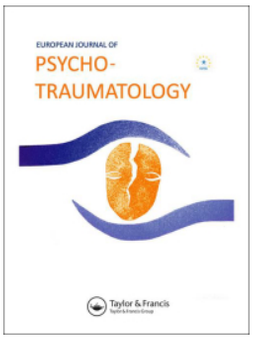

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STUDY PROTOCOL

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A biobank for complex post-traumatic stress disorder (C-PTSD) and PTSD: study protocol for a cross-sectional study

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ABSTRACT

Background Complex Post-Traumatic Stress Disorder (C-PTSD) is a severe mental illness recently defined in the International Classification of Diseases 11th edition. In addition to the classic PTSD symptoms of avoidance, re-experiencing, and hypervigilance, it includes disturbances in emotion regulation, negative self-concept, and interpersonal relationships. Emerging evidence suggests C-PTSD has distinct neurobiological profiles compared to PTSD, but comprehensive investigations are lacking. This study aims to explore the neural mechanisms associated with C-PTSD, identifying distinct and shared brain alterations in C-PTSD and PTSD, while establishing a biobank incorporating neuroimaging, inflammatory, physiological, genetic, and psychosocial measures.

Methods This cross-sectional study will compare three groups: individuals with C-PTSD ($n = 40$), PTSD ($n = 30$), and trauma-exposed healthy controls ($n = 30$). During a single visit, participants will undergo MRI scanning including structural, diffusion-weighted, resting-state, and task-based functional MRI. Blood samples will be collected for inflammatory marker analysis, and Genome-Wide Association Studies (GWAS). Participants will complete validated psychosocial self-report measures assessing trauma history, resilience, social support, emotion regulation, sleep quality, and mental health symptoms. Additionally, participants will wear an Actigraph smart watch for seven days to collect actigraphy-derived physiological data, including sleep patterns and heart rate variability. All de-identified data will be made openly available on the Open Science Framework upon publication of the main study findings, in accordance with ethical approvals and institutional guidelines for privacy and data security.

Conclusion This comprehensive protocol addresses significant gaps in understanding C-PTSD through its multimodal approach. By comparing C-PTSD, PTSD, and trauma-exposed controls, the study aims to identify neurobiological markers specific to C-PTSD, potentially supporting its diagnostic distinction and informing targeted treatment approaches. Integrating neuroimaging, inflammatory, genetic, and psychophysiological measures acknowledges the complex interactions between biological systems in trauma responses. Findings may help inform future research on personalized intervention strategies by identifying potential biological profiles and resilience factors associated with trauma-related outcomes.

Biobanco para el trastorno de estrés postraumático complejo (tept-c) y tept: protocolo de estudio para un estudio transversal

Antecedentes El Trastorno de Estrés Postraumático Complejo (TEPT-C) es una enfermedad mental grave, definida recientemente en la 11.ª edición de la Clasificación Internacional de Enfermedades. Además de los síntomas clásicos del TEPT (evitación, reexperimentación e hipervigilancia), incluye alteraciones en la regulación emocional, un autoconcepto negativo y en las relaciones interpersonales. La evidencia emergente sugiere que el TEPT-C presenta perfiles neurobiológicos distintos en comparación con el TEPT, pero se carece de investigaciones exhaustivas. Este estudio tiene como objetivo explorar los mecanismos neuronales asociados con el TEPT-C, identificando alteraciones cerebrales distintas y compartidas entre TEPT-C y TEPT, a la vez que se establece un biobanco que incorpora medidas de neuroimagen, inflamatorias, fisiológicas, genéticas y psicosociales.

Métodos Este estudio transversal comparará tres grupos: personas con TEPT-C ($n = 40$), TEPT ($n = 30$) y controles sanos expuestos a trauma ($n = 30$). Durante una sola visita, los participantes se someterán a resonancias magnéticas que incluyen resonancia magnética estructural, ponderada por difusión, en estado de reposo y funcional basada en tareas. Se recolectarán muestras de sangre para el análisis de marcadores inflamatorios y estudios de asociación del genoma completo (GWAS, por sus siglas en ingles). Los participantes completarán autoinformes psicosociales validados que evalúan el historial de trauma,

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KEYWORDS

Complex post-traumatic stress disorder (C-PTSD); PTSD; neuroimaging; inflammation; genetics; biomarkers; sleep; heart rate variability; emotion regulation; trauma

PALABRAS CLAVE

Trastorno de Estrés Postraumático Complejo (TEPT-C); TEPT; neuroimagen; inflamación; genética; biomarcadores; sueño; variabilidad de la frecuencia cardíaca; regulación emocional; trauma

HIGHLIGHTS

- This study protocol describes the creation of a biobank to investigate the biological and psychological mechanisms underlying complex post-traumatic stress disorder (C-PTSD) and post-traumatic stress disorder (PTSD).
- The study compares people with C-PTSD, PTSD, and trauma-exposed individuals without mental illness using brain scans, blood markers, genetic data, actigraphy-derived physiological data, and self-report questionnaires.
- The aim of this study is to identify biological markers that distinguish C-PTSD from PTSD, and to support future research into diagnosis, treatment, and resilience in people affected by trauma.

