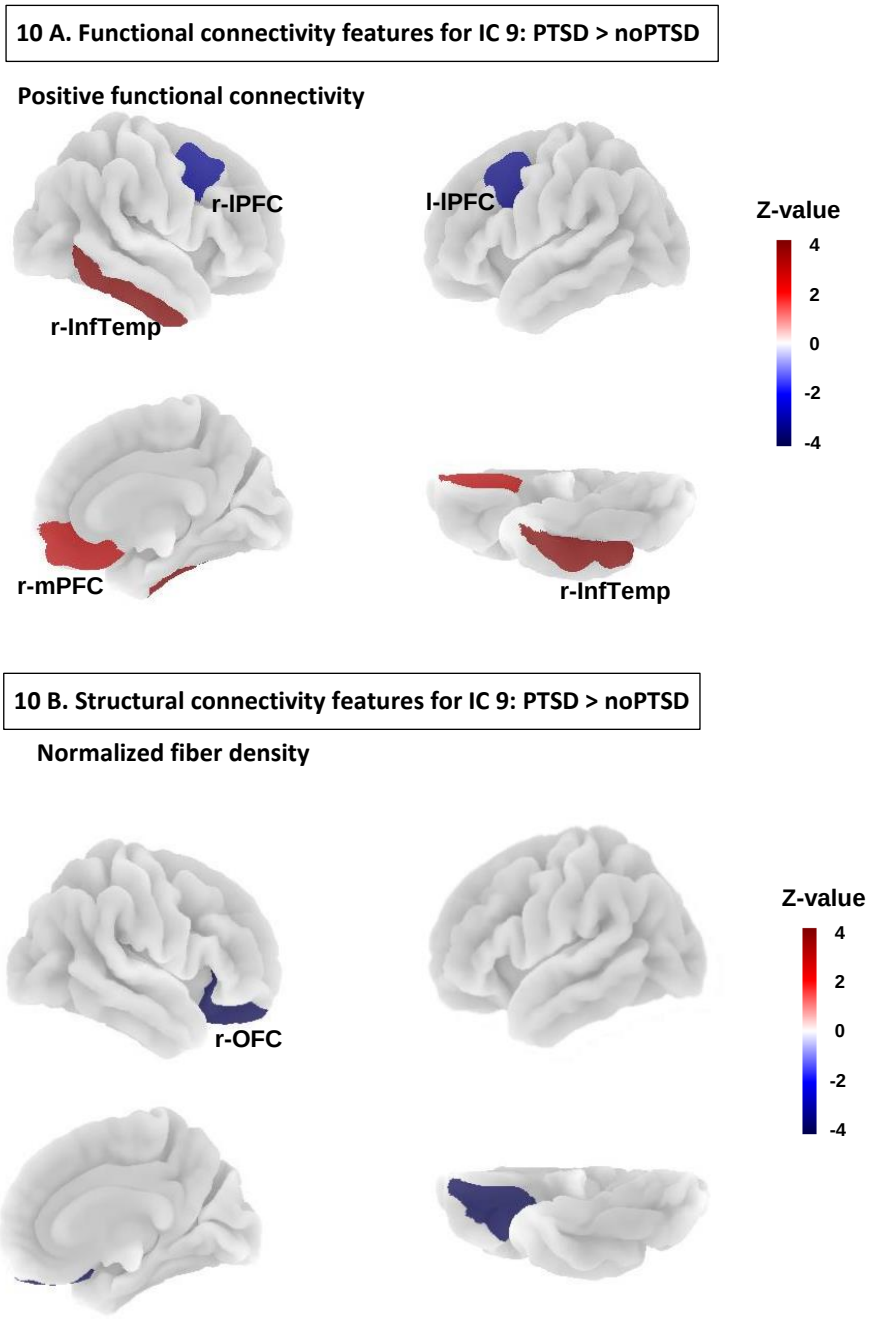
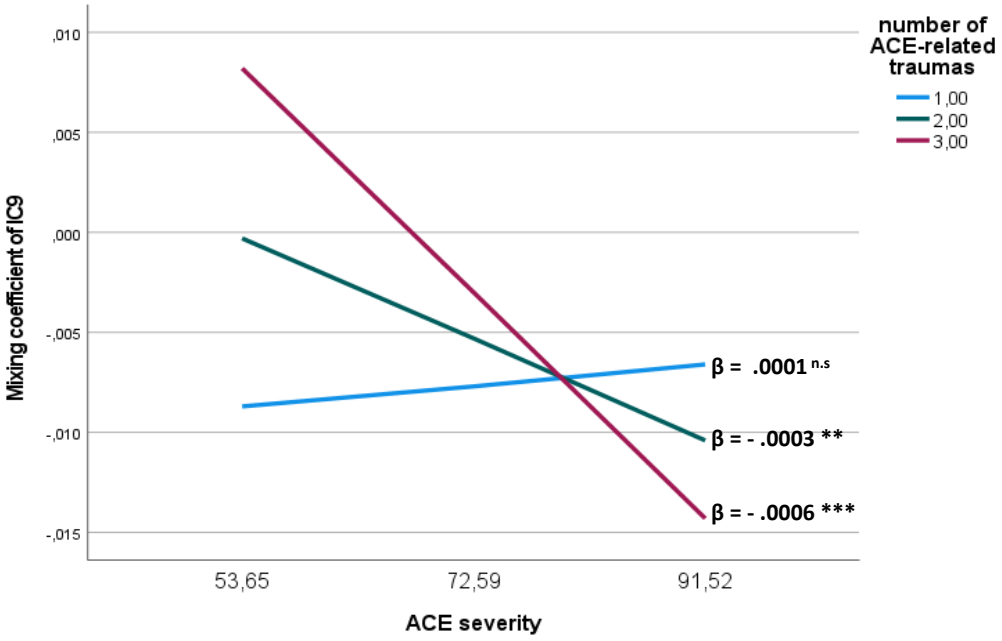


Figure 10. Back-reconstructed cortical functional and structural connectivity features for independent component 9, which differed between the PTSD and noPTSD groups. All features were transformed into Z scores and thresholded at z > 2 (hyperconnectivity in red) and z < -2 (hypoconnectivity in blue) for visualization 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.

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 S6. 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, β = -.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 11A). Although PTSD symptoms did not individually moderate the relationship between ACE severity and MC of IC9 (interaction term: t-value = -1.44, β = -.00000962, SE = .00000667, p = 0.1543), using Hayes' Model 2, with ACE severity as dependent 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 11B: F(2, 64) = 5.29, p = 0.0075, 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).

A. Relationship between ACE severity and joint mixing coefficient of IC9 as moderated by number of multiple ACE-related Trauma of the PTSD group.



B. Relationship between ACE severity and joint mixing coefficient of IC9 as jointly moderated by multiple ACE-related traumas and PTSD symptoms in the PTSD group.