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resiliencia, apoyo social, regulación emocional, calidad del sueño y síntomas de salud mental. Además, los participantes usarán un reloj inteligente Actigraph durante siete días para recopilar datos fisiológicos derivados de la actigrafía, incluyendo patrones de sueño y variabilidad de la frecuencia cardíaca. Todos los datos desidentificados se publicarán en Open Science Framework tras la publicación de los hallazgos principales del estudio, de acuerdo con las aprobaciones éticas y las directrices institucionales de privacidad y seguridad de datos.

Conclusión Este protocolo integral aborda importantes lagunas en la comprensión del TEPT-C mediante su enfoque multimodal. Al comparar el TEPT-C, TEPT y controles expuestos a trauma, el estudio busca identificar marcadores neurobiológicos específicos del TEPT-C, respaldando potencialmente su distinción diagnóstica e informar sobre enfoques terapéuticos específicos. La integración de medidas de neuroimagen, inflamatorias, genéticas y psicofisiológicas reconoce las complejas interacciones entre los sistemas biológicos en las respuestas al trauma. Los hallazgos podrían contribuir a la investigación futura sobre estrategias de intervención personalizadas al identificar posibles perfiles biológicos y factores de resiliencia asociados con los resultados relacionados con el trauma.

ABBREVIATIONS: ANCOVA: analysis of covariance; ANOVA: analysis of variance; ANTs: advanced neuroimaging tools; BDNF: brain-derived neurotrophic factor; CAGE-AID: conjoint screening questionnaires for alcohol and drug use; C-PTSD: complex post-traumatic stress disorder; CRP: C-reactive protein; CTQ-SF: childhood trauma questionnaire – short form; DASS-21: depression anxiety stress scales; DERS-16: difficulties in emotion regulation scale-16; DSM-5: diagnostic and statistical manual of mental disorders, Fifth edition; EDTA: ethylenediaminetetraacetic acid; FAIR: findable, Accessible, Interoperable, Reusable; FSSQ: Duke-UNC functional social support questionnaire; GWAS: genome-wide association studies; HPA: hypothalamic–pituitary–adrenal; HRV: heart rate variability; ICD-11: international classification of diseases, 11th Revision; IL-1: interleukin-1; IL-6: interleukin-6; IL-8: interleukin-8; ISI: Insomnia Severity Index; ITQ: international trauma questionnaire; LEC-5: life events checklist for DSM-5; MRI: magnetic resonance imaging; MP2RAGE: magnetization prepared 2 rapid acquisition gradient echoes; PRS: polygenic risk scores; PSQI: Pittsburgh sleep quality index; PTSD: post-traumatic stress disorder; QSM: quantitative susceptibility mapping; RDM: research data management; REDCap: research electronic data capture; RSA: resilience scale for adults; TNF-α: tumor necrosis factor-alpha; TR/TE: repetition time/echo time

1. Background

Complex Post-Traumatic Stress Disorder (C-PTSD) is a severe mental illness defined in the latest International Classification of Diseases (ICD-11) by the World Health Organization (2021). Unlike PTSD, which typically develops following single-event traumas and is characterized by re-experiencing, avoidance, and hyperarousal symptoms, C-PTSD additionally encompasses severe disruptions in emotion regulation, negative self-concept, and disturbed relationships (Maercker et al., 2022). C-PTSD commonly affects individuals exposed to prolonged interpersonal traumas, such as childhood adversity, domestic violence, or severe, recurring physical, psychological, or emotional abuse (Herman, 1992; Karatzias et al., 2017a).

Recent studies have begun to differentiate the neurobiological profiles of C-PTSD and PTSD. A systematic review by Stopyra et al. (2023) highlighted that while both disorders share brain aberrations in overlapping regions, C-PTSD is also associated with unique neural alterations. Both conditions are marked by significant neural abnormalities in regions traditionally implicated in stress and trauma responses, including the amygdala (involved in fear and threat detection), the dorsal anterior cingulate cortex (crucial for attentional control and emotional regulation), the hippocampus (linked to impairments in memory formation and retrieval of traumatic memories), and the prefrontal cortex (pivotal for emotion regulation and impulse control). However, a defining feature setting C-PTSD apart is the heightened activation of the insula, a region associated with self-awareness, emotional response, and interoceptive processing (Thomaes et al., 2012). Thomaes et al. (2012) demonstrated this distinctive neural signature of C-PTSD and importantly reported diminished insular activation in patients following a 6-month experimental intervention, suggesting potential neuroplasticity and treatment responsiveness. This insular sensitivity in C-PTSD underscores its unique neurobiological profile compared to PTSD and indicates that C-PTSD may involve distinct neurobiological mechanisms beyond those seen in PTSD. These neurobiological differences align with the distinct symptom profiles of the two conditions and support their separation in diagnostic classifications.

The pathophysiology of trauma-related disorders appears to involve complex interactions between neural circuits, inflammatory processes, and genetic vulnerabilities. Inflammatory cytokines, including IL-1, IL-6, and tumor necrosis factor-alpha (TNF-α), have been implicated in altering brain regions involved in stress and emotion regulation in both

PTSD and C-PTSD (Passos et al., 2015; Smith et al., 2011). These cytokines are known to affect neurotransmitter systems, particularly dopamine pathways, which are crucial for emotional and cognitive functioning (Felger et al., 2016). Elevated levels of these cytokines may disrupt neural circuits mediating fear, anxiety, and mood regulation, potentially contributing to symptom persistence (Smith et al., 2011). As such, these inflammatory markers not only reflect the ongoing inflammatory state but also interact with neural pathways, influencing the severity and progression of the disorders (Gill et al., 2009). Furthermore, genetic factors, particularly those related to the regulation of stress responses and hypothalamic–pituitary–adrenal (HPA) axis functionality, might explain differential susceptibility to trauma-related disorders (Maul et al., 2020).