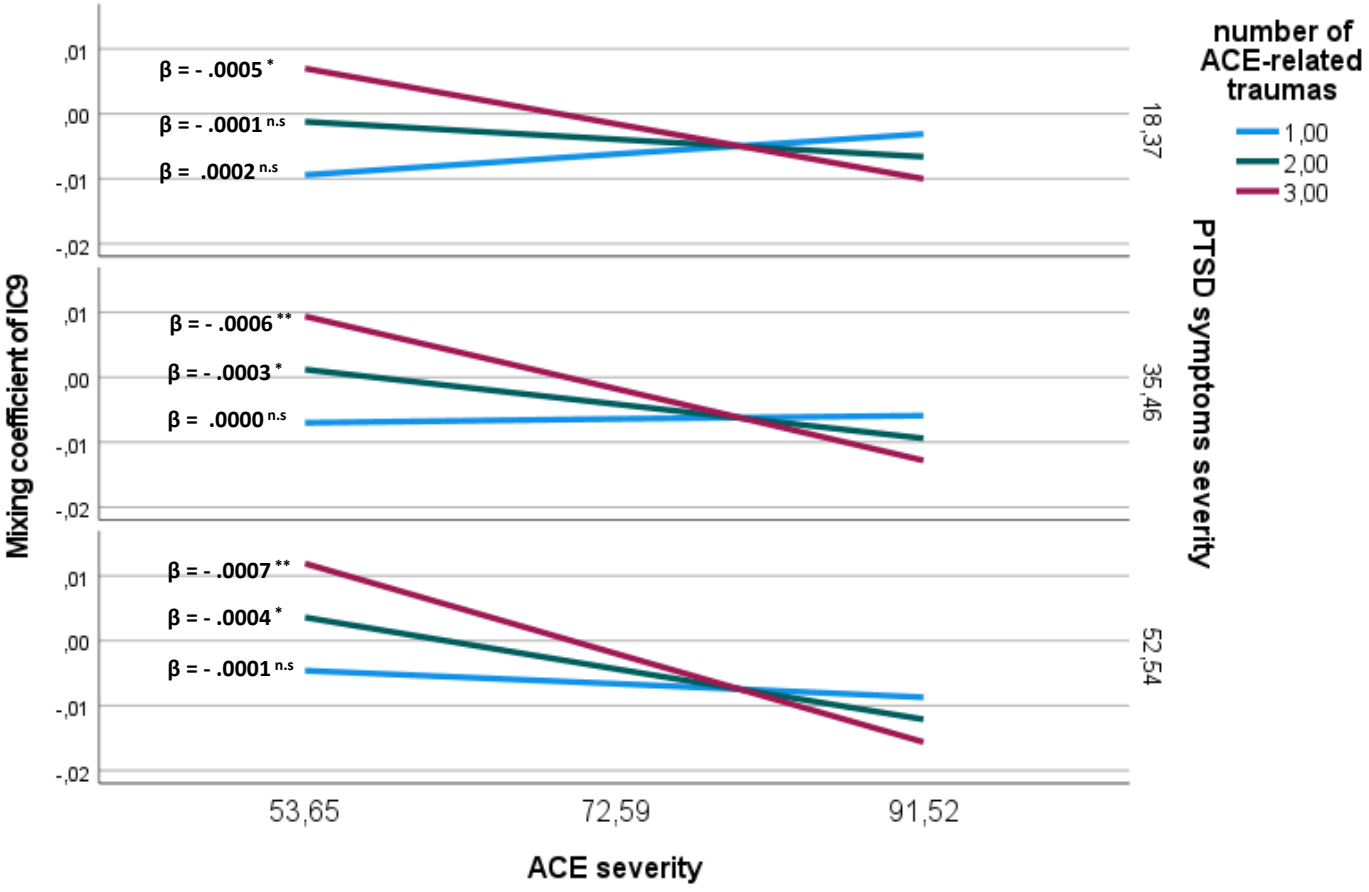


*Figure 11 shows the relation between ACE severity and joint mixing coefficient of IC9 as moderated by (A) number of ACE-related trauma events and (B) number of ACE-related traumas events and PTSD symptoms severity. PTSD symptom severity grouping is shown as ±1 standard deviation around the mean PCL 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 unstandardized regression coefficients (***p < 0.001; **p < 0.01; *p < 0.05; n.s - not significant).*

4.6 **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 ($p = 0.004$, Figure 9). 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 10A) in the left and right lPFC, a component of the central executive network, responsible for cognitive control and executive functioning (Marek and Dosenbach 2018; Olson et al. 2019). As hypothesized 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 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 and Holler 2014).

In examining the structural connectivity features, encompassing both the number of fibres (NOF) and normalized 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. 2024b). 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 and 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 and 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 S6). 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 and 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 S7). 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. 2023b; 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 11B), 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 and MacKinnon 2009). Future research with larger and more diverse samples, employing longitudinal designs, is warranted to validate and extend our findings.

4.7 **Conclusion**

The current study utilized 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.

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Data availability statement

The datasets generated and/or analysed 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.

Disclosure statement

None

4.8 **Supplementary Information**

Method

Study Procedure

The study protocol consisted of the administration of online questionnaires, a diagnostic interview, and MRI scanning sessions. The online questionnaires incorporated the Childhood Trauma Questionnaire (CTQ (Thombs et al. 2007)), the Brief Symptom Inventory (BSI (Derogatis 1975)), dissociative symptoms (specifically, the German version of the Dissociative Experience Scale (Spitzer et al. 1998)) and the Life Event Checklist (LEC) for PTSD (Bovin et al. 2016). The diagnostic session included the clinical version of the Structured Clinical Interview for DSM-5 (SCID-5 (First et al. 2016)). The diagnoses that were assessed included past, current and lifetime affective disorders, anxiety disorders, obsessive compulsive disorder (OCD), post-traumatic stress disorder (PTSD), attention deficit hyperconnectivity disorder (ADHD), and substance use disorder (SUD). Additionally, we diagnosed ACE-related PTSD in all participants.

We first asked participants to identify their three most traumatic childhood experiences, and the SCID PTSD module was then administered based on these specific traumatic events.

Measures

ACE severity was quantified using the sum of individual sub-types of ACE from the Childhood Trauma Questionnaire (CTQ). A detailed report on the CTQ has been reported in prior literature (Thombs et al. 2007). The CTQ consists of five questions for each type of exposure, and each question prompts participants to rate a particular event on a scale ranging from "Never True" to "Very Often True". Here, we calculated the abuse severity score as the sum of all abuse subtypes of the CTQ (i.e., sexual, physical and emotional abuse), the neglect severity score consisted of the sum of all neglect subtypes of the CTQ (i.e., emotional & physical neglect) and the overall ACE (CTQ total) was calculated as the sum of abuse and neglect scores.

The PTSD symptom severity (PTSS) was assessed using the Posttraumatic Stress Disorder Checklist for DSM-5 (PCL-5), which is a self-report measure that corresponds to each of the 20 core DSM-5 PTSD symptoms and asks respondents to rate how much each symptom has bothered them in the past month, scoring responses on a Likert scale ranging from 0 (not at all) to 4 (extremely) (Blevins et al. 2015). Symptoms are classified into four domains in accordance with the DSM-5 criteria for PTSD: re-experiencing, avoidance, negative changes in cognition and mood, and hyperarousal, with total PTSS score ranging from 0 to 80 and higher scores indicating more severe symptoms. The PCL-5 is regarded as the "benchmark" self-report measure of PTSD symptom severity, with strong test-retest reliability (r=0.84) as well as convergent and discriminant validity (Bovin et al. 2016; Harper et al. 2022; Keane et al. 2014).

The Life Events Checklist for DSM-5 (LEC-5) was used to assess participants' exposure to potentially traumatic events. The LEC-5 is a self-report measure comprising 17 items, each representing a different type of potentially traumatic event, such as natural disasters, accidents, and physical assault. Participants indicated whether each event happened to them personally, witnessed it, learned about it happening to a close family member or friend, was part of their job, or if they were unsure if it applied. The trauma load was calculated based on LEC-5 items that were not related to the CTQ and were associated with PTSD. Items 8 and 9, which pertain to sexual assault and other unwanted sexual activity, were excluded from the trauma load calculation due to their high correlations with the corresponding CTQ sexual

abuse items, suggesting significant overlap in assessing sexual trauma (CTQ sexual abuse & LEC-5 item 8; r=0.569, p<.001; CTQ sexual abuse & LEC-5 item 9; r=0.517, p< .001). The remaining 15 items were used to compute the trauma load (kindly see Table S5 below).