Sleep disturbances represent another critical dimension in trauma-related disorders, with research indicating that individuals with PTSD and C-PTSD often experience significant difficulties with sleep onset, maintenance, and quality (Pace & Bottary, 2018). These sleep problems may exacerbate other symptoms and hinder recovery. Autonomic nervous system dysregulation is another key physiological feature, with heart rate variability (HRV) emerging as an important biomarker in trauma-related disorders. Studies have demonstrated reduced HRV in individuals with PTSD, reflecting impaired parasympathetic functioning and autonomic flexibility (Chalmers et al., 2014). While less research has focused specifically on HRV in C-PTSD, preliminary evidence suggests that individuals with C-PTSD may exhibit even more pronounced reductions in HRV compared to those with PTSD, potentially reflecting the more pervasive regulatory difficulties characteristic of complex trauma (Liddell et al., 2016). Additionally, C-PTSD and PTSD frequently co-occur with other psychiatric conditions such as depression, substance use disorders, and anxiety disorders, which can complicate diagnosis and treatment approaches (Cloitre et al., 2013).

Despite these advances, there remains a significant gap in our understanding of the neurobiological underpinnings specific to C-PTSD. The complexities of C-PTSD stem from its distinct symptom profile, particularly disturbances in self-organization, which may contribute to broader functional impairments and a pervasive impact on individuals' lives (Karatzias et al., 2017b; Lewis et al., 2022). Whether these effects emerge through aberrant brain development during critical developmental periods, altered brain function in adulthood due to ongoing trauma, or inflammatory responses that modify neural circuits remains poorly understood. The current study aims to comprehensively explore the biological mechanisms associated with C-PTSD, including distinct and shared brain alterations in C-PTSD and PTSD. In addition to multimodal neuroimaging, we will examine inflammatory markers, genetic data, actigraphy-derived physiological measures (e.g. heart rate variability and sleep), and self-report psychosocial assessments. To support this objective, we will establish a biobank with samples from individuals with C-PTSD, PTSD, and trauma-exposed controls to enable future research into the complex biological and psychological correlates of trauma. This biobank will serve as a critical resource for investigating neural changes, sleep disturbances, inflammatory profiles, and the impact of comorbid mental health conditions in C-PTSD.

2. Methods

2.1. Design

This is an observational, cross-sectional study with three comparison groups: individuals with C-PTSD, individuals with PTSD, and trauma-exposed healthy controls, some of whom may have experienced severe psychological distress or adversity. As such, there are several ethical considerations relevant to the protection of participants' rights and well-being. This study has been approved by the Human Research Ethics Committee of the University of Queensland (2024/HE001951) and will be conducted in accordance with the Declaration of Helsinki and the Australian National Statement on Ethical Conduct in Human Research. Participants may experience distress when completing trauma-related questionnaires or during neuroimaging procedures. To mitigate this risk, all research staff are trained in trauma-informed approaches. Participants are informed they can skip questions they find distressing, take breaks as needed, or withdraw from the study at any time without penalty. A clinical psychologist is available on-site during data collection sessions, and participants are provided with mental health resources and referral information.

All participants will provide written informed consent prior to participating in any study procedures. The consent process will include a clear explanation of the study aims, procedures, potential risks and benefits, voluntary participation, and the right to withdraw at any time without penalty. Participants will have opportunities to ask questions and will be given sufficient time to consider their participation. This study protocol has been pre-registered on the Open Science Framework https://doi.org/10.17605/OSF.IO/Q6PBR.

2.2. Participants and recruitment

2.2.1. Sample size and power calculation

A power analysis was conducted using G*Power to determine the appropriate sample (Faul et al., 2007).

While our study investigates multiple outcomes including brain structure and function, inflammatory markers, genetic factors, and physiological measures, the power calculation was based on structural MRI outcomes, as these typically require larger sample sizes than behavioural measures (Szucs & Ioannidis, 2020). Specifically, we powered the study to detect medium effect sizes (Cohen's $d = 0.5$) in regional grey matter volumes within brain areas previously implicated in C-PTSD and PTSD, such as the insula, amygdala, hippocampus, and prefrontal cortex (Meng et al., 2016). With an alpha level of 0.05 and power of 0.9 in an analysis of variance (ANOVA) design with three groups, a total of 87 participants are required. To account for potential missing data or dropout, we aim to recruit 100 participants: 40 individuals with C-PTSD, 30 individuals with PTSD, and 30 trauma-exposed healthy controls. The larger sample size in the C-PTSD group reflects the primary focus of the study and our goal to support more detailed exploratory analyses of biological and psychosocial correlates specific to C-PTSD, particularly as the biobank grows in future phases.