Table S5. Lists the specific LEC-5 items included in the trauma load computation.

	noPTSD	*PTSD*	*Difference*	*P value*
LEC_01 Natural Disaster	1.22 ± 1.28	1.04 ± 1.27	T = 0.766 (df= 117)	0.445
LEC_02 Fire or Explosion	1.27 ± 1.13	1.10 ± 1.23	T = 0.745 (df= 117)	0.458
LEC_03 Road Accident (Car, Ship, Train, Plane)	2.41 ± 1.55	2.43 ± 1.58	T = -0.070 (df= 117)	0.945
LEC_04 Serious Accident At Work, At Home Or During A Leisure Activity	1.57 ± 1.49	1.23 ± 1.25	T = 1.360 (df= 117)	0.176
LEC_05 Being Exposed To A Pollutant	0.55 ± 0.96	0.49 ± 0.85	T = 0.392 (df= 117)	0.696
LEC_06 Violent Attack	2.57 ± 1.58	2.60 ± 1.69	T = -0.093 (df= 117)	0.926
LEC_07 Attack With A Weapon	1.00 ± 1.12	1.33 ± 1.41	T = -1.358 (df= 117)	0.177
LEC_08 Sexual Assault	1.37 ± 1.44	3.09 ± 1.44	T = -6.403 (df= 117)	< .001 *
LEC_09 Other Unwanted Or Uncomfortable Sexual Activity	2.25 ± 1.74	3.16 ± 1.47	T = -3.088 (df= 117)	0.003 *
LEC_10 Engaged In Combat Or Being In A War Zone	0.67 ± 0.77	0.56 ± 0.69	T = 0.858 (df= 117)	0.393
LEC_11 Captivity	0.59 ± 0.71	0.67 ± 1.02	T = -0.474 (df= 117)	0.637
LEC_12 Life-Threatening Illness Or Injury	1.63 ± 1.42	1.96 ± 1.42	T = -1.226 (df= 117)	0.223
LEC_13 Severe Human Suffering	1.22 ± 1.37	1.97 ± 1.54	T = -2.719 (df= 117)	0.008 *
LEC_14 Sudden Violent Death (Murder, Suicide)	1.10 ± 1.09	1.41 ± 1.16	T = -1.483 (df= 117)	0.141
LEC_15 Sudden Accidental Death	0.90 ± 0.94	0.76 ± 0.89	T = 0.829 (df= 117)	0.409
LEC_16 Serious Injury, Damage Or Death Caused By You To Someone Else	0.51 ± 0.82	0.64 ± 1.02	T = -0.754 (df= 117)	0.452
LEC_17 Any Other Highly Distressing Event Or Experience	1.39 ± 1.74	1.23 ± 1.68	T = 0.500 (df= 117)	0.618
Overall trauma load (All items in LEC excluding items 8 and 9)	2.04 ± 1.53	2.33 ± 1.80	T = -1.309 (df= 117)	< 0.001 *

Note: Data are reported as mean ± standard deviation. df degree of freedom. *: Significant at P < 0.05 level.

The diagnostic interview sessions were conducted by research assistants and doctoral students who have received SCID-II training. The diagnoses that were assessed included affective disorders, anxiety disorders, obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD), attention deficit hyperactivity disorder (ADHD), and substance use disorder (SUD). Past and current disorders were diagnosed based on the presence of DSM-5 criteria for each disorder. Psychotic disorders were an exclusion criterion. For the current study, only the lifetime PTSD diagnostics (i.e., current and/or past) was used.

Termed here as the number of ACE-related traumas, we diagnosed participants with ACE-related PTSD. Participants were first asked to identify their three most ACE-related traumatic childhood experiences. Based on these specific traumatic events, the SCID-5 PTSD module was

then administered. By focusing on the identified childhood traumas, the SCID-5 PTSD module provided a comprehensive assessment of the participants' PTSD diagnosed directly related to their adverse childhood experiences. This approach ensured that the diagnosis was specifically linked to early life traumas, allowing for an accurate evaluation of number of ACE directly contributing to PTSD.

Imaging data preprocessing

Preprocessing for both T1-weighted (T1w), diffusion and resting-state fMRI images was performed using Connectome Mapper 3 (CMP-v3.1.0; an open-source Phython3 neuroimaging processing pipeline software developed by the Connectomics Lab, University Hospital of Lausanne (CHUV)). CMP-v3.1.0 uses a combination of well-known neuroimaging software packages to implement full anatomical and diffusion processing pipelines from raw images (Tourbier et al. 2022). All images were controlled for quality. The preprocessing steps that were used in this study can be seen below.

T1 weighted MRI: T1w images were preprocessed, parcellated, and segmented into 83 ROI based on the first scale of Lausanne 2008 parcellation (Cammoun et al. 2012) using the FreeSurfer version 6.0.1 recon-all program. An in-depth explanation of the steps used by FreeSurfer's recon-all has previously been described elsewhere (Dale et al. 1999; Fischl et al. 2004). In brief, the white matter and pial surfaces were identified after motion correction, non-uniform intensity normalization and normalization, by creating a mesh around the white matter and pial voxels. Surface-based maps of each individual scan were created using spatial intensity gradients across tissue classes (Desikan et al. 2006). FreeSurfer morphometric procedures have been demonstrated to show good test-retest reliability across scanner manufacturers and across field strengths (Reuter et al. 2012). Visual inspection was done to inspect the anatomical accuracy of FreeSurfer's automated parcellations and segmentations. The Lausanne scale-1 atlas used in this study has 83 regions similarly to FreeSurfer’s Desikan-Killiany Atlas (Cammoun et al. 2012; Hagmann et al. 2008).

Diffusion weighted MRI: Preprocessing of diffusion data included denoising, bias field correction, and corrections for eddy currents and motion, using advanced techniques available in the MRtrix toolbox (Tournier et al. 2019). Anatomy-constrained probabilistic tractography was performed using the five-tissue-type (5TT) segmented T1w image and a second-order integration over fibre orientation distributions algorithm on the preprocessed diffusion image to produce an initial tractogram with 10 million streamlines (Tournier and , F.

Calamante 2010). The tractogram was filtered using SIFT2 method to enhance the quantitative accuracy of whole-brain streamlines reconstructions (Smith et al. 2015). Structural connectivity measures i.e., number of fibres and normalized density of fibres between the 83 brain regions were subsequently retrieved.

Resting-state functional MRI: The resting-state fMRI data preprocessing followed a structured pipeline. After discarding the first 5 volumes for signal stabilization, we performed despiking using AFNI 3dDespike implemented in nipype (Gorgolewski et al. 2011) to remove noise and outliers. Slice timing correction was applied using FSL's slicetimer, followed by motion correction using FSL's MCFLIRT (Jenkinson et al. 2002). Linear registration from T1 to mean BOLD was achieved using FSL's flirt (Jenkinson et al. 2002). We detrended the BOLD signal to remove linear trends. Nuisance regression included CSF, WM, and motion parameters. Band-pass filtering was performed with a frequency window of 0.008 to 0.09 Hz, and ROI-averaged time-series were computed for positive and negative correlational connectivity for the 83 brain regions in Lausanne scale-1 as in dMRI pipeline.

Results

2.1 | Correlation between joint mixing coefficient (MC) and clinical data.

To provide additional context, we conducted Pearson correlation analyses between the joint mixing coefficient of IC9 and all clinical data, including PCL-5 and CTQ subscales. Bootstrapped corrected correlation coefficients with 5000 replicates were calculated. A supplementary table showing these correlation coefficients is presented below.

Table S6. Pearson's correlations between IC9 and all subscales of CTQ and PCL.

	Pearson's r	p	95% Confidence Interval		Effect size	SE Effect size
			Lower	Upper	(Fisher's z)	
IC9 - CTQ total	-0.275 *	0.021	-0.486	-0.021	-0.282	0.122
IC9 - CTQ_abuse	-0.319 **	0.007	-0.529	-0.068	-0.330	0.122
IC9 - CTQ_neglect	-0.146	0.227	-0.336	0.084	-0.147	0.122
IC9 - CTQ_EA	-0.177	0.142	-0.399	0.083	-0.179	0.122
IC9 - CTQ_PA	-0.292 *	0.014	-0.458	-0.104	-0.301	0.122
IC9 - CTQ_SA	-0.228	0.057	-0.445	0.023	-0.232	0.122
IC9 - CTQ_EN	-0.085	0.483	-0.293	0.152	-0.086	0.122
IC9 - CTQ_PN	-0.185	0.124	-0.355	0.026	-0.188	0.122
IC9 - PCL_SUM	-0.174	0.149	-0.380	0.056	-0.176	0.122
IC9 - PCL_INTRU	-0.105	0.389	-0.290	0.108	-0.105	0.122

IC9 - PCL_AVOID	-0.220	0.068	-0.434	0.014	-0.223	0.122
IC9 - PCL_COMO	-0.150	0.216	-0.385	0.110	-0.151	0.122
IC9 - PCL_HYPE	-0.160	0.185	-0.350	0.066	-0.162	0.122
IC9 - ACErelatedtrauma	0.048	0.695	-0.268	0.334	0.047	0.122

Note. $n_{(PTSD\ group)}$ = 70; CTQ total= total score of Childhood Trauma Questionnaire, CTQ_abuse= sum score of all abuse subtypes, CTQ_neglect= sum score of all neglect subtypes, CTQ_EA= emotional abuse, CTQ_PA= physical abuse, CTQ_SA= sexual abuse, CTQ_EN= emotional neglect, CTQ_PN= physical neglect, PCL_SUM= total PTSS, PCL_INRU= intrusive PTSS, PCL_AVOID= avoidance PTSS, PCL_COMO= negative changes in cognition and mood PTSS, PCL_HYPE= hyperarousal PTSS. number of ACE-related traumatic events Confidence intervals based on 5000 bootstrap replicates. * p < .05, ** p < .01, *** p < .001.

2.2 | Complementary checks for post-hoc analyses.

To confirm that the observed interaction effect is not a tautology or due to high between-variable correlation, we conducted thorough checks of correlation between clinical data, the Variance Inflation Factor (VIF) for all variables and analysed the change in R-squared between the models (see Models 1 to 4 in the Table S7 below). Only ACE severity (CTQ total) and PTSD symptoms severity score (PCL_sum) were significantly correlated (see Table S6). However, the VIF values for all variables in the model were below 1.5, indicating no concerns regarding multicollinearity (O'brien 2007). Additionally, the R-squared value increased from 7.5% in the linear model to 22% in the moderation model. This indicates that the interaction terms explained an additional 14.5% of the variation in the outcome variable, demonstrating a significant improvement in the predictive power of our model.

***Table S7*. Pearson's correlations between all clinical variables included in moderation analysis.**

	Pearson's r	p	95% Confidence Interval		Effect size (Fisher's z)	SE Effect size
			Lower	Upper		
CTQ total – PCL_SUM	0.516 ***	< 0.001	0.362	0.657	0.571	0.122
CTQ total – ACErelatedtrauma	0.181	0.133	-0.024	0.379	0.183	0.122
PCL_SUM – ACErelatedtrauma	0.122	0.313	-0.093	0.338	0.123	0.122

Note. $n_{(PTSD\ group)}$ = 70; CTQ total= total score of Childhood Trauma Questionnaire, PCL_SUM= total PTSS, PCL_INRU= intrusive PTSS, PCL_AVOID= avoidance PTSS, PCL_COMO= negative changes in cognition and mood PTSS, PCL_HYPE= hyperarousal PTSS, number of ACE-related traumatic events Confidence intervals based on 5000 bootstrap replicates. * p < .05, ** p < .01, *** p < .001.

Table S8. The relationship between ACE severity and joint mixing coefficient of IC9 as moderated by number of multiple ACE-related Trauma of the PTSD group

	Models			
	(1)	(2)	(3)	(4)
	joint mixing coefficient of IC9	joint mixing coefficient of IC9	joint mixing coefficient of IC9	joint mixing coefficient of IC9
ACE severity (CTQ total)	- .0002 * (-.0001)	.0003 ns (.0002)	.0001 ns (.0002)	-.0006* (.0003)
TC	-	.0291 ** (.0092)	-	.0280 ** (.0093)
Interaction 1: CTQ total X TC	-	-.0004 ** (.0001)	-	-.0003 ** (.0001)
PTSS	-	-	.0007 ns (.0005)	.0006 ns (.0005)
Interaction 2: PTSS X TC	-	-	.00001 ns (.000007)	.0000 ns (.0000)
Intercept	-.006 (.002)	-.0332 (.0152)	-.0122 (.0166)	-.0496 (.0202)
R^2 **R^2 change** **p-value**	.075 - .027	.1967 .1115 .0022	.1050 .0282 .0609	.2165 .1296 .0075
Collinearity Statistics (VIF)	CTQ total = 1	CTQ total = 1.034 TC = 1.034	CTQ total = 1.363 PTSS= 1.363	CTQ total = 1.390 TC = 1.035 PTSS= 1.365

Note: $n_{(PTSD\ group)}$=70; CTQ total = total score of Childhood Trauma Questionnaire; PTSS = PTSD symptomatology; TC = number of ACE-related traumatic event; VIF= Variance inflation factor. The values in the column of each model represent the unstandardized beta coefficients with their standard error in brackets. Asterisks indicate the statistical significance of the bootstrapped unstandardized regression coefficients (***p < .001; **p < .01; *p < .05; ns=not significant).

CHAPTER V: DISCUSSION

This study employed multimodal neuroimaging techniques to explore the effects of ACE and related PTSD using sMRI, dMRI, and resting-state fMRI in a large clinical sample. While multimodal neuroimaging offers significant potential, its application in ACE research has been limited due to data heterogeneity, complexity, and a lack of established cohesive analytical framework.

We showed potential multimodal biomarkers, including structural alterations in the right superior parietal lobe (rSPL) in individuals with ACE using complementary analysis of sMRI and dMRI. Additionally, we identified functional alterations in the default mode network (DMN), central executive network (CEN), and the inferior temporal brain regions, as well as structural alterations in the orbital frontal region, in individuals with ACE-related PTSD using the joint analysis of sMRI, dMRI and resting state fMRI data.

Subsequent sections of this chapter will focus on elaborating on the research questions of this empirical work and how findings from both publications addressed them.

5.1 What are the structural brain abnormalities in individuals with ACE as revealed by complementary analyses of sMRI and dMRI data?

The first study employed a complementary multimodal neuroimaging approach, combining T1-weighted MRI (sMRI) to assess cortical morphometry and dMRI to examine white matter microstructure. This approach enabled an encompassing investigation of how ACE impacts GM regions and white matter tracts. By combining these modalities, the study was able to reveal brain alterations in response to ACE, particularly the relationship between cortical volume changes in the rSPL and WM tracts connected to rSPL and childhood abuse.

In our whole brain analyses, we found that the cumulative effect of ACE was associated with reduced local cortical area in the rSPL. Childhood abuse was negatively related to local cortical volume in the rSPL when controlled for childhood neglect. However, no significant result was found for neglect when abuse was controlled for. These findings imply that the effects of ACE were more pronounced for abuse than neglect in our sample particularly in terms of cortical volume of the rSPL. The rSPL forms part of the posterior-FPN and plays a key role in the “top-down” or goal-driven allocation of attention. Cytoarchitectonic research has demonstrated the heterogeneous nature of the SPL, with at least seven distinct subregions. The receptor distribution patterns and regional cytoarchitectonic features found three sub-

regions in Brodmann (BA) 5 and four in BA 7 (Scheperjans et al. 2005; Scheperjans et al. 2008). Functions of these regions were explored in a resting-state functional MRI study in healthy participants, and the results showed that each of the seven sub-regions was connected to several resting-state networks, with the most consistent connectivity observed with the visual and attention networks (Alahmadi 2021). While abnormalities in the rSPL have been associated with PTSD, PTSS and maternal stress (McQuaid et al. 2019a; Wang et al. 2021), the findings of this study suggest that ACE may specifically target cortical alterations in the rSPL, potentially impacting visual and attentional functions (Nkrumah et al. 2024b). Further exploratory analyses demonstrate that the rSPL serves as a key mediator in the relationship between childhood abuse and avoidance-related PTSD symptoms. This suggests that the rSPL plays a pivotal role in the development of avoidance behaviours in individuals with ACE. Consistent with a previous large-scale meta-analysis linking reduced rSPL volumes to PTSD (Wang et al. 2021), our results provide additional evidence that the rSPL may be a critical factor in the emergence of avoidance symptoms in individuals with a history of severe childhood abuse (Auxéméry 2018; Nkrumah et al. 2024b; Tan et al. 2013).