2.3. Eligibility criteria

Eligible participants must be adults aged 18 years or older, capable of providing informed consent, and fluent in English to ensure comprehension of questionnaires and instructions. Participants in the C-PTSD and PTSD groups must have a diagnosis confirmed by a psychiatrist or clinical psychologist at the time of enrolment. To ensure consistency with ICD-11 criteria, all participants in these groups also complete the International Trauma Questionnaire (ITQ), a validated self-report instrument designed to assess symptom-level alignment with ICD-11 diagnostic thresholds for PTSD and C-PTSD. While the ITQ does not replace structured clinical interviews, it enables standardized assessment of diagnostic criteria across participants. Trauma-exposed healthy controls are screened using the Life Events Checklist for DSM-5 (LEC-5) to verify trauma exposure and complete the ITQ to confirm that they do not meet symptom criteria for PTSD or C-PTSD. Individuals who meet diagnostic thresholds for either condition on the ITQ or report a current psychiatric diagnosis or major medical condition are excluded. Exclusion criteria include individuals under 18 years of age, non-fluent English speakers, individuals with contraindications for MRI (e.g. metal implants, claustrophobia), or those diagnosed with neurological conditions, bipolar disorder, schizophrenia spectrum disorders, or other major psychiatric or systemic medical conditions likely to affect brain structure, function, or inflammatory markers (e.g. autoimmune diseases). Additionally, individuals with severe or current substance use disorders will be excluded. However, participants with common psychiatric comorbidities such as depression, anxiety disorders, or Attention-Deficit/Hyperactivity Disorder (ADHD) will be included, as these are frequently observed in individuals with PTSD and C-PTSD and enhance the generalizability of our findings. Two study-affiliated psychiatrists are part of the research team and contribute to both diagnostic confirmation and participant referral, ensuring clinical oversight and diagnostic consistency.

2.4. Recruitment strategy

Participants with C-PTSD and PTSD will be recruited through three primary channels: (1) referrals from two study psychiatrists affiliated with The University of Queensland and its partner clinics, who will inform eligible patients about the study, (2) partnerships with trauma-focused organizations, particularly Bravehearts, an Australian organization dedicated to the prevention and treatment of child sexual abuse, (3) social media campaigns managed by the University of Queensland's media team and conducted via Facebook, Instagram, and LinkedIn, targeting individuals residing in the Brisbane area. Trauma-exposed healthy controls will also be recruited through social media campaigns.

Eligible participants with C-PTSD or PTSD who were not directly referred by a psychiatrist will be asked to provide a form completed by their treating clinician (psychiatrist or clinical psychologist) confirming their diagnosis prior to enrolment. All potential trauma-exposed controls will complete an online pre-screening questionnaire assessing demographics, clinical diagnoses, MRI safety, and trauma exposure, including the LEC-5. This pre-screening process allows us to selectively invite trauma-exposed healthy controls whose demographic characteristics (e.g. age, sex) and trauma exposure profiles (e.g. type and severity) are broadly comparable to those of the clinical group, prior to in-person assessment. While we do not apply formal statistical matching procedures, this group-level matching approach helps ensure analytical comparability across groups. Written informed consent will be obtained from all participants. An outline of the study design is provided in Figure 1.

2.5. Assessment procedures and materials

Participants who meet the eligibility criteria will attend a 2.5-h assessment session at the Centre for Advanced Imaging. During this session, participants will complete questionnaires, undergo MRI scanning, and provide blood samples. They will then be given an Actigraph smart watch to wear for seven days to monitor physiological data. Participants will receive $50 for completing the in-person