Additional analyses of WM tracts connected to the rSPL revealed a positive correlation between the extent of abuse-related cortical alterations in rSPL volume and the number, average length, and mean fractional anisotropy (FA) of these WM tracts (see Table 6). These findings suggest that as the impact of childhood abuse on rSPL volume increases, so does the negative effect on the microstructure of WM tracts connected to this region. This further highlights the structural abnormalities in both GM and WM within the rSPL, which are likely consequences of childhood abuse.

Overall, our findings from the CoMNA study contribute to a growing body of literature on the neurobiological consequences of ACE and emphasize the importance of considering the subtypes of maltreatment when investigating brain abnormalities (Grauduszus et al. 2024; Herzog and Schmahl 2018; Schalinski et al. 2016). By targeting the rSPL, future research and clinical interventions could potentially address the development of avoidance symptoms in individuals with ACE (Teicher et al. 2022). For example, interventions that focus on enhancing the connectivity between the rSPL and other brain regions involved in attention and emotional regulation, such as the dorsolateral prefrontal cortex (DLPFC) and limbic regions, may be particularly beneficial in addressing the cognitive and emotional challenges faced by individuals with ACE (Samson et al. 2024).

5.2 Structural and functional brain connectivity disruptions in ACE-related PTSD as revealed by the joint analyses of sMRI, dMRI and rs-fMRI.

The second study conducted a joint connectivity matrix independent component analysis (jcm-ICA) of sMRI, dMRI, and rs-fMRI at the connectivity level to identify distinct patterns of connectivity in individuals with PTSD as a result of ACE (Nkrumah et al. 2024a). This advanced technique enabled the simultaneous analysis of multiple neuroimaging modalities, revealing shared and distinct patterns of brain connectivity associated with ACE-related PTSD. Several key brain regions involved in self-referential processing, cognitive control, and social behaviour demonstrated significant neurobiological differences between individuals with ACE-related PTSD and ACE-exposed controls.

In terms of functional connectivity, individuals with PTSD exhibited hypoconnectivity in the lateral prefrontal cortex (lPFC), a region associated with cognitive flexibility and decision-making (Cole et al. 2014), compared to ACE-exposed controls. Consistent with other studies (Cisler and Herringa 2021; Olson et al. 2019; Zhu et al. 2023), this may explain why individuals with PTSD struggle to adapt their thoughts and behaviours in response to changing situations. Contrariwise, hyperconnectivity was observed in the right medial prefrontal cortex (rmPFC), involved in self-referential processing (Horn et al. 2014), and the right inferior temporal gyrus, involved in face perception and recognition (Tromans et al. 2012). Increased connectivity in the rmPFC may reflect an enhanced focus on internal experiences, such as rumination and intrusive thoughts related to past trauma (Harnett et al. 2021; Olson et al. 2019; Valencia et al. 2024). Hyperconnectivity in the right inferior temporal gyrus may suggests heightened neural responsiveness to visual stimuli, particularly emotional faces, which may contribute to the re-experiencing of traumatic memories (Cisler and Herringa 2021; Spielberg et al. 2015; Wang et al. 2016).

Additionally, the JoMNA study examined structural connectivity, focusing on the number of fibres and the normalized fibre density (NFD) of white matter pathways connecting brain regions. Individuals with PTSD showed reduced NFD in the right orbitofrontal cortex (rOFC), a region implicated in social behaviour and emotional regulation (Eluvathingal 2006). This suggests alterations in the microstructure of WM tracts connecting the rOFC may impact the ability of individuals with ACE-related PTSD to regulate emotions and interact effectively with others (Choi et al. 2019; Eising et al. 2021; Samson et al. 2024; Watts et al. 2021).

Overall, these findings provide insights into the neurobiological consequences of ACE-related PTSD and highlight the potential for targeting these brain regions in future

interventions (Cisler and Herringa 2021; Wang et al. 2016). By understanding the specific brain alterations associated with ACE and PTSD, clinicians can develop more effective treatments to address the cognitive, emotional, and social challenges faced by individuals with these conditions.

5.3 Potential multimodal neuroimaging biomarkers in understanding the neurobiological underpinnings of ACE and related PTSD.

Multimodal neuroimaging techniques, such as CoMNA and JoMNA, are essential for advancing our understanding of the neurobiological underpinnings of ACE and related mental health outcomes such as PTSD. By providing a more comprehensive examination of brain changes associated with ACE, these methods can help us to develop more targeted and effective interventions to prevent and treat PTSD resulting from childhood trauma.

Both CoMNA and JoMNA studies employed in this work underscore the importance of multimodal neuroimaging (MN) in revealing potential brain biomarkers that enhance our understanding of the neurobiological underpinnings of ACE and related mental health outcomes. By combining multiple imaging modalities, these approaches provide a more comprehensive representation of brain structure and function in individuals exposed to ACE and PTSD.

The findings from the first study suggest that alterations in cortical volume and white matter integrity in the rSPL may serve as potential biomarkers for PTSD avoidance symptoms following childhood abuse. This narrows the focus of prior research perspective which highlighted the diversity in therapeutic responses among individuals with histories of childhood maltreatment and a range of psychopathologies, including mood disorders, anxiety, depression, and PTSD (Nanni et al. 2012; Thomas et al. 2019). For instance, it is well-documented that depressed individuals with a history of ACE frequently exhibit poor responses to treatment and are at significantly higher risk for developing recurrent and persistent depressive episodes (Nanni et al. 2012). From this perspective, Frodl et al. (2010), suggested that trauma-related structural changes in the prefrontal cortex (PFC) and hippocampus could mediate the development of depressive and anxiety-related disorders in individuals with a history of childhood trauma (Frodl et al. 2010). The CoMNA study's findings add specificity to this body of work, emphasizing the role of the rSPL in PTSD avoidance symptoms rather than in broader psychopathology. This refinement enhances our understanding of symptom-specific neural alterations related to ACE and associated mental health outcomes. Given the growing evidence that individuals with ACE often show distinct

clinical trajectories (Teicher et al. 2022; Teicher and Samson 2013), the CoMNA findings underscore the critical need for identifying neurobiological markers, such as those in the rSPL, to better inform personalized treatment strategies. Such biomarkers have the potential to tailor interventions according to the unique neurodevelopmental impacts of childhood maltreatment and the development of PTSD later in life.

The second study further identifies potential MN connectivity disruptions in key brain networks associated with cognitive functioning, emotional processing, and social behaviour in individuals with ACE-related PTSD. The involvement of these brain networks is particularly relevant given their established roles in trauma-related psychopathology (Aruldass and Daskalakis 2023; Harnett et al. 2021; Lanius et al. 2015). For instance, previous studies such as those by Harnett et al., (2021) found that altered resting-state functional connectivity in the PFC at two weeks post-trauma was negatively related to PTSD symptoms at three months, leading to difficulties in cognitive functioning and exacerbating PTSD symptoms. Similarly, the same study reported significant alterations of FC between the right inferior temporal gyrus and DMN. The JoMNA findings regarding hyperconnectivity in the mPFC aligns with this, suggesting that trauma-exposed individuals may experience overactivation in this region, leading to persistent intrusive thoughts and hypervigilance. In addition to our observed functional dysconnectivity in the lPFC, the structural connectivity findings in OFC could highlight potential MN biomarkers that could inform neuroscientifically driven interventions aimed at addressing abnormalities in prefrontal brain regions in individuals with PTSD and ACE. For example, individuals showing specific connectivity disruptions in the mPFC or lPFC may benefit from interventions targeting emotional regulation and cognitive control, while those with more pronounced white matter damage in the OFC may require therapies focused on enhancing neuroplasticity in the frontal brain regions (Ireton et al. 2024; Samson et al. 2024; Teicher et al. 2022). The integration of MN biomarkers into clinical practice could pave the way for highly individualized interventions, improving treatment efficacy and potentially reducing the long-term burden of mental health disorders stemming from childhood maltreatment.