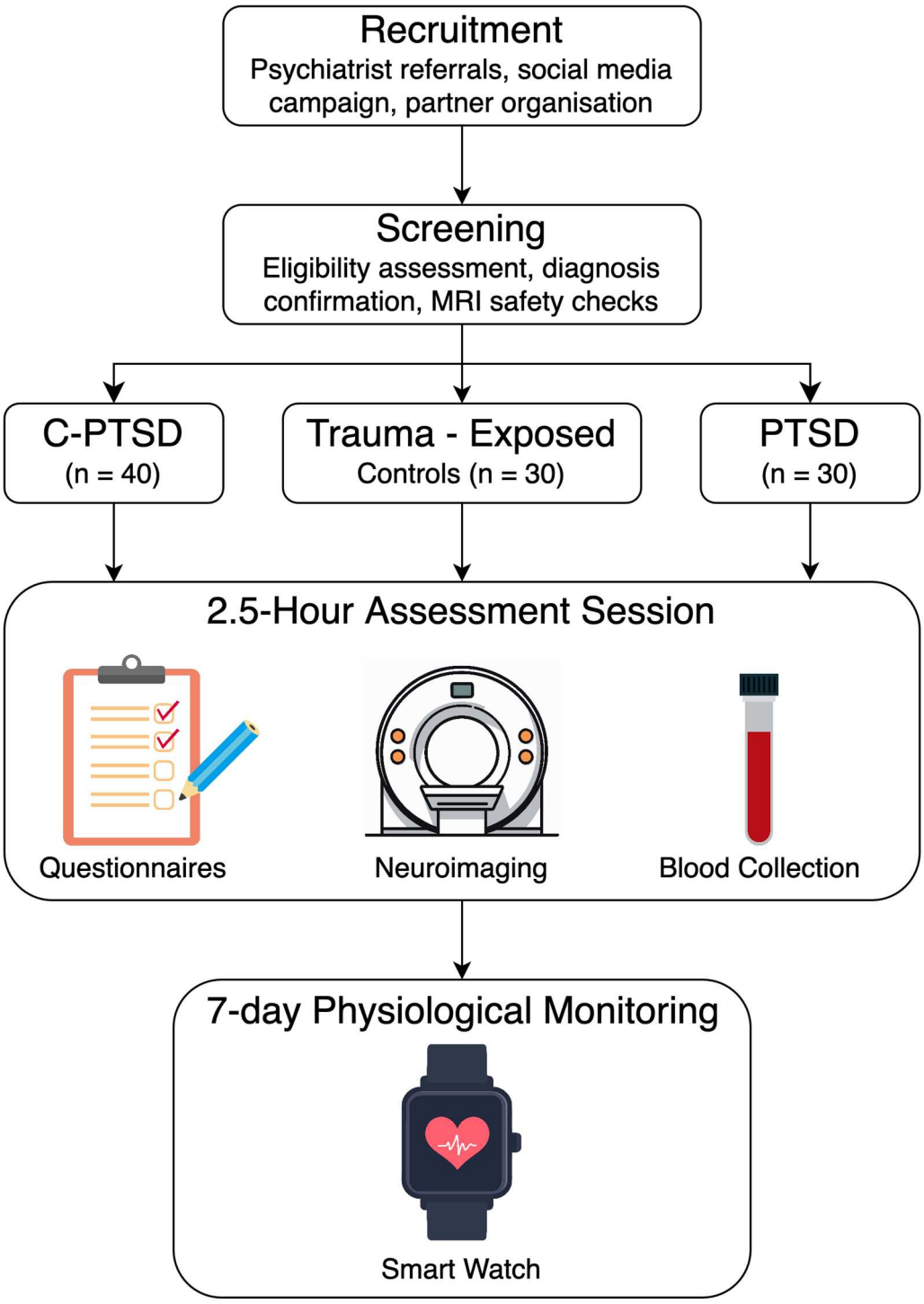

Figure 1. Study design overview. MRI = magnetic resonance imaging; C-PTSD = complex post-traumatic stress disorder; PTSD = post-traumatic stress disorder.

component of the study and an additional $10 upon return of the smart watch, in accordance with the University of Queensland's participant compensation guidelines. A summary of all collected measures is provided in Table 1.

2.6. Self-report measures

Participants will provide general demographic and background information such as age, sex, ethnicity, education level, height, weight, handedness, marital status, sexual orientation, employment status and household income, along with details regarding current medications, personal history of psychiatric conditions, and family history of mental illness. Participants will be asked to provide information about their current psychotropic medications and any psychological treatments they are receiving. These variables will not be used as exclusion criteria but will be documented to allow for consideration in future analyses. Participants will complete the following validated questionnaires:

Table 1. Summary of study measures.

Measure	Full name	Measures	Items	Time (min)
Psychological assessments				
ITQ	International Trauma Questionnaire	ICD-11 PTSD and C-PTSD diagnoses	12	5–10
LEC-5	Life Events Checklist for DSM-5	Traumatic event exposure	17	5–10
RSA	Resilience Scale for Adults	Resilience	33	10–15
FSSQ	Duke-UNC Functional Social Support Questionnaire	Social support	8	5
DASS-21	Depression Anxiety Stress Scales	Depression, anxiety, and stress symptoms	21	5–10
CTQ-SF	Childhood Trauma Questionnaire – Short Form	Childhood abuse and neglect	28	5–10
ISI	Insomnia Severity Index	Insomnia severity	7	2–5
PSQI	Pittsburgh Sleep Quality Index	Sleep quality o	19	5–10
DERS-16	Difficulties in Emotion Regulation Scale-16	Emotion regulation	16	5
CAGE-AID	Conjoint Screening Questionnaires for Alcohol and Drug Use	Substance use problems	4	2
Brief-COPE	Coping Orientation to Problems Experienced Inventory	Coping strategies	28	10
Neuroimaging measures				
MP2RAGE	Magnetization Prepared 2 Rapid Acquisition Gradient Echoes	Brain morphometry, cortical thickness, volumetrics	N/A	7
DWI	Diffusion-Weighted Imaging	White matter microstructure, structural connectivity	N/A	10
rs-fMRI	Resting-State Functional MRI	Functional connectivity	N/A	10
T2w	T2-weighted Imaging	Myelin Mapping	N/A	5
QSM	Quantitative Susceptibility Mapping	Iron content, tissue microstructure	N/A	7
tb-fMRI	Task-Based Functional MRI	Neural responses to emotional stimuli	N/A	16
Biological samples				
Inflammatory Markers	Blood Sample	Inflammatory Assays	N/A	5
Genetic Analysis	Blood Sample	DNA Extraction, GWAS, polygenic risk scores	N/A	5
Physiological monitoring				
Actigraph	ACLEAP2 Smart Watch	Sleep data and heart rate variability	N/A	7 days

Note: Administration times are approximate and may vary based on individual participants. PTSD = post-traumatic stress disorder; C-PTSD = complex post-traumatic stress disorder; DSM-5 = Diagnostic and Statistical Manual, 5th Edition; N/A = not applicable; MRI = magnetic resonance imaging; DNA = Deoxyribonucleic Acid; GWAS = Genome-Wide Association Study.