In conclusion, the findings from these two studies offer compelling evidence of the long-lasting effects of ACE on brain structure and function. By examining both structural and functional changes, the studies provide a more comprehensive understanding of the neurobiological consequences of early adversity and PTSD. Importantly, these results have significant implications for developing targeted interventions to address the mental health

challenges associated with ACE, particularly in brain networks such as the DMN, CEN, SN, and regions like the inferior temporal cortex, SPL and orbitofrontal cortex (Lanius et al. 2015). Addressing these neurobiological disruptions may enhance therapeutic precision and efficacy for individuals impacted by childhood trauma.

5.4 Prospective applications and future direction of multimodal neuroimaging in ACE research.

MN offers significant potential for advancing our understanding of the neurobiological underpinnings of ACE and related mental health disorders. By combining multiple imaging modalities—such as structural MRI, functional MRI, diffusion MRI, and others—MN can provide a more comprehensive view of the brain's structural and functional changes associated with ACE. This comprehensive approach opens numerous potential applications, from early diagnosis to prognosis, and personalized treatment strategies aimed at mitigating the long-term effects of ACE.

Looking at the rich information provided by a few longitudinal studies and several cross-sectional unimodal studies which tend to focus on either structural or functional changes in isolation (Teicher et al. 2020; Teicher et al. 2022; Teicher and Samson 2016), it may be beneficial to implement larger, multisite, and multimodal studies (Spisak et al. 2023). These large-scale studies could significantly enhance the richness of available data by gathering information from diverse populations across multiple research sites (Koutsouleris and Fusar-Poli 2024), improving both the power and reliability of findings from MN research (Spisak et al. 2023). This diversity in MN data would also allow researchers to examine variations in the prevalence and severity of ACE, as well as how different types of childhood maltreatment influence neurodevelopment at several scales and mental health outcomes. Furthermore, larger, multisite and MN studies in ACE would provide stronger statistical power and greater generalizability, ensuring that findings are more robust and applicable across different demographic groups and environments (Dwyer et al. 2018; Koutsouleris et al. 2016; Nichols et al. 2017; Pomponio et al. 2020; Spisak et al. 2023). With access to data from various imaging modalities, such studies could better investigate the complex neurobiological pathways involved in ACE, ultimately offering more comprehensive insights into more specific, personalized treatment strategies aimed at mitigating the long-term effects of ACE.

Another key advantage and potential application of MN in ACE research is the rich information provided by the individual modalities and the ability to extract multimodal biomarkers from MN data. This could be done using data-driven methods. Unlike the model-

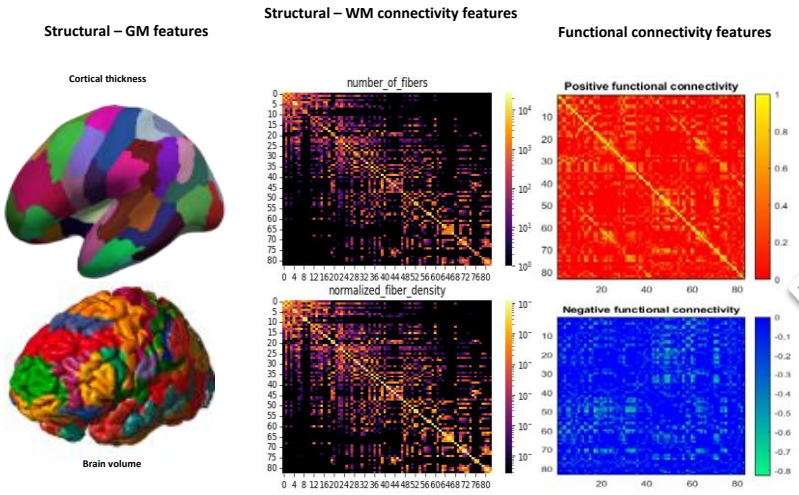
driven approaches mostly applied in several neuroimaging research (including that on ACE), which rely heavily on predefined hypotheses about brain region interactions (e.g., general linear models, dynamic causal modelling, or structural equation modelling), data-driven methods offer a more exploratory approach (Calhoun and Sui 2016). Another important factor is that model-driven methods may overlook important relationships not included in the initial hypotheses. Using data-driven methods, such as machine learning and multivariate methods, we could identify structural, functional, and connectivity features from multiple modalities. This could be done using techniques such as independent component analysis (ICA) and principal component analysis (PCA), which enable us to explore the entire dataset across all voxels, providing a broader, more comprehensive view of the brain's structural, functional, and connectivity features. For example, in our second study, we used PCA and jICA to identify features across multiple modalities, demonstrating the ability of data-driven approaches to detect neurobiological changes. In a large population or multisite and multimodal samples, these features could serve as MN biomarkers because they offer optimal information about the population without requiring prior knowledge.

These MN biomarkers could be complemented by utilizing full images to build a joint dataset that includes both extracted features and the full imaging data, providing a more comprehensive view (kindly see Figure 12A below). The combined dataset can then be used to build predictive models with robust cross-validation techniques, which have great potential to distinguish between individuals at higher or lower risk for mental health disorders following childhood maltreatment. These predictive models would integrate a wide range of factors, from brain volume and white matter microstructure to functional connectivity patterns and epigenetic, and psychometric data such as overall psychosocial burden, allowing for a more holistic view of mental health. By incorporating these biomarkers into predictive models, researchers can develop tools that accurately identify individuals who are most likely to develop psychopathology, such as PTSD, depression, or anxiety, in response to ACE (Teicher et al. 2022). This approach is also geared towards advancing precision psychiatry, enabling the tailoring of treatment approaches based on an individual's specific neural profile, ultimately improving intervention outcomes and reducing the long-term burden of ACE-related mental health disorders (Kéri et al. 2024; Koutsouleris and Fusar-Poli 2024; Spisak et al. 2023). The proposed framework for potential future application of MN in mega, multi-site and ACE studies can be found in the Figure 12 below. Applications at the clinical level can be done either using individual fully-processed image or multimodal data (see Figure 12C below).

In conclusion, MN represents a transformative tool in ACE research, offering comprehensive insights into the neurobiological pathways affected by early trauma. By combining data from multiple imaging modalities, MN enables a more nuanced understanding of how ACE alters brain structure and function, as well as how these changes relate to mental health outcomes. The potential clinical applications of MN are vast, ranging from using MN data to build predictive models for early diagnosis and prognosis to applying these models in personalized treatment strategies, all aimed at mitigating the long-term effects of ACE. Furthermore, an improved understanding of the neurobiological development and progression of mental health disorders through MN findings can guide public health interventions. This knowledge can support early screening initiatives for at-risk individuals and inform community-based prevention programs to help reduce mental health risks associated with ACE. As the field advances, larger, multisite, and multimodal studies will be critical for shaping the future of ACE research, ultimately improving mental health outcomes for those affected by childhood maltreatment.