1. The International Trauma Questionnaire (ITQ) (Cloitre et al., 2018) is an 18-item self-report measure specifically developed to assess ICD-11 PTSD and C-PTSD diagnoses. The ITQ has demonstrated good psychometric properties with internal consistency (Cronbach's $\alpha = 0.87–0.93$), test-retest reliability ($r = 0.86$), and discriminant validity in distinguishing between PTSD and C-PTSD symptoms across diverse trauma-exposed populations (Cloitre et al., 2018; Hyland et al., 2017).
2. The Life Events Checklist for DSM-5 (LEC-5) (Gray et al., 2004) is a 17-item assessment tool screening for exposure to 16 potentially traumatic events with an additional item for other stressful events. The LEC has shown good convergent validity with measures of trauma-related psychopathology ($r = 0.39–0.63$) and temporal stability (*kappa* = 0.61) (Gray et al., 2004).
3. The Resilience Scale for Adults (RSA) (Friborg et al., 2003), a 33-item scale measuring resilience across six factors, namely perception of self, planned future, social competence, structured style, family cohesion, and social resources. The RSA demonstrates high internal consistency (Cronbach's $\alpha = 0.76–0.87$), good test-retest reliability ($r = 0.69–0.84$), and convergent and discriminant validity (Friborg et al., 2003; Windle et al., 2011).
4. The Duke-UNC Functional Social Support Questionnaire (FSSQ) (Broadhead et al., 1988): An eight-item measure of social support strength with excellent internal consistency (Cronbach's $\alpha = 0.81–0.92$), good construct validity when compared to other social support measures, and demonstrated predictive validity for health outcomes (Bellón Saameño et al., 1996; Broadhead et al., 1988).
5. The Depression Anxiety Stress Scales (DASS-21) (Lovibond & Lovibond, 1995) is a 21-item measure assessing depression, anxiety, and stress symptoms. The DASS-21 has shown excellent internal consistency (Cronbach's $\alpha = 0.88–0.94$) across subscales, good convergent and discriminant validity with other measures of depression and anxiety, and satisfactory construct validity in clinical and non-clinical samples (Brown et al., 1997; Lovibond & Lovibond, 1995).
6. The Childhood Trauma Questionnaire – Short Form (CTQ-SF) (Bernstein et al., 1994), retrospectively assesses childhood abuse and neglect across five domains: emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect. The CTQ-SF has 28 items and demonstrates high internal consistency (Cronbach's $\alpha = 0.79–0.94$), good test-retest reliability over 2–6 months ($r = 0.79–0.86$), and good convergent validity with clinician-rated interviews of childhood maltreatment (Bernstein et al., 1994, 2003).
7. The Insomnia Severity Index (ISI) is a seven-item questionnaire assessing insomnia severity with excellent internal consistency (Cronbach's $\alpha = 0.90–0.92$),

convergent validity with sleep diary measures (r = 0.32–0.91), and sensitivity to detect changes in perceived sleep difficulties with treatment (Bastien et al., 2001).

8. The Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989), a 19-item measure evaluating sleep quality over a one-month period across seven components. The PSQI shows good internal consistency (Cronbach's α = 0.70–0.83), test-retest reliability (r = 0.85), and ability to distinguish between good and poor sleepers with high sensitivity (89.6%) and specificity (86.5%) (Buysse et al., 1989; Carpenter & Andrykowski, 1998).
9. The Difficulties in Emotion Regulation Scale-16 (DERS-16) (Bjureberg et al., 2016), a shortened 16-item version of the DERS, assesses emotion regulation difficulties. The DERS-16 demonstrates excellent internal consistency (Cronbach's α = 0.92–0.94), good test-retest reliability (r = 0.85), and strong convergent and concurrent validity with the original 36-item version (r = 0.92–0.98) (Bjureberg et al., 2016; Miguel et al., 2017).
10. Conjoint Screening Questionnaires for Alcohol and Drug Use (CAGE-AID) (Brown & Rounds, 1995): A 4-item screening tool for substance use problems adapted from the original CAGE questionnaire. The CAGE-AID demonstrates good sensitivity (0.79) and specificity (0.77) for identifying substance use disorders, with adequate test-retest reliability (*kappa* = 0.67) (Brown & Rounds, 1995; Hinkin et al., 2001).
11. Coping Orientation to Problems Experienced Inventory (Brief-COPE) (Carver, 1997): A 28-item tool assessing 14 distinct coping strategies. The Brief-COPE has shown acceptable internal reliability across subscales (Cronbach's α = 0.50–0.90), adequate test-retest reliability, and good construct validity in trauma-exposed populations (Carver, 1997; Cooper et al., 2008).

2.7. Neuroimaging protocol

Participants will undergo multimodal MRI scanning on a Siemens Magnetom Prisma 3 T whole-body MRI at the Centre for Advanced Imaging. The MRI protocol (approximately 50 min in total duration) includes a comprehensive set of sequences to assess brain structure and function. High-resolution T1-weighted structural imaging will be acquired using an MP2RAGE sequence (TR = 4000 ms; TE = 2.99 ms; voxel size = 0.8 mm^3; acquisition time = 6 min) to assess brain morphometry, cortical thickness, and volumetric measures. Diffusion-weighted images will be acquired in the anterior-posterior direction with TR = 5000 ms, TE = 75 ms, voxel size = 2 mm^3, and 122 diffusion directions: 13 at b = 0 s/mm^2, 50 at b = 1000 s/mm^2, and 60 at b = 3000 s/mm^2 to examine white matter microstructure and structural connectivity. The total acquisition time is 11 min. Two reverse-phase encoded b = 0 s/mm^2 images will be acquired in the posterior-anterior direction before and after the diffusion sequence, (approximately 1 min). Resting-state functional MRI (TR = 1000 ms; TE = 30 ms; voxel size = 2.0mm^3; acquisition time = 8.5 min) will be acquired to assess intrinsic functional connectivity patterns while participants are instructed to relax with eyes open, fixating on a cross. T2-weighted imaging (TR/TE = 3200 ms/563 ms; voxel size = 0.8 mm^3; acquisition time = 4.5 min) will provide complementary structural information and will be used in combination with T1-weighted images to generate T1/T2 ratio maps for estimation of intracortical myelin content. Quantitative susceptibility mapping (QSM; multi-echo GRE sequence; TR = 70 ms; TE = 45 ms; voxel size = 0.7 mm^3; acquisition time = 3 min) will be used to evaluate iron content and tissue microstructure. Finally, task-based functional MRI (TR = 1500 ms, TE = 30 ms; voxel size = 2.0 mm^3; 4 runs, total acquisition time = 14 min) will be performed using an emotional faces paradigm where participants view faces displaying different emotions (happy, sad, and fearful expressions) as well as object stimuli, with neural responses to these emotional stimuli being recorded. During structural scans, participants will have the option to watch a silent movie or close their eyes to minimize movement, and cushioned padding will be used to reduce head motion throughout all sequences.

2.8. Blood collection, inflammatory assays and genetic analysis

A 40 mL blood sample will be collected from each participant using standard venipuncture techniques performed by a certified pathology collector. A 20 mL sample will be centrifuged for serum extraction and frozen at −80°C for subsequent analysis of inflammatory markers, including C-reactive protein (CRP), interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-8 (IL-8), brain-derived neurotrophic factor (BDNF), and tumor necrosis factor-alpha (TNF-α), amongst others. The remaining 20 mL will be drawn into EDTA vacutainers for preservation of white blood cells, processed under controlled conditions, and frozen at −80°C within. These samples will be used for subsequent DNA extraction and genomic analyses, including genome-wide association studies (GWAS) to calculate polygenic risk scores (PRS) related to stress response regulation.

All biological samples will be stored at the University of Queensland in secure, access-controlled biorepository facilities located at the Human Studies Unit. Serum and whole blood samples will be stored at

−80°C in freezers equipped with continuous temperature monitoring and emergency backup power. All storage and handling procedures comply with institutional and national biospecimen guidelines. Remaining samples will be retained for a minimum of 15 years and may be used in future ethically approved research, in accordance with participant consent.

2.9. Sleep and autonomic function monitoring

Participants will be provided with an Actigraph smart watch (ACLEAP2) to wear continuously for seven days. The device will record comprehensive sleep data including sleep onset latency, frequency of awakening after sleep onset, total sleep time, sleep efficiency, and sleep stages. The ACLEAP2 also incorporates advanced photoplethysmography sensors that continuously record heart rate and heart rate variability (HRV) metrics during both sleep and daytime activities, as well as body temperature, energy expenditure, and physical activity breakdown (sedentary, light, moderate, vigorous, very vigorous). After the seven-day monitoring period, participants will return the device using a prepaid envelope provided by the researchers. Data will be downloaded and processed using the manufacturer's software (ActiLife 7) with specialized algorithms for sleep scoring and HRV analysis.

2.10. Data management

All data will be stored in a password-protected database on a secure University of Queensland research data management (RDM) server, accessible only to study investigators. Psychometric and clinical data will be collected and managed using REDCap (Research Electronic Data Capture), a secure, web-based platform designed to support data capture for research studies. REDCap is widely used in clinical trials and academic health research globally, offering audit trails, user access control, and real-time data validation to ensure accuracy and security of sensitive information (Harris et al., 2009). Upon completion of the study, all data will be made available in de-identified format for open-access sharing in accordance with the FAIR (Findable, Accessible, Interoperable, Reusable) data principles, which promote data transparency and reusability in scientific research (Wilkinson et al., 2016). In addition to open access sharing of de-identified data, we are committed to fostering collaboration and long-term growth of this biobank. All data collected through this protocol will be made available for future ethically approved studies, with the goal of expanding this resource into a large-scale, collaborative platform for C-PTSD and PTSD research.

2.11. Data derivatives and primary statistical analysis plan

Neuroimaging data will be processed using standard pipelines including those implemented in Advanced Neuroimaging Tools (ANTs) (Avants et al., 2011), FreeSurfer (Fischl, 2012), FSL (Jenkinson et al., 2012) and MRtrix3 (Tournier et al., 2019), among others. Key derivatives will include grey matter volume, white matter microstructure, cortical thickness, and functional connectivity. Additional derived metrics will include core demographic variables, individual questionnaire items, subscale and total scores, GWAS data, polygenic risk scores (PRS), as well as peripheral inflammatory markers.