A

Extraction of multimodal biomarkers



MN Biomarkers extracted using data driven methods (e.g. PCA, ICA, CCA)

Genetic and psychometric data

B

Building predictive models

- Preprocess: regress out nuisance covariates, standardize data, scale data
- Model training and optimization to predict individual psychopathology or symptomology or both :
  - Cross-validation: nested cross-validation framework
  - Training and Learning algorithm: unsupervised and supervised (e.g. SVM-lin/rbf, GB)
  - Access accuracy of prediction / Model prediction performance
- Initial model application

C

Clinical model application

Raw / processed unimodal data → Optimal predictive model → Risk for mental health disorders following childhood maltreatment → Tailored treatment

Figure 12. Proposed framework for multimodal brain data-based prediction: from research to clinic. Data driven methods to extract multimodal biomarkers: PCA (Principal Component Analysis), ICA (Independent Component Analysis) and CCA (Canonical Correlation Analysis). Machine Learning Algorithms for building predictive models: SVM (Support Vector Machine) using SVM-lin: Linear kernel or SVM-rbf: Radial Basis Function kernel and GB (Gradient Boosting). The best-performing model or an average of a set of models from (B) would be selected as the optimal model.

5.5 **Limitations**

Despite the strengths of this work, several limitations should be acknowledged. While specific limitations have been discussed in individual chapters, there are also some general limitations that highlight opportunities for future research.

Sample Size:

The relatively small sample size, particularly in Study 1 (n=78), may limit the generalizability of our findings. While Study 2 (n=119) offers a larger sample size, even larger samples, as proposed in section 5.4, would further improve the statistical power of our analyses and the accuracy of our predictions. This would allow for a more comprehensive analysis across diverse populations and enhancing the generalizability of our findings. Such improvements are important for characterizing individual differences and refining multimodal biomarkers, ultimately contributing to more precise models better suited for potential clinical applications. A recent publication by Bhaumik et al. (2023), conducted a simulation study covering the whole brain with 87 regions to determine the power associated with commonly used sample sizes in neuroimaging studies. Their findings suggest that a sample size of 60 is adequate to achieve a power of 0.80. Although both of our studies exceed this threshold, increasing the sample size through a multicentre, multimodal approach would further strengthen our results and allow for a more robust investigation of individual differences and the development of more precise biomarkers.

Causality

The cross-sectional design of both studies precludes causal inferences regarding the relationship between ACE, brain abnormalities, and PTSD. Additionally, both cross-sectional studies rely on retrospective reports of childhood adversity, and while they assume that ACE has a causal effect on later outcomes, this assumption cannot be rigorously tested within the constraints of our current study design. Despite this limitation, self-report measures are widely used in ACE research as they offer valuable insights into individuals' subjective experiences (Danese and Widom 2023; Danese and Widom 2024; Kendall-Tackett 2024). For example, subjective reports of ACE have been shown to have a stronger association with emotional disorders in adulthood than objective assessments (Danese and Widom 2023). This suggests that self-reported adversity may also be more closely linked to brain alterations, as it captures personal context and perceived impact of early-life trauma. While our cross-sectional studies provide a valuable insight, further longitudinal studies are necessary to

establish the temporal dynamics of these changes and determine whether brain alterations precede or follow the development of PTSD.

Neurobiological Mechanisms

Multimodal neuroimaging provides valuable insights into brain structure and function, but it does not fully capture the complexities of the mechanisms underlying ACE and PTSD. Neuroimaging alone lacks the capacity to account for the interplay of genetic and epigenetic factors alongside the cumulative impact of environmental influences, all of which collectively shape neurodevelopmental pathways and affect susceptibility to mental health conditions like PTSD following childhood maltreatment (Teicher and Samson 2016). Genetic factors, such as variations in genes related to the hypothalamic-pituitary-adrenal (HPA) axis, have been linked to altered stress responses and emotional regulation, potentially increasing PTSD risk in certain individuals (Aliev et al. 2020; Naninck et al. 2015). Additionally, epigenetic modifications—such as DNA methylation changes in response to environmental stressors—add further complexity to this relationship, as these modifications dynamically influence gene expression and may contribute to the neural adaptations observed in ACE survivors (Colich et al. 2020; Vasquez and Renault 2015; Weder et al. 2014). Moreover, environmental factors, including socioeconomic status, quality of social support, and cumulative lifetime stress, also interact with genetic and epigenetic variables, creating a complex framework of neurobiological responses to ACE. As proposed in Figure 12, integrating genetic, epigenetic, and environmental data with multimodal neuroimaging may offer a more comprehensive understanding of how these factors collectively influence brain structure and function in individuals with ACE. Such an integrative approach holds promise for developing more accurate predictive models, enhancing the translation of research findings into effective intervention and treatment strategies.

Methodological Considerations

While multimodal neuroimaging offers a comprehensive approach to understanding brain function and structure, it is not without limitations. For example, the different imaging modalities often have varying spatial and temporal resolutions and produce data in different scales and formats, which complicates data integration and interpretation. Recent developments in MN data registration (Lange et al. 2024), data processing (Tourbier et al. 2022) and cohesive analytical frameworks (Koutsouleris et al. 2023; Qu et al. 2024) have led to significant progress in addressing these challenges, enabling the effective integration and

interpretation of diverse multimodal neuroimaging datasets. However, further advancements in computational methods are still needed to fully harness the potential of multimodal neuroimaging and extract meaningful insights.

By addressing these limitations and exploring new avenues of research, future studies can contribute to a more comprehensive understanding of the neurobiological underpinnings of ACE and PTSD and inform the development of more effective prevention and treatment strategies.

5.6 **Clinical Applications**

Building upon the proposed framework highlighted in section 5.4 above, the application of MN and predictive models has the potential to transform the management of mental health outcomes in individuals with a history of ACE (Chopra et al. 2024a; Lee et al. 2024; O'Halloran et al. 2016; Tejavibulya et al. 2022). These models, in addition to multimodal neuroimaging data, can incorporate clinical and demographic information to identify individuals at high risk of developing mental health disorders following childhood maltreatment. By identifying individuals at risk early on, targeted interventions could be implemented to prevent or mitigate the development of psychopathology such as PTSD. In addition to risk assessment, predictive models can serve several critical functions in clinical practice:

Tailor treatment approaches

Predictive models could link specific neurobiological markers to distinct psychopathologies, enabling the design of personalized treatment plans (Bzdok and Meyer-Lindenberg 2018; Chopra et al. 2024b). This precision approach ensures that therapeutic interventions align with the unique neurobiological and psychological needs of each individual, enhancing treatment efficacy.

Monitor treatment response

By leveraging longitudinal MN data, predictive models can track changes in brain structure and function over the course of treatment (Jin et al. 2021). This capability could allow clinicians to evaluate the effectiveness of interventions, refine therapeutic strategies, and make data-driven adjustments to optimize patient outcomes. For example, treatment-response models using linear time-invariant dynamical systems can be used effectively represent continuously varying treatment doses and their effects on outcomes over time (Soleimani et al. 2017).

Identify early signs of relapse

By monitoring for changes in neurobiological markers, predictive models could help identify individuals who may be at risk for relapse, allowing for early intervention to prevent symptoms recurrence. For example, recent research has explored biological factors that may enhance relapse prediction, including endocrine measures like cortisol levels and neurobiological markers such as brain atrophy in medial frontal regions (Ansell et al. 2012; Moeller et al. 2016; Sinha 2011). Integrating these biological markers with traditional symptom monitoring could potentially improve the accuracy of relapse prediction.

Integrating MN and predictive modelling into clinical practice could transform personalized psychiatry and improve outcomes for those with ACE.

CHAPTER VI: SUMMARY

This work focuses on the application of multimodal neuroimaging (MN) to investigate the neurobiological underpinnings of ACE and related PTSD. By combining multiple neuroimaging modalities, the research provides a more comprehensive understanding of the brain changes associated with childhood maltreatment and the development of PTSD.

Key findings include:

- Identification of potential neurobiological markers: The studies have identified alterations in specific brain regions, such as the right superior parietal lobule that may serve as potential biomarkers for PTSD avoidance symptoms following child abuse.
- Disruption of brain networks: Disruptions in key brain networks involved in cognitive control, emotional processing, and social behaviour have been observed in individuals with ACE-related PTSD.
- Development of predictive models: The research has laid the groundwork for building predictive models that could be used to identify individuals at risk for psychopathology and tailor treatment approaches.