Given the primary aim of establishing a biobank to support future large-scale research, the statistical analyses presented here are exploratory. We plan to examine group differences (C-PTSD vs. PTSD vs. trauma-exposed controls) in key biological outcomes, including grey matter volume (from T1 MRI), white matter microstructure (from DWI), inflammatory markers (e.g. IL-6, CRP), and physiological data (e.g. HRV, sleep metrics). These will be assessed using ANOVA or ANCOVA models, with covariates including age, sex, current psychotropic medication use, trauma load (e.g. CTQ scores), and comorbid diagnoses.

Associations between biological and psychological variables (e.g. DERS-16, resilience scores, depressive symptoms) will be examined using multiple linear regression and multilevel models where appropriate (e.g. nested models for tract-specific metrics across individuals). Categorical clinical outcomes (e.g. C-PTSD vs. PTSD) may also be modelled using logistic regression. Although statistical matching will not be applied due to sample size, we will evaluate covariate balance between groups and adjust accordingly in multivariate models.

Missing data will be assessed for randomness. Where feasible, multiple imputation will be used for missing questionnaire or physiological data. Sensitivity analyses will compare imputed vs. complete-case results. MRI datasets with significant artefacts or missing sequences will be excluded from specific analyses but retained in the overall biobank.

3. Discussion

This protocol outlines a comprehensive study designed to investigate the neurobiological underpinnings of C-PTSD, with a particular focus on distinguishing it from PTSD and examining shared and distinct neural mechanisms. The establishment of a biobank incorporating neuroimaging, inflammatory markers, genetic data, actigraphy-derived physiological data (e.g. sleep and heart rate variability), and

psychosocial assessments represents a significant advancement in trauma research that has several important implications.

Previous research has largely focused on isolated aspects of trauma responses, such as specific brain regions or individual inflammatory markers (Hori & Kim, 2019; Stopyra et al., 2023). Our approach recognizes that trauma impacts multiple interconnected biological systems simultaneously, potentially revealing patterns and relationships that would not be apparent when examining these systems in isolation. The inclusion of trauma-exposed healthy controls is another important feature of this protocol. By comparing individuals with C-PTSD and PTSD to those who have experienced trauma but not developed these disorders, we can better understand resilience factors that may protect against the development of trauma-related psychopathology. This may have significant implications for preventive interventions, particularly for individuals at high risk of trauma exposure due to their occupation or circumstances.

The assessment of sleep and autonomic function using continuous monitoring represents an innovative approach to understanding the physiological dimensions of trauma responses. Sleep disturbances and autonomic dysregulation are common in trauma-related disorders (Cox et al., 2017; Nagpal et al., 2013), but they have rarely been incorporated into comprehensive biomarker studies. The seven-day continuous monitoring period will provide ecologically valid data on these important physiological parameters, potentially identifying new treatment targets or biomarkers for monitoring treatment response.

From a clinical perspective, this research has several potential implications. First, identification of distinct biological markers for C-PTSD could support the diagnostic differentiation between PTSD and C-PTSD, potentially leading to more targeted treatment approaches. Second, while the current cross-sectional design does not permit treatment recommendations, identifying biological correlates of specific symptom clusters may help guide future research into personalized intervention approaches. Third, the comprehensive assessment of resilience factors may inform preventive interventions for individuals at risk of developing trauma-related disorders.

The cross-sectional design of this study is a limitation that prevents conclusions about causality and developmental trajectories. While our approach can identify correlations between trauma exposure, neurobiological markers, and clinical symptoms, it cannot definitively determine whether observed differences represent predisposing factors, consequences of trauma, or compensatory mechanisms. Future longitudinal studies building on our findings will be essential to clarify these relationships. Additionally, while our sample size is adequate for detecting medium effect sizes in primary group comparisons, it may limit our ability to conduct more complex multivariate analyses or to examine the effects of specific trauma types or timing. The establishment of our biobank, however, will facilitate future studies with larger sample sizes through data sharing and collaboration. Given the intensive nature of the study protocol, we anticipate potential challenges in participant recruitment. These challenges are compounded by the lack of direct treatment benefit to participants. To address this, we have adopted several mitigation strategies: participants are reimbursed for their time; assessments are scheduled flexibly, including outside of typical work hours; and recruitment is supported through strong community partnerships and targeted outreach via social media. We also emphasize the value of participants' contribution to research on trauma and mental health in all study materials.

This protocol aims to contribute to the growing body of research on C-PTSD as a distinct diagnostic entity with specific neurobiological correlates. By integrating multiple biological systems and psychological measures, we hope to advance our understanding of trauma-related disorders and ultimately improve outcomes for affected individuals. In line with open science principles, all data from this study will be made publicly available in de-identified format to facilitate broader use by the research community. Importantly, the biobank is designed to serve as a foundation for ongoing data collection, enabling future expansion through collaborative projects, longitudinal follow-up studies, and the inclusion of additional clinical and control populations.

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Author contributions

AM, CD and LO have contributed to the conception, design, acquisition and analysis of the work. LO has drafted the manuscript. All authors have approved the submitted version and agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

Disclosure statement

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

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Data availability statement

The data that support the findings of this study are currently being collected. Upon study completion, de-identified data will be made publicly available, in accordance with FAIR data principles. A DOI and full access details will be provided upon data release.

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