Based on these findings, a framework for future research applications is proposed, including:

- Larger, multisite, and multimodal studies: To enhance the generalizability and statistical power of the findings.
- Predictive modelling: To develop tools for identifying individuals at risk and tailoring treatment approaches.
- Clinical applications: To improve intervention outcomes and reduce the long-term burden of ACE-related mental health disorders.

Overall, this work contributes to a growing body of evidence on the neurobiological consequences of ACE and highlights the potential of MN to inform the development of more effective prevention and treatment strategies. MN has the potential to enhance the way we understand and treat ACE-related mental health disorders. By providing a more comprehensive and nuanced picture of brain changes associated with ACE, MN can help us to identify individuals at risk, predict symptom severity, and tailor interventions to the specific needs of each individual.

Die vorliegende Arbeit konzentriert sich auf die Anwendung multimodaler Neuroimaging (MN) Methoden und Analysen, zur Untersuchung der neurobiologischen Grundlagen von aversiven Kindheitserfahrungen (Adverse Childhood Experiences, ACE) und der damit verbundenen Posttraumatische Belastungsstörung (PTSD). Durch die Kombination mehrerer Bildgebungsmodalitäten liefert diese Methode ein umfassenderes Verständnis der Veränderungen im Gehirn mit Kindesmisshandlung und der Entwicklung von PTSD verbundenen sind.

Zu den wichtigsten Erkenntnissen gehören:

- Identifizierung potenzieller neurobiologischer Marker: Die Analysen haben Veränderungen in bestimmten Gehirnregionen identifiziert, wie beispielsweise den rechten superioren Parietallappen, die als potenzielle Biomarker für Vermeidungssymptome von PTSD nach Kindesmissbrauch dienen könnten.

- Veränderung von Gehirnnetzwerken: Störungen in wichtigen Netzwerken des Gehirns, die an kognitiver Kontrolle, emotionaler Verarbeitung und sozialem Verhalten beteiligt sind, wurden bei Personen mit ACE-bezogener PTSD beobachtet.

- Entwicklung von Vorhersagemodellen: Diese Untersuchung hat den Grundstein für den Aufbau von Vorhersagemodellen gelegt, die zur Identifizierung von Personen mit hohem Risiko für Psychopathologie und zur Anpassung von Behandlungsansätzen eingesetzt werden könnten.

Basierend auf diesen Erkenntnissen wird ein Rahmen für zukünftige Forschungsanwendungen vorgeschlagen, einschließlich:

- Größere, multizentrische und multimodale Studien: Um die Generalisierbarkeit und statistische Aussagekraft der Ergebnisse zu erhöhen.

- Vorhersagemodellierung: Um Tools zur Identifizierung von Risikopersonen und zur Anpassung von Behandlungsansätzen zu entwickeln.

- Klinische Anwendungen: Um die Behandlungsergebnisse zu verbessern und die langfristige Belastung durch ACE-bedingte psychische Störungen zu reduzieren.

Insgesamt trägt diese Arbeit zu einem wachsenden Wissensstand über die neurobiologischen Folgen von ACE bei und unterstreicht das Potenzial von MN für die Entwicklung effektiverer Präventions- und Behandlungsstrategien. MN hat das Potenzial, die Art und Weise, wie wir ACE-bedingte psychische Störungen verstehen und behandeln, zu verbessern. Durch ein umfassenderes und differenzierteres Bild der mit ACE verbundenen Gehirnveränderungen kann MN dazu beitragen, Risikopersonen zu identifizieren, die Schwere von Symptomen vorherzusagen und Interventionen auf die spezifischen Bedürfnisse jedes Einzelnen abzustimmen.

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CURRICULUM VITAE

PERSONAL

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EDUCATION

August, 2020 to date	Doctoral Candidate at Medical Faculty Mannheim, Heidelberg University.
September, 2018 – September, 2019	MSc Neuroimaging from King's College London.
September, 2013 – July,2017	BSc. Physics (Biomedical Physics) from Kwame Nkrumah University of Science and Technology, Kumasi-Ghana.

RESEARCH EXPERIENCE

PhD research	Exploring the effect of adverse childhood experience on the brain using the joint analyses of multimodal neuroimaging data. (August, 2020 - Present)
Post MSc	"Imaging of the Cerebellum at UHF MRI" (December, 2019)
MSc Projects	"The impact of early life institutional deprivation on brain structure at young adulthood— A Diffusion Tensor Based Morphometry Study" (September, 2019).
	"Facial features role in house processing – An empirical fMRI review" (May, 2019).
BSc Project	"Shielding of Multi-Detector CT Rooms: Comparison of DIN, NCRP and BIR Approaches." (May, 2017)

SCHOLARSHIPS, GRANTS & AWARDS

Heidelberg University Graduate Academy Scholarship for the promotion of early career researchers (1000€)

Grant of from the GRK2350 to explore resting state networks in ACE using data from A1 and B5 (500€)
Grant of from the International Society for Magnetic Resonance in Medicine (500€)

SOCIETIES

Member of the International Society for Magnetic Resonance in Medicine
Member of the Organization for Human Brain Mapping
Member of the European College of Neuropsychopharmacology

INTERNATIONAL CONFERENCES/WORKSHOPS:

“2024 OHBM Annual Meeting & Exhibition” 23-27 June, 2024 in Seoul.
“Junior Researcher Symposium on Translational Cognitive Neuroscience of Trauma and Affective Disorders” July, 2023 at King's College London.
“2023 ISMRM & ISMRT Annual Meeting & Exhibition” 6-9 June, 2023 at Metro Toronto Convention Centre (MTCC), Toronto, ON, Canada.
“DeGPT congress 2024” 23 February, 2024 in Vienna, Australia
“ISMRM Workshop on Diffusion MRI: From Research to Clinic.” 10-14 October, 2022 at Amsterdam.
“Combining Magnetic Resonance and Artificial Intelligence” organized by BC-ISMRM on 11th July, 2019 at London.
“CogX 2019” organized by the CogX group on 10th June 2019 to 13th June 2019 at London.

CERTIFICATES

Certificate of Participation: ISMRM Workshop on Diffusion MRI: From Research to Clinic.
Certificate of Award to the Commonwealth Masters’ Shared Scholarship Scheme, 2018/2019.
Certificate of Participation, International Day for Medical Physics, Accra-Ghana, November 2016. Organized by Ghana Society for Medical Physics.

PUBLICATIONS

* First-authorships

Nkrumah, R. O.*, Demirakca, T., von Schröder, C., Zehirlioglu, L., Valencia, N., Grauduszus, Y., Vollstaedt-Klein, S., Schmahl, C., & Ende, G. *(accepted on 9th November 2024 at the European journal of psychotrauma*). Brain connectivity disruptions in PTSD related to early adversity: a multimodal neuroimaging study.

von Schröder, C., **Nkrumah, R. O**., Demirakca, T., Schmahl, C., & Ende, G. *(accepted for publication at Scientific report*). Dissociative Experiences Alter Resting State Functional Connectivity after Childhood Abuse.

Valencia, N., Seeger, F. R., Seitz, K. I., Carius, L., **Nkrumah, R. O**., Schmitz, M., Bertsch, K. and Herpertz, S. C. (2024). Childhood maltreatment and transdiagnostic connectivity of the default-mode network: The importance of duration of exposure. J Psychiatr Res 177, 239–248, https://doi.org/10.1016/j.jpsychires.2024.07.022

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Priovoulos, N., Roos, T., Ipek, Ö., Meliado, E., **Nkrumah, R.,** Klomp, D. and Zwaag, W., 2021. A local multi-transmit coil combined with a high-density receive array for cerebellar fMRI at 7 T. NMR in Biomedicine. https://doi.org/10.1002/nbm.4586

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